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Epilepsy in Children

Clinical and Social Aspects

Edited by Željka Petelin Gadže

EPILEPSY IN CHILDREN – CLINICAL AND SOCIAL ASPECTS

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http://dx.doi.org/10.5772/1140
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Notice

First published in Croatia, 2011 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

Additional hard and PDF copies can be obtained from orders@intechopen.com

Epilepsy in Children - Clinical and Social Aspects
Edited by Željka Petelin Gadže
p. cm.
ISBN 978-953-307-681-2
eBook (PDF) ISBN 978-953-51-6487-6

Meet the editor

Assist. Prof. Željka Petelin Gadže, M.D., Ph.D., born on the 11th August 1976 iz Zagreb, Croatia, after graduation on the Medical School of the University of Zagreb, started to work at the Department of Neurology of the Medical School and University Hospital Centre Zagreb, where she specialized in neurology in May 2007, and defended doctoral dissertation "Apoptosis of blood and cerebrospinal fluid lymphocytes in patients with multiple sclerosis" in December 2004. Since 2007 she works at the Referral Centre for Epilepsy of the Ministry of Health and Social Welfare of the Republic of Croatia, and since 2010 she is the head of the Electroencephalographic Laboratory and Division for Minimally Invasive Neurosurgical Treatment of Neurological Diseases at the University Hospital Centre Zagreb. She has published around 90 papers in the field of neurology, and held numerous lectures at domestic and international neurological congresses. Her interests in neurology are epileptology and electroencephalography, especially epilepsy surgery.

Contents

Preface

Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book "On The Sacred Disease", in which he refuted the idea that the upheaval was the work of spirits and wisely related it to the brain. This concept was not fully accepted until modern era (John Hughlings Jackson, 1873). Classically, epilepsy is defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. According to WHO epilepsy accounts for about 1% of the total burden of disease worldwide, about the same as breast cancer in women and lung cancer in men.

Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology – they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

Author Takao dedicated the chapter to the clinical and experimental investigations in polymicrogyria, that were reviewed with special reference to the epileptogenicity of this malformation. The cortical hyperexcitability in polymicrogyria may be reduced by the inhibitory neuronal network constructed by a population of aberrantly migrating inhibitory interneurons, which are mobilized from the ganglionic eminence during the development of polymicrogyria. Authors Kanemura and Aihara wrote about epileptic patients with continuous spikes and waves during slow sleep, in which mentioned electroencephalographic findings were associated with frontal lobe growth disturbance. They state that seizures and paroxysmal anomaly durations may be influenced by prefrontal lobe growth, which relates to neuropsychological problems.

Authors Isam et al wrote the chapter about neonatal seizures. Neonatal seizures are common and the incidence is variable according to age and maturity of the neonate,

weight and the severity of the underlying condition. It has been estimated that the incidence rate of clinical seizures varies from 1.1 to 8.6 per 1000 live births. No period carries the danger of seizures to the individual person like the first four weeks of life, because of immaturity of the brain cells that are more vulnerable to injury and because of wide range of factors that might cause seizures in this period. Neonatal seizures tend to be brief, because immature neurons are unable to sustain repetitive activity for a long period of time, and to be focal or multifocal. It requires immediate evaluation because of the variable conditions that might insult developing and vulnerable neurons of neonate, some of which might endanger the life of neonate. Some time seizures might be the first and probably the only manifestations of underlying significant dysfunction of the central nervous system of the newborn infant. Furthermore, these seizures are sometimes difficult to be diagnosed clinically, resulting in delaying treatment and worsening of short and long term prognosis. There is still a great debate about pathophysiology, clinical classification, electroencephalographic (EEG) significance and treatment of neonatal seizures.

Chapter by authors Dan, Pelc et al is dedicated to patients with Angelman syndrome, that, compared to many other neurodevelopmental disorders, has the remarkably high risk for epilepsy. In particular, early-childhood onset of refractory epilepsy with atypical absences and myoclonic seizures with predisposition to developing non-convulsive status epilepticus is a common presentation. This may be due to propensity to hypersynchronous neuronal activity, which might be related to abnormal GABA-mediated transmission due to lack of UBE3A expression, or other factors. On the one hand, non-epileptic stereotyped or paroxysmal events (including motor or behavioural manifestations) may lead to overdiagnosis. On the other hand, the epileptic nature of relatively subtle manifestations such as absences, myoclonias or non-convulsive status epilepticus may be under-recognised in the context of behavioural and motor features. The neurocognitive effects of seizures are difficult to evaluate. There is a major need for evidence on which to base rational treatment.

A diagnostic scheme for patients with epileptic seizures and with epilepsy proposed by ILAE Commission (2001) newly adopted the concept of “epileptic encephalopathy” as one of the new key terms. It is defined as a condition in which epileptiform abnormalities are believed to contribute to the progressive disturbance in cerebral function, but this definition may be ambiguous. Authors Raidah et al state that the proposal include 8 syndromes: early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, myoclonic status in non-progressive encephalopathies, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epilepsy with continuous spike-waves during slow-wave sleep. To these syndromes, the migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci may be reasonably added. In the chapter authors concentrate on the epileptic encephalopathies that occur only in infancy.

The frontal lobes of the brain constitute more than a third of the human cerebral cortex and are characterized by a complex functional organization supporting higher level

integration circuits. The complexity of the frontal lobe, in terms of its neuroanatomy and connections, determines a marked variability in the epileptic manifestations with fast and inter- and intra-hemispheric propagation. Vago et al discuss about the epilepsies involving the frontal lobe – they describe the characteristic EEG discharges, neuropsychological and behavioral consequences, in the light of the complexity of frontal regions, and they also focus on the interactions between EEG features, demographic variables and neuropsychological outcome.

Authors Readnower et al discuss about the novel neuroprotective strategies and targets of intervention in epilepsy. Development of new anticonvulsive therapies designed as both an anticonvulsive as well as a neuroprotectant would be the best way to treat acute seizure conditions and to possibly prevent the development of chronic epilepsy. One of the newer broad spectrum antiepileptic drug, widely used in the management of epilepsy, is zonisamide (ZNS). Narasimhan et al state that zonisamide is effective as adjunctive therapy for refractory partial seizures, and as monotherapy for newly diagnosed or refractory partial seizures. It can also be administrated in patients with post-operative seizures, may be useful in the treatment of patients with progressive myoclonic epilepsy (studies have found it to be useful in Unverricht-Lundborg disease), West syndrome, and brain tumour related epilepsy.

Chapter by Jung et al will provide practical recommendations to guide the management of the ketogenic diet in childhood epilepsy and give a review on the current state of ketogenic diet. Special chapter written by Günel et al is dedicated to the physiotherapy for children with cerebral palsy.

Epilepsy affects 1-2% of children. In childhood, epilepsy is more common in the first year of life, and its incidence decreases progressively with increasing age, affecting approximately 100 children per 100,000 births in the first year of life, 40 children for every 100,000 births in subsequent years, and approximately 20 individuals per 100,000 adolescents. In 75% of these cases, seizures are well controlled with antiepileptic drugs and in the remaining 25% epilepsy is refractory to pharmacological treatment and surgical approach should be considered. Terra et al state that surgery for epilepsy in childhood has become an effective method in treating this condition, and should be indicated as early as possible. Peculiarities of epilepsy in children should be considered to achieve optimal results. Although a reduction of seizures is the primary goal of surgery, the maintenance of cognitive and motor development milestones is essential to allow the child have a quite normal life in adulthood. Extratemporal epilepsy in children closes more cases compared to those observed in adults, but still dominates the temporal lobe as the site of ictal onset, and surgical results are very encouraging. Surgical option should take in account several factors such as child´s age, underlying pathology and lesion extension. Neuronal plasticity can be an ally for the development of minor post-operative neurological deficits. Authors Park and Kim state that callosotomy in pediatric epilepsy is a valuable tool to control seizures early on, in order to protect the developing brain from further damage and to give chance to recover neuropsychological function from damage done by

seizure itself as well as seizure medication. They advocate that one stage total callosotomy in young patients with medically intractable epilepsy without localizing lesions is especially effective in drop attacks and secondary generalized epilepsy. With improvement in microsurgical techniques, excellent seizure outcome as well as functional outcome may be reached without previously known high rate of morbidity and mortality.

Authors Hocaoglu and Koroglu state that childhood epilepsy has a significant effect on the child himself and the family because of its psychological and social results. In the studies the increasing economical responsibility of the families whose children undergo chronic diseases is distinctively described. Still, epilepsy in childhood is different from the other chronic diseases due to the fact that its sudden symptoms and early unpredictable effects are all specific for itself. In many studies about epilepsy, despite the fact that the patient's quality of life and relationship with the family are examined, in few ones problems belonging to family members that result from epilepsy are pointed. Clinicians should consider both neurological and psychosocial factors, including the family system, when treating psychopathology in children with epilepsy. The chapter by Stevanovic et al systematically reviewed synthesizing different studies that evaluated health-related quality of life (HRQOL) in children and adolescents with epilepsy over 12 past years. The affected domains, predictors, and impacts on HRQOL of specific and non-specific treatments were reviewed. Previous reviews evaluated methodological issues in HRQOL assessment, components of theoretical model, and determinants of HRQOL in pediatric epilepsy. Based on the findings and evidence found, it could be concluded that children and adolescents have more affected HRQOL in physical, psychological, and social domain than healthy children and adolescents.

It is important for all of us to raise the awareness and reduce social barriers for individuals with epilepsy. Together we can hope that we will identify ways to improve the treatment of patients with epilepsy and the livelihood of all individuals with epilepsy.

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Part 1

Ethiology and Pathogenesis of Epilepsy: Data from Research

1

Polymicrogyria: A Clinical and Experimental Approach to Epilepsy

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1. Introduction

Polymicrogyria is the presence of an excess number of abnormally small gyri that produce an irregular cortical surface. Although polymicrogyria is associated with severe epilepsy in 65% of patients (Guerrini & Filippi, 2005), few data concerning the epileptogenic zone and its relationship with the polymicrogyric tissue are available due to the fact that patients with polymicrogyria are rarely considered to be suitable candidates for epilepsy surgery (Chassoux et al., 2008). An experimental model in which a single or few microgyri are generated by a freezing insult suggests a widespread area of functional disruption that extends beyond the visualized abnormality (Redecker et al., 2000). However, the detailed mechanism of epileptogenesis has not yet been well characterized for polymicrogyria (Sisodiya, 2004). In this chapter, clinical and experimental investigations in polymicrogyria were reviewed with special reference to the epileptogenicity of this malformation.

2. Definition and pathogenesis of polymicrogyria

Polymicrogyria is a cerebral cortical malformation characterized by an excessively folded cortical ribbon of miniature, individually thin convolutions, which may be fused together or piled on top of one another (Sisodiya, 2004). The cortical surface is irregular, and the convolutions can appear wider than expected, with a bumpy surface, like cobblestones or morocco leather (Graham & Lantos, 2002). There are two subtypes: unlayered type and four-layered type. In unlayered polymicrogyria, the external molecular layer is continuous and does not follow the profile of the convolutions, and the underlying neurons have radial or vertical distribution but no laminar organization (Ferrer, 1984). Polymicrogyric area may be distributed by focal, multi-lobar, or diffuse in the cerebral cortex. This brain malformation is thought either to be resulted from early exogenous insult from the 13th to 18th week of gestation or to be genetically determined (Ferrer & Catala, 1991). In four-layered polymicrogyria, there are two neuronal layers (2nd and 4th layers) under the molecular layer (1st layer), separated by an intermediate layer with many fibers and few cells (cell-sparse 3rd layer) (Graham & Lantos, 2002). Polymicrogyric 2nd and 3rd layers are thought to be correspond to the normal cortical layers II, III, IV, and layer V, respectively, in which horizontal neuronal lamination is usually spared. Four-layered polymicrogyria is believed to be resulted from a perfusion failure limited to one or more arterial vascular beds, occurring between the 20th and 24th week of gestation. This would lead to intracortical

laminar necrosis with delayed damage of the distal section of radial glial fibers, with consequent late migration disorder and post-migratory overturning of cortical organization (French, 1989).

Experimental polymicrogyria can be modeled by the excitotoxic brain lesions during the period of neuronal migration. Ibotenate is an agonist of the N-methyl-D-aspartate (NMDA) complex receptor . Experimental studies have demonstrated that an intracerebral injection of ibotenate induces excitotoxic brain lesions mimicking a variety of neuronal migration disorders including microgyria (Takano et al., 2005). After the radial glial fibers and surrounding neural tissues were damaged by ibotenate, the corresponding area within the cortical plate collapsed (Figure 1A). As the surrounding neurons migrate along the radial fibers, the cortical plate rolled inward and became infolded, forming microgyria (Figure 1B). Thus, the damage to intermediate cortical layers would produce a difference in growth rate between outer and inner cortical layers, with consequent excessive folding of the cortical surface (Figure 1C) (Takano et al., 2005).

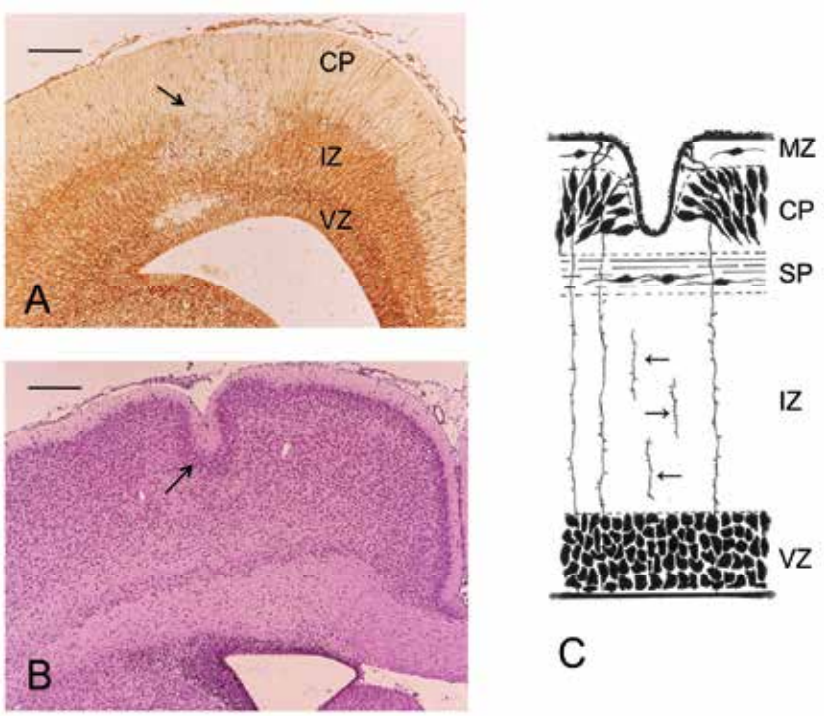

Fig. 1. A: Cortical lesions 1 day after ibotenate injection shown by vimentin immunohistochemistry. Note the disrupted neuronal arrangement in the cortical plate and intermediate zone, lacking the vimentin-positive radial glial fibers (arrow). B: Cortical infolding mimicking microgyria (arrow) 5 days after ibotenate injection. Hematoxylin-eosin staining. C: Cerebral cortex illustrating the histogenetic development of the microgyria. After the radial glial fibers were damaged (small arrows), its corresponding area within the cortical plate collapsed. As the surrounding neurons migrate along the radial fibers, the cortical plates roll in and infold. MZ, marginal zone; CP, cortical plate; SP, subplate; IZ, intermediate zone; VZ, ventricular zone. Scale bar, A = 120 µm, B = 160 µm.

3. Congenital bilateral perisylvian syndrome and epilepsy

Several specific syndromes are associated with cerebral polymicrogyria. Congenital bilateral perisylvian syndrome (CBPS) was first described by Kuzniecky and coworkers (1993), and it is characterized by pseudobulbar palsy, cognitive deficits, and bilateral perisylvian abnormalities such as polymicrogyria (Table 1). Pseudobulbar palsy is one of the striking clinical symptoms of CBPS, however, the oropharyngoglossal dysfunction, such as abnormal tongue movement and the presence of dysarthric speech, may be difficult to investigate in young children. Moreover, epilepsy is an additional diagnostic manifestation of this syndrome, but the mean age at seizure onset has been estimated to be 7.9 years (Kuzniecky et al., 1994). Therefore, in the pediatric population, CBPS is likely to have different manifestations than in adults (Gropman et al., 1997).

Essential criteria (present in 100% of cases)
Oropharyngoglossal dysfunction
Moderate to severe dysarthria
Bilateral perisylvian malformations on imaging
Additional criteria (present in > 85% of cases)
Delayed milestones
Epilepsy (usually atypical absence and atonic seizures)
Mental retardation
Abnormal EEG
Other criteria (present in ≦ 50% of cases)
Arthrogryposis multiplex
Other limb malformations
Infantile spasms

Table 1. Criteria for the diagnosis of congenital bilateral perisylvian syndrome (CBPS) (Kuzniecky R, et al. (1993))

Three cases of epilepsy with congenital bilateral or unilateral perisylvian polymicrogyria are presented as follows.

Case 1: This male child showed complex partial seizures (CPS) at 3 years of age. Electroencephalogram (EEG) revealed focal spikes on the bilateral frontal areas, and carbamazepine (CBZ) was started. No feeding difficulties and drooling were observed, but expressive language development was mildly delayed. Brain computed tomography (CT) was not able to reveal the cortical abnormalities at 3 years of age. His epileptic seizures were well-controlled by the administration of CBZ, but CPS reappeared due to withdrawal at 16 years of age. Brain magnetic resonance imaging (MRI) showed narrow and deep sylvian fissures and their surrounding pachygyric cortex on fluid-attenuated inversion-recovery

(FLAIR) image (Figure 2A). Although no pseudobulbar disorders have yet been recognized, his expressive language skills have been still delayed, and he was diagnosed to have pervasive developmental disorders.

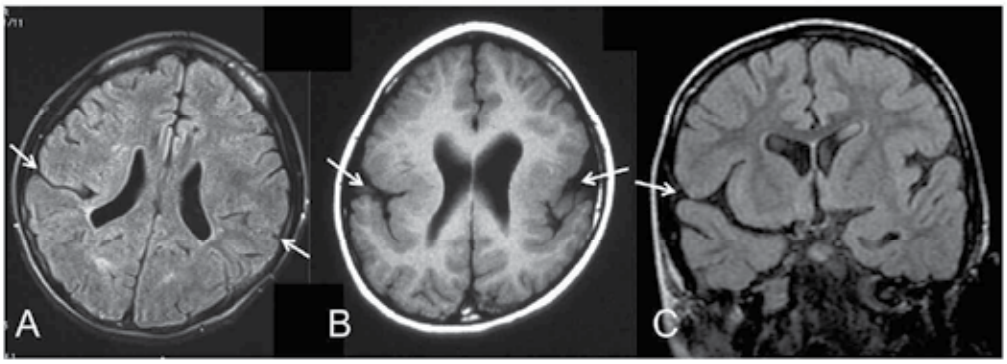

Fig. 2. Brain magnetic resonance imaging (MRI) findings of three patients with perisylvian polymicrogyria. Fluid-attenuated inversion-recovery (TR/TE/ TI = 8002/133/2000 ms) (A, C), and T1-weighted MRI (TR/TE = 500/9 ms) (B). A: Case 1. Narrow and deep sylvian fissures (arrows) and their surrounding pachygyric cortex were found. B: Case 2. The bilateral perisylvian cortical dysplasia are accompanied with bilateral dysplastic insula (arrows). C: Case 3. Note the dysplastic right perisylvian cortex with broad and thickened gyri (arrow).

Case 2: This male child was referred to our hospital because of epileptic seizures which he suffered at 12 years of age. His school performance was normal, and he has not shown any developmental abnormalities and pseudobulbar disorders. His seizure type was CPS, which included behavioral arrest, lateralized tonic posturing with head and eye deviation, and facial automatisms. Interictal EEG showed focal spikes on the left front-temporal area. These clinical findings suggested a diagnosis of temporal lobe epilepsy. Brain MRI revealed bilateral perisylvian cortical dysplasia, accompanying with an abnormality of the insula and of the parietal cortex on T1-weighted image (Figure 2B). The frequency of his epileptic seizures was monthly, and partial or transitory improvements have been obtained with CBZ, zonisamide or phenytoin.

Case 3: This female child manifested generalized tonic-clonic seizures or left partial seizures during sleep at 4 years of age. Her psychomotor development was mildly delayed, accompanied with mild left hemiparesis. Initial EEG showed focal slow spikes with frequent associated diffuse slow spikes and waves. In brain MRI, the right perisylvian cortex was dysplastic showing the appearance of pachygyria with broad and thickened gyri, suggesting right perisylvian polymicrogyria (Figure 2C). Her generalized or partial seizures were refractory to the administration of valproate or CBZ, respectively. Four months later, her sleep EEG demonstrated continuous bilateral and diffuse slow spike and waves, mainly at 1.5 ~ 2.5 Hz, persisting through all the slow sleep stages (Figure 3). These characteristic clinical features were considered as the diagnosis of the epilepsy with continuous spikes and waves during slow sleep.

More immature anomalous brain lesions may be associated with an enhanced capacity for epilepsy and resultant refractory seizures (Takano et al., 2006). However, the epilepsy

related to polymicrogyria may have variable types and severity, including cases with good outcome and spontaneous remissions, even after a period of intractability. Surgical treatment of epilepsy may be applicable to a very limited number of patients in whom large resections are feasible, because the epileptogenic zone in polymicrogyria remains largely unknown.

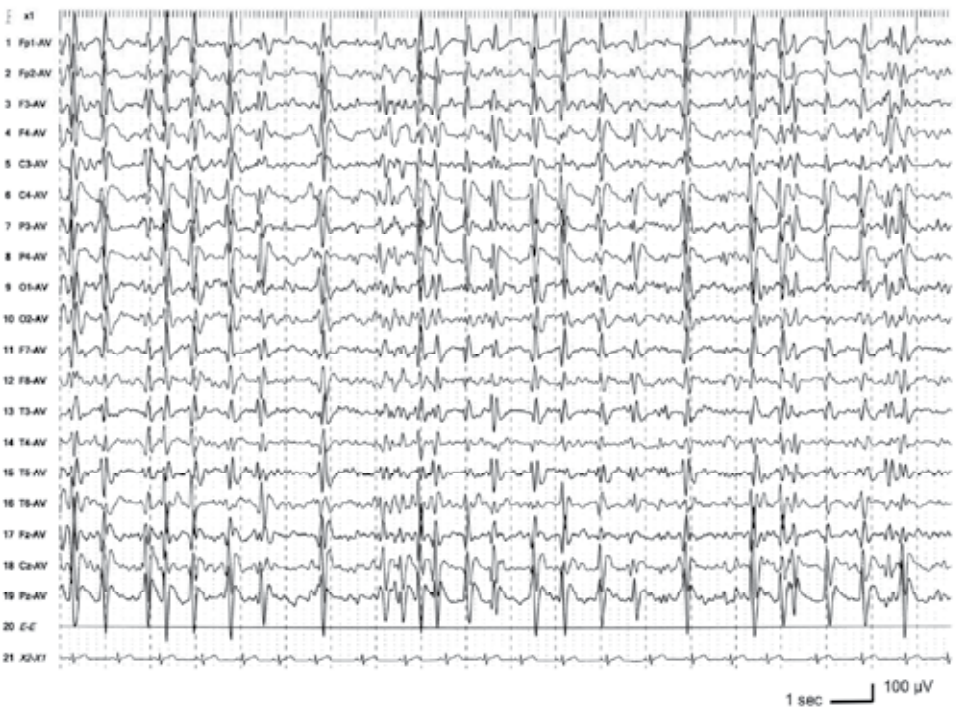

Fig. 3. Sleep EEG of Case 3. Note the continuous bilateral and diffuse slow spike and waves.

4. Epileptogenicity in experimental polymicrogyria by freeze lesion model

Polymicrogyria can be modeled in rats with a transcortical prenatal or neonatal freeze lesion, which mimics the histological characteristics of a human four-layered polymicrogyria. This experimental model does not have spontaneous epileptiform activity in vivo, but several investigations have been presented concerning the epileptogenicity of this malformation.

4.1 Upregulation of glutamate receptor subunits

Glutamate receptors are widespread in the nervous system where they are responsible for mediating the vast majority of excitatory synaptic transmission in the brain and spinal cord. The glutamate receptor family is composed of several distinct subtypes, which are pharmacologically distinguished by four agonists: NMDA, amino-3-hydroxy-5-methylisoxazoleproprionic acid (AMPA), kainate, and quisqualate. Electrical kindling stimulation in prenatal freeze lesion rat revealed the significant prolonged after discharges in both of the cortex and hippocampus, the early development of hippocampal kindling,

and the spontaneous cortico-hippocampal spikes. Immunoreactive expression for NMDA receptor subunit 1 and 2B was shown to be markedly upregulated not only in the microgyria, but also in the hippocampus (Takase et al., 2008). These investigations indicate that dysplastic cortex of microgyria can be highly seizure susceptible lesion by a certain brain insult such as kindling or excitable cortical stimulation.

4.2 Alterations in ion channels

Na+, K+-ATPase contributes to the asymmetrical distribution of sodium and potassium ions across the plasma membrane and to maintenance of the membrane potential in many types of cells (McGrail et al., 1991). A decrease in α3 subunit expression may cause neurons to be less effective in restoring their normal electrochemical gradient and membrane potential after repeated membrane depolarization, resulting in hyperexcitability (Li & Stys, 2001; Vaillend et al., 2002). Alterations in this protein are thought to play a significant role in many human neurological disorders, including epilepsy. It has been demonstrated that there was a significant decrease in α3 subunit of Na+, K+-ATPase immunoreactivity in the neuropil of freeze lesion cortical layer V in paramicrogyral area, where is an area that typically exhibits evoked epileptiform activity. The significant decrease in Na+, K+-ATPase in the paramicrogyral cortex is suggested to contribute to epileptogenesis (Chu et al., 2009).

4.3 New excitatory or inhibitory rewiring

The electrophysiological studies by cortical slices demonstrated that the field potentials evoked by stimulation within a few millimeters of the microgyrus have characteristics typical of epileptiform activity. These results imply that the epileptiform activity in polymicrogyria can be generated outside the lesion itself, which is a focal zone adjacent to the microgyria and called paramicrogyral area (Jacobs et al., 1996; Jacobs et al., 1999). Jacobs and Prince (2005) recorded isolated whole cell excitatory postsynaptic currents (EPSCs) and $GABA_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) from layer V pyramidal neurons in the region of paramicrogyral area. They demonstrated that the conductance or the frequency of IPSCs or EPSCs was significantly larger or greater in paramicrogyral cells compared with controls. These findings imply that there is an increase in numbers of functional excitatory synapses on both interneurons and pyramidal cells in the paramicrogyral cortex, because the cortical afferents unable to find appropriate targets within the malformed region may instead synapse in the adjacent paramicrogyral area.

4.4 Downregulation of $GABA_A$ receptor subunits

Synaptic inhibition in the mammalian brain is mediated principally by γ-aminobutyric acid (GABA) receptors. The most widespread ionotropic receptor activated by GABA is designated $GABA_A$. The majority of $GABA_A$ receptors contain a variable combination of α, β, and γ subunits, showing a specific regional and cellular distribution (Fritschy & Mohler, 1995). Functional studies demonstrated that the subunit composition of receptor subtypes determines their electrophysiological and pharmacological properties (Barnard et al., 1998; Narahashi, 1999). In adult rats with freeze-lesioned microgyria, widespread regionally differential reduction of $GABA_A$ receptor subunits α1, α2, α3, α5, and γ2 was observed within the microgyral area and the lateral to the dysplastic cortex. It has been also observed that the downregulation of $GABA_A$ receptor subunits involved the ipsilateral hippocampal formation, as well as restricted contralateral neocortical areas, indicating widespread

disturbances in the neocortical and hippocampal network (Redecker et al., 2000). The downregulation of $GABA_A$ receptor subunits might contribute to the widespread cortical hyperexcitability in patients with polymicrogyria.

5. Interneurons and epileptogenicity of polymicrogyria

The proper functioning of the cerebral cortex is dependent on two classes of neurons: a) excitatory , projecting neurons, with pyramidal somatodendritic morphology using glutamate as a neurotransmitter, which typically send their axons to distant cortical as well as subcortical targets; b) inhibitory local circuit interneurons, whose axonal arborization is typically restricted to the neocortex and does not project into the white matter (Druga, 2009). These neurons primarily use GABA as a neurotransmitter. The majority of cortical neurons belong to the category of pyramidal cells. Cortical GABAergic interneurons represent about 20-30% of the total number of neocortical neurons (Druga, 2009).

We previously demonstrated the intracerebral injection of ibotenate produces excitotoxic brain lesions to mimic neuronal migration disorders (Takano et al., 2004). We also reported that subventricular zone cells play an important role in the formation of cortical dysplasia (Sawai et al., 2009). Biotinylated dextran amine (BDA) are highly sensitive tools for anterograde and retrograde pathway tracing studies of the nervous system. The high molecular-weight BDA yields sensitive and exquisitely detailed labeling of axons and terminals using preferentially anterograde transport. In the brains injected with BDA to the ganglionic eminence, BDA-positive fibers were derived from the dorsolateral part of the subventricular zone (Figure 4A), and BDA-labeled neurons were specifically located within

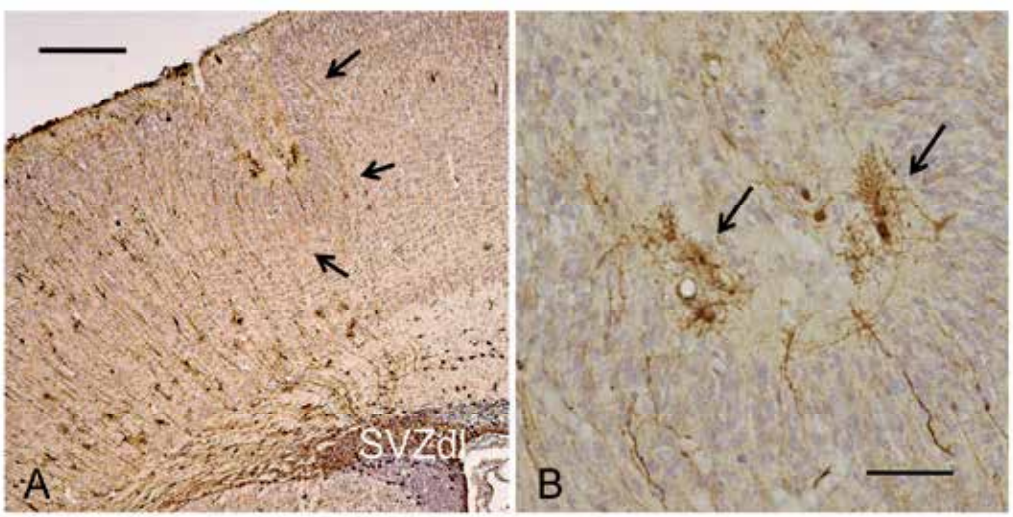

Fig. 4. Biotinylated dextran amine (BDA) tracer immunohistochemistry with hematoxylin double staining 5 days after ibotenate injection. A: Numerous BDA-positive radially oriented fibers extended from the dorsolateral part of the subventricular zone (SVZdl) and reached the pial surface in the frontparietal cortex. Note the microgyria (arrows). B: Higher magnification of microgyria in A. Note the BDA-positive neurons in the microgyric cortex (arrows), which were mobilized out of the ganglionic eminence. Scale bar, A = 120 μm, B = 80 μm.

the polymicrogyric area of the parietal cortex (Figure 4B). This experiment demonstrated that the interneurons are mobilized to the microgyric area out of the ganglionic eminence, which thus leads to the construction of a part of the abnormal neuronal arrangement of this microgyria (Takano et al., 2010). Polymicrogyria is not invariably associated with epilepsy, and the pathogenetic basis of epileptogenesis in polymicrogyria is also unclear. It is suggested that one of the factors that might explain why some patients with polymicrogyria do not develop epilepsy may be due to the fact that a population of aberrantly migrating inhibitory interneurons are present in the microgyric area.

6. Conclusion

The cortical hyperexcitability in polymicrogyria may be reduced by the inhibitory neuronal network constructed by a population of aberrantly migrating inhibitory interneurons, which are mobilized from the ganglionic eminence during the development of polymicrogyria.

7. Acknowledgment

This work was supported by the Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research (C) (22591125).

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2

Sequential Prefrontal Lobe Volume Changes in Epileptic Patients with Continuous Spikes and Waves During Slow Sleep

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1. Introduction

Epilepsy with continuous spikes and waves during slow sleep (CSWS), which is one of the prototypes of electrical status epilepticus during slow wave sleep (ESES), is a rare disease that affects children and is associated with deterioration of one or more cognitive functions, behavioral disturbances, spike and spike-wave discharges increased during slow wave sleep, and epileptic seizures. The pattern of deficits characteristic of ESES occurs mainly in the first decade of life. Almost all CSWS patients present with seizures (Smith & Poley, 2008). Seizures are typically nocturnal, partial motor or generalized convulsions (Tassinari et al., 2005).

Although the most prominent feature of epilepsy is seizure, the condition may also involve mental health problems, including hyperactivity, inattention, learning disabilities, other disease-related quality of life impairments, and psychopathology (Noeker et al., 2005). Nearly all investigators have reported a high prevalence of behavioral problems in children with epilepsy. Electroencephalographic monitoring can detect subclinical spike frequency, which may affect attention and other aspects of cognitive functioning in various ways, even in the absence of clinical seizures. Although any attempt to equate epileptiform activity with epilepsy is generally discouraged, the occurrence of a paroxysmal change in cerebral electrical activity simultaneously accompanied by cognitive impairment meets generally accepted definitions of an epileptic seizure. Neuropsychological impairment occurs in almost all cases of CSWS, usually being coincidental with the detection of ESES and representing one of the crucial signs of the syndrome (Tassinari et al., 2005). CSWS is characterized by an impairment of neuropsychological abilities, frequently associated with behavioral disorders (reduced attention span, hyperkinesis, aggressiveness and difficulty interacting with the environment), hyperactivity, learning disabilities and, in some instances, psychotic regressions. These manifestations strongly correlate with frontal lobe dysfunction (Jasper et al., 1995; Fuster, 1997). These mental and behavioral disorders can persist even after CSWS has ceased. Their severity and persistence seem to be correlated with the duration and severity of ESES (Billard et al., 1990; De Negri, 1994). The goal of evaluation and treatment of CSWS must not necessarily be a seizure-free state, but improvements in seizure control, alertness, mood and behavior. We have already studied and reported prefrontal lobe volumes in a patient with CSWS using three-dimensional (3D) magnetic resonance imaging (MRI) (Kanemura et al., 2009). However, the data cannot be

generalized to all CSWS cases because the investigation included evaluation of only one case. Many unanswered questions remain with regard to CSWS, such as its clinical significance, pathophysiology and treatment. Further studies are needed to confirm and elaborate on these anatomical observations and extend the systematic study of cognitive, social and moral development, and to clarify outcomes for many children with CSWS.
In the present study, there were three cases with disappearance of the paroxysmal anomalies, yet in these cases there was no improvement of the neuropsychological impairments. By contrast, in the two cases with shorter seizure and paroxysmal anomaly durations, there was remarkable improvement of behavioral disturbances. In several diseases of the central nervous system, conventional MRI has proven to be sensitive for detecting changes over time. Stronger correlations have been found between disability and MR markers such as the quantitative assessment of cerebral atrophy in various brain diseases. On the basis of these previous observations, we serially measured frontal and prefrontal lobes volumes by 3D MRI-based volumetry in children with CSWS and discussed the pathogenesis of ESES-induced brain damage. Finally, we also discussed the role of some prognostic factors such as the duration of CSWS period.

2. Methods

2.1 Subjects

We studied five patients between 9 and 12 years of age. The criterion for inclusion in the study was the finding of the presence of spike-and-wave discharges in at least 85% of non-rapid eye movement (REM) sleep, which were verified by two consecutive electroencephalography (EEG) recordings over a period of more than 1 month. All patients underwent EEG recordings while awake and during afternoon sleep. The clinical profiles are summarized in Table 1.

Case	Age (y)	Age at seizure onset (y)	CSWS after seizure onset (y)	Duration of CSWS period (months)	FIQ (pre)	FIQ (post)	Behavioral problems	Seizure outcome	Final drugs
1	10	4	2.2	14	85	67	HA, PSP	none	VPA+CLB
2	11	5	1.8	19	88	62	PSP, HA, IA, IP	1-3x/month	VPA+ESM
3	12	5	2.9	21	73	52	PSP, HA, IP	none	VPA+CLB
4	9	3	2.1	5	ND	86	HA(+)→(-)	none	VPA+CLB
5	11	5	1.5	5	89	87	HA(+)→(-)	none	VPA+CLB

CSWS, epilepsy with continuous spikes and waves during slow sleep; FIQ full intelligence quantity; ND, not done, HA, hyperactivity; PSP, poor school performance; IA, inattention; IP, impulsivity; IQ (pre), IQ at the appearance of CSWS; IQ (post), IQ at 4 years after the appearance of CSWS; VPA, valporate sodium; CLB, clobazam; ESM, ethosuximide

Table 1. Clinical characteristics of the patients in this study

All patients were followed up regularly for more than 3 years after the onset of seizures. During the active ESES phase, sleep EEG recordings were performed at least once every 3 months. Subsequently, EEGs were recorded during afternoon sleep once every 2-3 months for more than 1 year after the disappearance of ESES. For each patient we examined familial antecedents for epilepsy/febrile convulsion, personal antecedents, psychomotor development, neurologic examination and cerebral MRI. All patients had normal findings on routine MR studies. All patients have shown behavioral disturbances or cognitive impairments. Two patients, with a CSWS duration of less than 6 months, showed remarkable improvements of behavioral disturbances. By contrast, three patients with a CSWS duration of greater than 1 year presented progressive cognitive and behavioral deteriorations, even after seizures and paroxysmal EEG activities disappeared. Formal IQ testing was carried out in all cases. Informed consent was obtained from the parents. Clinical courses of all patients are outlined briefly below.

2.1.1 Case 1

The first patient was a male who presented with complex partial seizures at 4 years of age. The patient was born normally, and his psychomotor development was normal before the onset of seizures. The patient's history of illness and the family history were noncontributory. EEG revealed sharp waves at bilateral centro-temporal regions superimposed on normal background activity. Carbamazepine (CBZ) was started initially. At 6 years of age, he started exhibiting atypical absence seizures. On the EEG, the ESES pattern was revealed (Fig. 1). He became irritable, hyperactive, aggressive and disinhibited, displaying difficulty interacting with his environment. Treatment was changed to using valproate sodium (VPA). However, no improvement of his clinical state was recognized. Clobazam (CLB) was started in addition to VPA, which led to improvement. Eleven months after replacement of antiepileptic drugs (AEDs), the ESES pattern resolved with no further seizures. However, he presented a progressive cognitive and behavioral deterioration up to the present, and IQ dropped from 85 to 67 of total score. The duration of the CSWS period was 14 months.

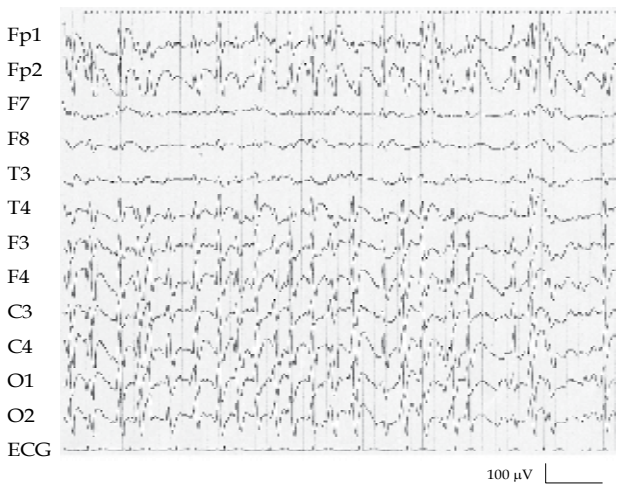

Fig. 1. Electroencephalography (EEG) tracing taken during sleep in case 1. Such patterns occupied 85 % to 90% of the hours normally given to slow-wave

2.1.2 Case 2

This patient was an 11-year-old male, the second child of healthy parents. He had normal initial psychomotor development. At age 5 years, he started with sporadic, generalized tonic-clonic seizures, which were controlled by VPA. A sleep EEG recording showed focal spike and wave discharges over the right central and temporal leads (C4-T4). At age 7 years, he started with atypical absence seizures. On the EEG, the ESES pattern was revealed. He became hyperactive, aggressive and disinhibited, and exhibited difficulty interacting with his environment. Treatment was changed to using CLB. However, the improvement of his clinical state was not fully recognized. Ethosuximide (ESM) was started in addition to VPA, which led to improvement. The ESES pattern resolved with a reduction in the rate of seizures. However, he presented a progressive cognitive and behavioral deterioration, including poor school performance, hyperactivity, and impulsiveness. The duration of the CSWS period was 19 months.

2.1.3 Case 3

This patient was a 12-year-old male. Delayed psychomotor development was recognized before the onset of seizures, but behavioral deterioration, including hyperactivity, was not recognized. At the age of 5 years, he had his first episode of clonic seizures of his right upper-limb. His clinical seizures were controlled by CBZ transiently. At the age of 7 years, he started with atypical absence seizures. On the EEG, the ESES pattern was revealed. He became irritable, hyperactive and aggressive, showing difficulty interacting with the environment. Treatment was changed to using VPA, but improvements to his clinical state were not recognized. Treatment was changed to using VPA with CLB, which led to improvement. The ESES pattern resolved with no further seizures. However, he exhibited a cognitive and behavioral deterioration, including poor school performance, hyperactivity, and impulsiveness. The duration of the CSWS period was 21 months.

2.1.4 Case 4

This patient was a 9-year-old male. He had normal initial psychomotor development before the onset of seizures. At the age of 3 years, he had his first episode of clonic seizures of left upper-limb. The EEG showed focal spike and wave discharges in the right frontal and central leads (F4-C4) superimposed on normal background activity. His clinical seizures were transiently controlled by CBZ. At the age of 5 years, he started with atypical absence seizures. On the EEG, the ESES pattern was revealed. He presented behavioral disturbances such as hyperactivity. Treatment was changed to using VPA, yet the improvements to his clinical state were not noted. Treatment was changed to using VPA with CLB, which led to gradual improvement. The ESES pattern resolved with no further seizures. There was considerable improvement of behavioral disturbances. The duration of the CSWS period was 5 months.

2.1.5 Case 5

This patient was an 11-year-old female who had normal initial psychomotor development and was described in our previous report (Kanemura et al., 2009). At the age of 5 years, she had her first episode of complex partial seizure. EEG revealed sharp waves at bilateral centro-temporal regions superimposed on normal background activity. Her clinical seizures were transiently controlled by CBZ. At 6 years of age, she started with atypical absence

seizures. On the EEG, the ESES pattern was revealed. She presented behavioral disturbances such as hyperactivity. Treatment was changed to using VPA. However, improvements to her clinical state were not recognized. Treatment was changed to include VPA and CLB, which led to gradual improvement. The ESES pattern resolved with no further seizures. There was considerable improvement of behavioral disturbances. The duration of the CSWS period was 5 months.

2.2 Serial 3D-MR volumetric study

The longitudinal 3D MRI studies were performed six times (at the onset of the ESES pattern, 6 months, 1, 2, 3 and 4 years after the onset of ESES) in all cases.
The control group consisted of 13 age-matched children ranging in age from 5 to 12 years. Clinical indications for MR imaging were suspected speech delay, brain trauma, brain tumor, short stature and migraine, which turned out to be neurologically and / or psychologically insignificant during a 2-4 year follow-up period after this study. All subjects had normal findings on routine MR studies.
All MRI scans were performed on the Siemens 1.5 Tesla by Signa Advantage. The 3D MRI data were acquired by the fast spoiled gradient recalled echo in steady state with three dimensional Fourier transformation. 3D images of the whole brain surface were obtained from the 124 sections using Advantage Windows RP 3D analyzer (Siemens, Wisconsin, MW, U.S.A.). Thereafter, the frontal lobe was delineated and confirmed by our published method (Kanemura et al., 2003). Finally, we measured the frontal and prefrontal lobe volumes by the volume measurement function of Workstation on the 3D images.

3. Results

Measured volumes for frontal and prefrontal lobe, and prefrontal to frontal lobe volume ratio are shown in Fig. 2 (A; frontal lobe volume, B; prefrontal lobe volume, C; prefrontal to frontal volume ratio). Frontal and prefrontal lobe volumes revealed growth disturbance in all cases compared with those of normal subjects (Fig. 2A and 2B). In addition, prefrontal to frontal lobe volume ratios increased serially in normal subjects, whereas the ratios stagnated or decreased in all cases of CSWS (Fig. 2C). In cases 4 and 5, with shorter seizure durations and CSWS periods, ratios were soon restored to a more normal growth ratio. On the other hand, growth disturbances of the prefrontal lobes were persistent in cases 1, 2 and 3, which all had longer seizure durations and CSWS periods (Fig. 2C).

4. Discussion

Seizure discharge of generalized nonconvulsive status has been postulated to cause neuronal damage. Various childhood epileptic syndromes associated with dramatic activation of the epileptiform activities during slow wave sleep may manifest with progressive psychomotor decline, which cannot be attributed to known metabolic or organic causes. CSWS is the main representative syndrome, which is frequently encountered in pediatric syndromes associated with epilepsy or cognitive and language dysfunction. Nowadays, it is appreciated that CSWS often accompanies epileptic syndromes associated with partial or generalized seizures, occurring during sleep, as well as atypical absences when awake. Thus, the five patients described in this report had clinical features that were consistent with the criteria proposed for CSWS.

Many CSWS children develop severe cognitive and language deterioration that is unresponsive to medical treatment as the disease progresses (Smith & Hoeppner, 2003). During the CSWS period, there is the appearance of a further decrease in performance; a marked impairment of IQ, deterioration of language, temporo-spatial disorientation, behavioral changes and, rarely, psychotic features have been described (Tassinari, 1992). Patients with CSWS had lower scores in tests measuring their lexical, morphosyntactic, and pragmatic skills compared to controls (Debiais et al., 2007). Furthermore, language impairment was found to be just as severe in patients in remission as those still in an active phase (Debiais et al., 2007). Paroxysmal anomalies in CSWS may be associated with a disruption of all cognitive functions, with sometimes a greater impairment of logical-structural intelligence and of infrastructural intelligence, possibly in relation to a previously different intellectual organization (Tassinari et al., 2005).

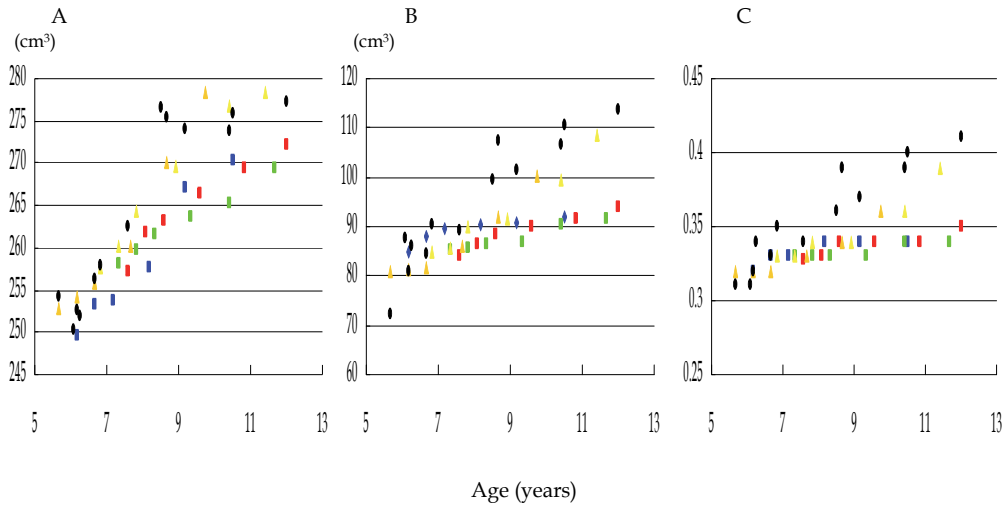

Fig. 2. Volume measurements of five cases with CSWS and normal subjects. Serial changes in frontal lobe volume (A), prefrontal love volume (B), and prefrontal to frontal lobe volume ratio (C). Scatter plots for the case 1 (blue squares), case 2 (green squares), case 3 (red squares), case 4 (gold triangles), case 5 (yellow triangles) and age matched normal subjects (black diamonds). Frontal and prefrontal lobe volumes revealed growth disturbance in all cases compared with normal subjects. In addition, prefrontal to frontal lobe volume ratio increased serially in the normal subjects, whereas its increases are declined in all cases. The case 4 and 5 with shorter seizure duration and CSWS period were soon restored to a more normal growth ratio. On the other hand, growth disturbances of the prefrontal lobes in cases 1,2 and 3 with longer seizure durations and CSWS period were persistent.

Concerning the CSWS-related neuropsychological disturbances, several authors have underlined the parallel, though not perfectly overlapping, course of CSWS and mental and behavioral abnormalities (De Negri et al., 1995). There is a well-documented increased incidence of attention deficit hyperactivity disorder (ADHD) and behavioral disorders, which are likely to be independent of the degree of seizure control (Schubert, 2005). Hyperactivity has been reported in about half of the cases of behavioral and cognitive disturbances. Disturbances of personality with psychotic characteristics have been

described, as well as a global cognitive regression and impairment of affective development, with aggressiveness and outbursts of rage (Gordon, 1990; Roulet et al., 1991). These disorders are often progressive and insidious with devastating effects on cognition and behavior, although the children generally have few or sometimes no classic seizures. The manifestation of neuropsychological disorders coincided with the onset and disappearance of ESES EEG expression rather than with the outcome of clinical seizures (Morikawa et al., 1992). Abnormal collecting behavior, characterized by increased, indiscriminate acquisition behavior and diminished discarding behavior, will occur following damage to prefrontal regions, but not after damage elsewhere in the brain (Anderson et al., 2005). In Landau-Kleffner syndrome (LKS) the paroxysmal activity permanently affects the posterior temporal area and results in auditory agnosia and language deficits, whereas in CSWS the frontal lobes are more involved and other cognitive disturbances predominate (Smith & Polkey, 2008). Thus, epilepsies associated with CSWS in childhood may affect the prefrontal cortex and leave residual mental and behavioral abnormalities as profound and as permanent as the loss of speech in LKS.

MRI is currently the most effective method for detecting gross structural lesions in patients with various brain diseases. There is little question that recent advances in neuroimaging, particularly MRI, have revolutionized the evaluation and management of epilepsy and seizure disorders. Given the possibility that some functional changes may have a structural correlate, MRI could also play a pivotal role in elucidating the mechanisms underlying epileptogenesis. However, neuroradiological abnormalities in patients with CSWS can be found only in 30-60 percent of cases (Galanopoulou et al., 2000). In pure forms of this syndrome, no gross structural lesions are detected by CT or MRI scans (Beaumanoir, 1992). On the other hand, in accordance with histopathologic examinations, the development of permanent neurological impairment may be associated with progressive brain atrophy (Trapp et al., 1998). Within these analyses, quantitative MRI investigations have been performed to evaluate neurological abnormalities in children with epilepsy. Hippocampal volumes are large in patients with prolonged febrile convulsion when compared with controls by quantitative hippocampal volumetry (Scott et al., 2002). Thus, quantification of brain volume is a useful way to characterize the normal growth and abnormal development in patients with epilepsy. Furthermore, prospective and serial analysis with brain volumetry may support the pathogenesis of CSWS-induced brain damage.

All cases presented in this report revealed growth disturbance of the frontal lobe, especially the prefrontal lobe in quantitative volumetric analysis. Volumetric analysis of the brain may predict function in corresponding regions. Our results showed enhanced vulnerability of prefrontal cortex during early development coincident with CSWS. In our findings, the frontal and prefrontal lobe volumes, especially the prefrontal to frontal lobe volume ratio, showed growth disturbance during the CSWS period, and even after paroxysmal anomalies in CSWS have ceased. Our results suggest that children with CSWS may have frontal lobe dysfunctions even if paroxysmal anomalies had ceased or further afebrile seizures had not appeared. The temporal development of the frontal and prefrontal lobe volumes in longitudinal studies of CSWS patients is still unclear. To the best of our knowledge, no attempt has been made to measure individual cerebral lobes in patients with CSWS. Our study therefore may be the first to evaluate growth retardation of the frontal and prefrontal lobes in patients with CSWS.

Regardless of the prior cognitive status and development, the appearance of CSWS is associated with emergence of new cognitive and behavioral abnormalities (Tassinari et al., 2005). A cluster of problems that appear to be more common in children with epilepsy is the

disruptive behavioral disorder group: ADHD, oppositional defiant disorder, and conduct disorder. ADHD is described in approximately two thirds of the reported cases (Boel & Casaer, 1989; Guerrini et al., 1998). Hyperactivity and oppositional behaviors are highly associated. Aggressiveness, deficits in relatedness and inhibition, bizarre behavior, emotional lability and psychotic behavior have also been described (Roulet-Perez et al., 1993; Kyllerman et al., 1996). These manifestations may be correlated with frontal lobe dysfunction (Jasper et al., 1995; Fuster, 1997). Thus, these symptoms constitute frontal lobe syndrome (Roulet-Perez et al., 1993). In some of CSWS children, the seemingly generalized epileptiform abnormality represents true secondary bilateral synchrony (Morrell et al., 1995). The most common location for a lesion to produce secondary bilateral synchrony is in the frontocentral region, followed by the temporal and parietal cortex (Blume & Pillay, 1985; Wasterlain et al., 1993). Secondary bilateral synchrony originated in the frontal lobe in nearly half of patients, significantly more often than the incidence of frontal spikes among controls (Blume & Pillay, 1985). Frontal foci may easily elicit sustained bisynchronous discharges which often spread diffusely. CSWS, which develops within a broader age range, with multiple focal or predominantly frontal paroxysmal anomalies, may be comprehensively associated with more generalized neuropsychological and/or mental regression. However, paroxysmal anomalies in our patients were not always predominant in frontal regions. Blume et al. reported the presence of more than one spike focus in 96% of patients and three or more foci in 77% suggested that secondary bilateral synchrony results from a complex interaction of multiple potentially epileptogenic regions (Blume & Pillay, 1985). A complex interaction of multiple cortical epileptiform discharges may act through thalamic and callosal connections to create bisynchronous epileptiform paroxysms. Independent of etiology and individual area of initial epileptic activity, patients with CSWS may be characterized by a consistent specific neuronal network of activation. In a recent study, the activation in the perisylvian/prefrontal network was associated with both activation in the thalamocortical network and deactivation in the default mode network (Siniatchkin et al., 2010). Our results and these findings suggest that children with CSWS may have abnormalities in the frontal lobe even if the epileptic focus is not frontal.

Long-term prognosis for the seizure disorder is good, with less than 20% of patients suffering from persistent, usually rare, seizures (Bureau, 1995). However, the long-term prognosis for neuropsychological consequences is not nearly as good as was once thought. Therefore, in considering outcomes for children with CSWS, it is necessary to consider the control of seizures on one hand and the incidence of neurological impairments, either transitory or persistent, on the other. The duration of epilepsy seems to be a significant prognostic factor. In our study, prefrontal growth made rapid recovery in patients with a shorter duration of CSWS. The CSWS duration in three of the patients with poor outcomes was longer than in those who had better prognosis. This finding suggests that seizure and the duration of paroxysmal anomalies may be associated with prefrontal lobe growth, which is associated with neuropsychological problems. Our results are agreement with the findings that CSWS patients with the longest persistence of spike-and-wave discharges over time are most affected (Smith & Polkey, 2008).

The pathophysiology of CSWS is complex and far from being elucidated. The relation between the density of paroxysmal anomalies and neuropsychological regression is based on clinical findings, notably, the parallel between paroxysmal anomalies duration and ultimate neuropsychological outcome, as well as between the neuropsychological disturbances and the location of the interictal epileptic focus (Tassinari et al., 2005; De Negri, 1994; Morikawa et al., 1992). In addition, the most convincing theory maintains that focal

epileptic activity produces a disturbance in the maturation of cortical zones, mainly in the associative areas (Praline et al., 2003). Nonconvulsive status epilepticus (SE) in adult animals leads to widespread neuronal necrosis in vulnerable regions (Wasterlain et al., 1993). Furthermore, inhibition of brain growth, DNA and protein synthesis, and myelin formation and of synaptogenesis may lead to altered brain development (Wasterlain et al., 1993). Rat pups as young as 2 weeks old demonstrate seizure-induced elevation in serum neuron-specific enolase accompanied by histological evidence of damage as a result of status epilepticus (Sankar et al., 1997). Furthermore, in our previous study, a longer active seizure period as frequent spike-waves coupled with the occurrence of frequent seizures in patients with benign childhood epilepsy with centro-temporal spikes may be associated with prefrontal lobe growth disturbance (Kanemura et al., 2011). Our results are in agreement with these findings. Patients with CSWS require regular and prolonged clinical and EEG follow-up.

The same disorder that causes seizures may also have the potential to limit intellectual development in many patients. People with learning disabilities represent an important subgroup within the population of patients with epilepsy. On the other hand, the interface between epilepsy and behavior disorders has a long and checkered history. The coexistence of intellectual deficits and behavioral abnormalities may substantially interfere with the medical assessment of seizures. If the relationship between the occurrence of paroxysmal anomalies and the onset of a neuropsychological deterioration is accepted, an aggressive therapy can be justified (Tassinari et al., 2005). This may require modification of antiepileptic therapy, psychosocial intervention, or the use of psychotropic medication. Our study demonstrated that clinical seizures and EEG discharges responded well to a benzodiazepine such as CLB when combined with VPA in four of 5 patients. The study by Liu et al. has demonstrated a dramatic improvement in the clinical findings and occurrence of the CSWS phenomenon with administration of low-dose benzodiazepines in a cohort of 18 children with language, behavioral, and neuropsychologic deterioration (Liu & Wong, 2000). In agreement with Tassinari et al. (Tassinari et al., 2005), benzodiazepines in combination with VPA seem to be the most effective treatment at present. However, the patients in our study have exhibited mental and behavioral disorders even after the CSWS period has ceased. Inutsuka et al. reported that the effects of short cycles of high-dose diazepam and ACTH-Z (tetracosactide Zn) therapy were temporary at best (Inutsuka et al., 2006). The potential for early reversibility of clinical and EEG abnormalities with benzodiazepine, however, will improve the outcomes for children with CSWS. Further investigations may clarify whether deficits of cognition and behavior are transient or permanent. In addition, the sample in this study is too small to discuss the pathophysiology and outcome of CSWS. Further studies are needed to confirm and elaborate on these anatomical observations by 3-D MRI based volumetry to extend the systematic study of cognitive, social, and moral development, and to predict the likely outcome of CSWS for many children with CSWS.

5. Conclusion

This study revealed the frontal and prefrontal lobe volumes, and the prefrontal to frontal lobe volume ratio in particular showed growth disturbances during the CSWS period, and even after CSWS had ceased. The duration of symptoms such as seizure and paroxysmal anomalies in the patients with poor outcomes was longer than in those who had better prognosis. These findings suggested that the durations of seizure and paroxysmal anomalies may be associated with prefrontal lobe growth, which relates to neuropsychological

problems. These findings in our study provide further support for the integral involvement of the prefrontal cortex in CSWS.

6. Acknowledgment

This research was supported in part by Grants-in-Aid for Scientific Reasearch C (22591124 and 22591123).

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Part 2

Clinical Presentation of Epilepsy and Epileptic Syndromes of Childhood

3

Neonatal Seizures

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1. Introduction

A seizure is defined as paroxysmal disturbances in neurological function of neurons which manifested clinically as alteration in motor, behavioral and/or autonomic functions. No period carry the danger of seizures to the individual person like the first four weeks of life because of immaturity of brain cell which render it more vulnerable to injury and because of wide range of problem that might cause seizures operate in this period. Neonatal seizures tend to be brief, because immature neurons are unable to sustain repetitive activity for long period of time and to be focal or multifocal. It requires immediate evaluation because of the variable conditions that might insult developing and vulnerable neurons of neonate, some of which might endanger the life of neonate. Some time seizures might be the first and probably the only manifestations of underlying significant dysfunction of CNS of newborn infant. Furthermore, these seizures are sometime difficult to be diagnosed clinically resulting in delaying treatment and worsening short and long term prognosis. There is still a great debate about pathophysiology, clinical classification, EEG significance and treatment of neonatal seizures.

2. Incidence

Neonatal seizures are common: and the incidence is variable according to age and maturity of the neonate, weight and the severity of the underlying condition. The real incidence has not been established clearly, although it had been estimated that the incidence rate of clinical seizures varies from 1.1 to 8.6 per 1000 live births [1 - 3]. Preterm newborn exhibits higher risk for neonatal seizures than term newborn and both lower birth weight and gestational age confers increased risk [2, 4, 5]. In term infant the incidence range from 0.7 to 2.7 per 1000 live births and from 57.5 to 132 per 1000 live births in preterm infants [6,7]. In those weighing less than 1,500 g, the incidence ranges from 19 to 57.5 per 1,000 live births, While in infants who's weight more than 2,500 g, the incidence is as low as 2.8 per 1,000 live births [3]. Scher and colleagues reported that seizures occurred in 3.9% of neonates of less than 30 weeks' conceptional age and 1.5% in neonates older than 30 weeks [8, 9]. Additionally, seizures may account for up to 3.4 % of all admission to neonatal intensive care unit [7].

3. Pathophysiology

A clinical seizure results from excessive synchronized depolarization of the neurons within the central nervous system resulting in excessive synchronous electrical discharge. Why this

excessive depolarization of the neurons might occur remains unknown. Theories were suggested include the following:

1. Imbalance between excitatory and inhibitory neurotransmitter like excessive excitatory amino acid (e.g. glutamate) or deficient inhibitory neurotransmitter (e.g. Gama Amino Butyric Acid, GABA) [10].
2. Failure of energy production due to disruption of ATP dependent resting membrane potentials resulting in failure of sodium potassium pump which in turn leading to movement of sodium into the neuron and potassium out of the neuron.[11,12]
3. Neuronal hyper excitability state in the neonatal period, as evidenced by the extremely low threshold to seizures in general and that this is the period of highest incidence of seizures across the life span [13, 14]. Among the factors that cause increase excitability are incomplete myelination and neuropeptides particularly corticotrophin releasing hormone (CRH) [15, 16].
4. Experimental and clinical evidence exists for early microglial activation and inflammatory cytokine production in the developing brain in both hypoxia/ischemia [17,18] and inflammation [19,20] Importantly, microglia have been shown to be highly expressed in immature white matter in rodents and humans during cortical development [21].
5. Genetic predisposition as most of the cases of Benign Familial Neonatal Seizures (BFNS) are due to mutations in two genes, *KCNQ2* and *KCNQ3*, which encode subunits of a type of voltage-gated potassium ion (Kv) channel. Of about 70 BFNS families so far studied genetically, 60% have mutations in *KCNQ2*, and 5% have mutations in *KCNQ3*. The cause in the remaining cases is unknown. Some are likely due to mutations in portions of the *KCNQ2* and *KCNQ3* genes that do not encode amino acids but may affect channel expression (e.g., enhancers, promoters, introns). It is possible that one or more additional BFNS genes remain undiscovered [22].
6. Idiopathic as in the cases of Benign Non Familial Neonatal Seizures (BNFNS), also called fifth day disease were the pathophysiology remains unknown [23, 24].

4. Causes

The causes of neonatal seizures are divers and voluminous. It covers the entire spectrum of neurological disorders of the newborn. In practice, knowing the cause is vital for neonatologist regarding therapeutic and prognostic issues. For example, neonatal seizures due to transient metabolic disorders of newborn like hypocalcemia and hypoglycemia are easily to be treated by correction of metabolic derangement and are usually associated with favorable outcome regarding neurodevelopment and future epilepsy risk. In contrast, neonatal seizures caused by structural abnormalities of the brain are difficult to control and associated with poor outcome. The causes of neonatal seizures can be grouped under the following heading (table 1):

1.	**Brain insults**
a.	Hypoxic ischemic encephalopathy
b.	Intracranial infections
c.	Intracranial hemorrhage

	d. Cerebrovascular infarction
	e. Structural malformation of brain
2.	**Metabolic disorders**
	a. Hypocalcemia
	b. Hypoglycemia
	c. Hyponatremia
	d. Hypernatremia
	e. Pyridoxine deficiency
3.	**Inborn error of metabolism**
	a. Urea cycle disorder
	b. Aminoacidopathies
	c. Biotinidase deficiency
	d. Mitochondrial disorder
	e. Defects in beta oxidation
	f. Glucose transporter deficiency
	g. Peroxisomal disorder
	h. Pyridoxine deficiency
	i. Non ketotic hyperglycinemia
4.	**Neonatal epileptic syndrome**
	a. Benign idiopathic neonatal seizures
	b. Benign familial neonatal seizures
	c. Ohtahara's syndrome
	d. Early myoclonic encephalopathy
5.	**Miscellaneous**
	a. Polycythemia
	b. Accidental local anesthetic drug injection
	c. Withdrawal syndrome
	d. Drug toxicity

Table 1. Causes of neonatal seizures

1. **Brain insults**: *hypoxic ischemic encephalopathy* is the most common cause of neonatal seizures accounting for about two third of all cases [25, 26]. The seizures are usually begin within the first 24 hours after birth and are associated with obtundation [27, 28, and 29]. In one study, 60% of these neonates developed seizures within the first 12 hours [30]. The frequency and the severity of seizures are usually parallel to the severity of the encephalopathy and about one third of them will be epileptic in the future [25]. The seizures types include subtle (the most common), focal and multifocal clonic and myoclonic. *Intracranial infection* account for 5 to 10 % of seizures [31]. Could be acquired prenatally or postnatally and it is more common in developing countries. Bacterial meningitis usually causes seizures later in the first post natal week (late onset) [32], the most common bacterial pathogens are group B streptococci, listeria, Escherichia coli and other gram negative bacteria. Congenital infection caused by such pathogen as toxoplasmosis, rubella and CMV virus may cause seizures which may be the sole manifestation but it usually tend to occur later in the neonatal period or early infancy. Encephalitis caused by various viruses such as herpes simplex virus (HSV) and enteroviruses may cause seizures. Some of these viruses acquired from birth canal during labor and other from the environment. HSV encephalitis is one of the most

important viruses causing encephalitides in the neonatal period. Seizures tend to occur in 57% of neonate who have CNS disease and 22% of neonate who have the disseminated form of the disease but rarely in the skin eye mouth disease form [33]. The neonatal form of HSV encephalitis is caused more often by type 2 HSV that the newborn acquires during delivery from maternal genital lesions. Fetal scalp monitoring may be a risk factor for acquiring the virus. Neuroimaging studies in neonatal HSV encephalitis often show diffuse brain abnormalities [25]. Because of the severity of the condition and poor outcome, any patient with neonatal seizure and suspected to have neonatal HSV, appropriate diagnostic tests should be obtained and the empirical acyclovir therapy should be initiated immediately. *Intracranial hemorrhage* account for about 10% of all cases of neonatal seizures [27]. In preterm infants, small intraventricular hemorrhage limited to the germinal matrix do not result in seizures, usually they present with poor activity and feeding with unexplained drop of hematocrit. When the hemorrhage is extensive, the seizures are a common correlates and may account for 45% of preterm infants who had EEG documented seizures [28]. Persistent tonic seizures are the most typical but subtle seizures can also occur. They commonly occurs between 3-7 days of age [32]. In full term neonates, subarachnoid, subdural and intraparenchymal hemorrhage are common causes. Subarachnoid hemorrhage tends to occur in healthy looking full term infant delivered vaginally. Classically seizures occur in the second day and have been named as well –baby with seizures [34]. They resolve rapidly with good prognosis. On the other hand, subdural hematomas are usually results from trauma and commonly associated with cerebral contusion. Focal rather than multifocal seizures are common and they tend to occur in the first two post natal days. Subdural hematoma after the second day of life in a neonate who was discharged from hospital should raise the possibility of non accidental injury. *Cerebrovascular infarction* is another cause of neonatal seizures and it can results from both arterial and venous occlusion. Arterial occlusion causes infarction of area supplied by a single artery. The middle cerebral artery is most frequently involved. Risk factors include trauma, congenital heart disease, coagulopathy and metabolic disturbances. Arterial occlusion leads to porencephalic cyst which in cases of multiple vascular involvement can leads to encephalomalacia and hydraencephaly. Focal neurological seizures are common and the neonate has abnormal neurological examination. The severity and localization of seizures are variable according to the location and the extent of infarction. On the other hand, cerebral venous thrombosis might result in seizures in 68% [35]. The occlusions usually occur in the superior saggital sinus, sigmoid/transverse sinus or multiple venous sinuses [25]. Polycythemia, dehydration, persistent pulmonary hypertension, infections, thrombophilic disorders and Extracorporeal membrane oxygenation [36, 37] are among the documented risk factors for venous thrombosis. *Structural malformation of the brain* is another cause for neonatal seizures. In one study they account for 1.8% of studied cases [38]. Fifty percent of patients with holoprosencephaly (failure of complete separation of cerebral hemispheres and deep gray nuclei) have neonatal seizures [39]. Lissencephaly (malformation of the brain in which the cortical surface is smooth or contain thick broad gyri) is commonly associated with seizures which are usually refractory to treatment [40]. Cerebral dysgenesis and neuronal migration disorders are rare causes of seizures in the neonatal period, they may be caused by a specific inborn error of metabolism that disturbs early fetal development. For example, nonketotic hyperglycinemia, pyruvate dehydrogenase deficiency, and maternal hyperglycinemia frequently are associated with corpus callosal dysgenesis while peroxisomal disorders

and fatty acid oxidation defects have been associated with migration abnormalities [25, 41]. Neurocutaneous syndromes like tuberous sclerosis and Sturge Weber syndrome might also present neonatal seizures.

2. **Metabolic disorders:** can also cause neonatal seizures. The severity of neurological symptoms is directly correlated with the duration of metabolic disturbances (42). Hypocalcemia nowadays account for about 3% of all cases of neonatal seizures, mostly are focal and occurs in the first 72 hours of life (29, 43). Most common causes are low birth weight especially those associated with intrauterine growth retardation, infants of diabetic mothers, and hypoxic ischemic encephalopathy. The incidence of hypocalcemia is inversely proportional to gestational age and birth weight. Other causes of hypocalcemia include maternal hypercalcemia, primary hypoparathyroidism, X linked hypoparathyroidism and DiGeorge syndrome (43). Hypomagnesaemia often associated with hypocalcemia, but it does not seem to cause seizures in isolation without hypocalcemia (25). One study shows that approximately 50% of cases being associated with congenital cardiac defects which if present should raise the possibility of particular causes of hypocalcemia such as DiGeorge syndrome (44). Hypoglycemia is another cause of neonatal seizures; common causes include intrauterine growth retardation, prematurity, infant of diabetic mothers, birth asphyxia, intracranial hemorrhage and infection. The most common symptoms of hypoglycemia in intrauterine growth retardation, in addition to seizures, are jitteriness, hypotonia, stupor and coma (45). Seizures and other neurological symptoms are rapidly relieved by correction of hypoglycemia. Failure of relieving seizures and hypoglycemia after adequate correction should raise the possibility of underlying metabolic or endocrine problems. Hyponatremia, hypernatremia and pyridoxine deficiency can also produce neonatal seizures but are less common.
3. **Inborn errors of metabolism:** are relatively rare causes of neonatal seizures. They should be suspected in any healthy neonate who deteriorates and develop encephalopathy and seizures after initiation of feedings. Metabolic disorders that can cause neonatal seizures include *urea cycle disorder, aminoacidopathies, biotinidase deficiency, mitochondrial disorders, defects in beta oxidation, glucose transporter deficiency and peroxisomal disorder*. Disturbances of amino acid or organic acid metabolism are often the most common inborn errors of metabolism that present with neonatal seizures [42]. Some of these disorders are treatable and some are not. *Pyridoxine dependency* is a rare disorder of pyridoxine metabolism , that produces sever seizures in the first few days of life and are resistant to antiepileptic drugs but can controlled with high dose of intravenous pyridoxine [46-50]. On the other hand neonatal *non-ketotic hyperglycinemia* (glycine encephalopathy) is a rare non treatable cause of neonatal seizures due to a defect in cleavage of the excitatory amino acid glycine. It usually present with myoclonic seizures in the second or third day of life associated with static encephalopathy [51].
4. **Neonatal epileptic syndromes:** these includes *benign idiopathic neonatal convulsions* or called fifth day fits which was first described by Dehan and colleagues in 1977 [52]. They may account for as many as 5% of seizures in the full term neonates [42]. It usually appears in otherwise healthy full term infants in the first week of life (mostly 4-6 days) and resolve within 24 to 48 hours after onset. The seizures are usually brief (1 to 3 minutes) but rarely prolong and might end with status epilepticus. They are mostly focal clonic and rarely focal tonic, fluctuating between right and left, and the infant is normal between the attacks. History and examination of neonate is normal, family

history is negative and they have no subsequent increase risk of epilepsy but some studies report increased risk of minor neurological impairment [53,54]. The etiology remain unknown, many theories had been postulated including zinc deficiency [55], rotavirus infection [56] and mutations in the neuronal potassium channels KCNQ2 [57], but none were confirmed. The interictal EEG shows a theta pointu alternant pattern. The EEG background consists of predominantly sharply contoured theta (4 to 7 Hz) activity that is discontinuous and intermixed with other sharp activity [25]. The diagnosis is that of exclusion and the treatment with anticonvulsant is controversial. *Benign familial neonatal convulsions* are rare disorder of autosomal dominant inheritance with incomplete penetrance, usually occurs in the first week of life after an initial seizure – free period. The neonate is otherwise healthy but with family history of neonatal seizures [58-60]. The seizures are focal clonic or focal tonic, sometimes associated with apnoeic spells or eye deviation to one side. The interictal EEGs can be normal, but ictal findings typically consist of an initial electrodecremental event (flattening of the EEG) followed by bilateral spike and slow wave discharges, often accompanied by rhythmic clonic activity [59]. Two chromosomal loci were implicated: one on chromosome 20q13[61] and one on chromosome 8q[62-64] and the Genes responsible for this disorder are potassium channel genes, referred to as KCNQ2 for the chromosome 20q gene [65,66] and KCNQ3 for the chromosome 8q gene[64]. There is no consensus on the treatment, some use phenobarbital to control acute seizures and continued for the first 3 months [22]. Two sever catastrophic epileptic syndromes have also been identified in the neonatal period namely Ohtahara's syndrome and early myoclonic encephalopathy. Both can present with seizures shortly after birth usually in the first 10 days. The infants with these two encephalopathies have sever neurological disease, with developmental delay and intractable seizures [42]. Seizures in *Ohtahara's syndrome* characterized by frequent tonic spasms (100-300 per day) often in clusters[67]and the EEG characterized by burst suppression pattern, both in sleep and waking. The etiology is usually related to malformation of cortical development like Aicardi syndrome or porencephaly. The seizures are resistant to treatment and the prognosis is poor and they may evolve into infantile spasms. On the other hand, seizures in *early myoclonic encephalopathy* characterized initially by fragmentary myoclonic jerk which replaced later by partial seizures, massive erratic myoclonus and infrequently tonic seizures [25]. The EEG characterized by burst suppression pattern, with periods of suppression (4-12 sec) that are seen during sleep [68]. The etiology may be related to inborn error of metabolism especially propionic academia, non ketotic hyperglycinemia and D-glyceric acidemia [68-70]. The seizures are resistant to treatment, the infants are severely neurologically abnormal and they may die early in the first year of life.

5. **Miscellaneous:** cause include polycythemia, accidental local anesthetic drug injection in the scalp, withdrawal syndromes associated with maternal drug use, and the drug toxicity like theophylline. Recently, neonatal seizures provoked by electrolyte abnormalities secondary to dehydration and renal failure from intestinal obstruction secondary to congenital duodenal atresia had been reported [71].

5. Clinical manifestations and classification

Clinically neonatal seizures are different in manifestations and classification when compared with older infants, children and adult. The reasons for this difference are related to difference in mechanisms causing seizures in immature brain and incomplete myelination

of neurons. Most seizures are subtle, difficult to be recognized and can easily be mistaken for common normal rhythmic and jerky neonatal behaviors. It might be fragmented, disorganized with abnormal spread leading to a multi focal appearance. Generalized tonic clonic seizures are very rare if ever occur in neonatal period because the arborization of axons and dendritic processes as well as myelination is incomplete in the neonatal brain. A seizures discharge, therefore, cannot readily be propagated throughout the neonatal brain to produce a generalized seizure [72]. The five clinical types of neonatal seizures adopted by Volpe [73] are the most widely accepted classification, these include;

Subtle: are the most common type in both term and preterm neonates, constitute about 50% of all neonatal seizures. Usually they manifest as mild paroxysmal alteration in behavioral, motor or autonomic function that are not clonic, tonic or autonomic and they are commonly missed or mistaken for normal neonatal behavior. They are often originated in subcortical area and have no EEG correlate. The most common manifestations are:

- *Ocular*: are the most common clinical findings in both term and preterm neonates. They are usually consisting of staring, horizontal or vertical sustained deviation of the eyes or eye blinking.
- *Oral:* can manifest as swallowing movement, tongue thrust, lip smacking or chewing movement.
- *Limb*: manifest as bicycling of legs, boxing or swimming movement of the arms or other stereotypic limb movement.
- *Autonomic*: include alteration in blood pressure and/or heart rate, excessive salivation, pupillary dilatation and central apnea associated with tachycardia.
- *Apnea*: is a rare manifestation of neonatal seizures, commonly associated with normal or exaggerated heart rate when evaluated within 20 second after the onset. It is more common in term infant and usually associated with eye signs. Apnea alone in preterm neonate should raise the possibility of other underlying problem than neonatal seizures.

Most of subtle seizures occurs in combination and prolong video EEG monitoring failed to demonstrate any associated abnormal electrographic discharge [27, 74].

Clonic: are more common in term than preterm neonates and usually associated with electrographic seizures. They involve abnormal slow rhythmic movement of group of muscles of face, neck, limbs or trunk involving one side of body or both sides simultaneously in a non synchronous manner.

Multifocal clonic: are clonic seizures occurring in several parts of the body. Also they are seen primarily in term neonates figure 1.

Clonic and multifocal clonic are easily to be diagnosed clinically but sometime they may be difficult to be differentiated from non epileptic movement s like jitteriness.

Tonic: they involve sustained flexion or extension of axial or appendicular muscles groups. It could be focal or generalized. The generalized tonic seizures can result in a posture resemble that of decerbrate (tonic extension of all limbs) or decorticate (tonic flexion of upper limbs and tonic extension of lower limbs). The generalized tonic seizures are usually associated with normal EEG tracing. On the other hand, focal seizures are characterized by sustained posturing of single limb or sustained a symmetrical posturing of the trunk or eyes usually accompanied by apnea, flushing or cyanosis. Usually the EEG is abnormal in focal tonic seizures [75].

Fig. 1. Multifocal clonic fit with involvement of muscle of face, neck, trunk and limbs. Written informed consent was obtained from parents.

Myoclonic: these manifests as random single rapid contraction of groups of muscle the limbs, face, or trunk. It might be generalized, focal or fragmentary [75]. Occurrence at more rapid speed and predilection for flexor group of muscles can distinguish it from clonic seizures. EEG might be normal or shows changes including burst suppression pattern, focal sharp wave and hypsarrhythmia. If the myoclonus is related to sleep or hypoxic ischemic injury, the EEG shows no abnormal changes [27, 30, 76]. Myoclonic neonatal seizures carry the worst prognosis regarding the neurodevelopmental out come and some of it might progress to infantile spasm.

These clinical types of neonatal seizures should be differentiated from the more common repetitive, rhythmic and jerky movement made by normal newborn. Provoking by stimulation, elimination by passive flexion or soothing touch and presence of normal heart rate of value in differentiation.

Other classification of neonatal seizures depends on correlation between clinical events and occurrence of electrical seizures activity on EEG trace

- Electroclinical: when the clinical events overlaps in time with electrographic seizures activity.
- Clinical only: when the clinical events occurs in the absence of any EEG seizures activity. It's significant is not clear.
- Electrographic only: EEG shows electrical seizures without any coincidental clinical seizures activity. There is evidence that they have a similar impact on long term outcome as electroclinical seizures [77.78].

6. Investigations

Neonatal seizures are one of the neonatal emergencies that are required urgent treatment and evaluation. Because of the wide range of differential diagnosis, investigations should be guided by history and clinical examination but some investigations should be obtained in nearly all neonates with seizures. These investigations include basic biochemistry test, CSF, neuroimaging and EEG. Other tests might not be needed routinely and are suggested by history and clinical examination such as screening for TORCH, inborn error of metabolism and intoxications. The goal of determining the cause of neonatal seizures is to treat and prevent cases and to determine the prognosis. The investigations can be grouped under the following heading:

- **Septic screen**: because infections are common and readily treatable cause of neonatal seizures, investigations such as blood culture, urine culture and CSF analysis should urgently obtained when we suspect such cases as meningitis, ventricullitis and brain abscess. In such cases, empirical antibiotics should be started pending the results of investigations. When viral encephalitis is suspected especially herpes simplex virus, investigations including PCR and viral culture for HSV should be obtained while the neonate is empirically treated with antiviral agent such as acyclovir.
- **TORCH screening:** should be considered in any neonate with seizures and stigmata of congenital infection as micro or hydrocephaly, hepatosplenomegaly, skin rash, small for gestational age, thrombocytopenia and chorioretinitis.
- **Metabolic screen:** including serum electrolyte (Na, Ca, and Mg), blood sugar, arterial blood gas, anion gap, urine pH and reducing substances, blood ammonia for urea cycle abnormalities, urine and serum aminoacidogram, serum and CSF lactate/ pyruvate ratio and screening test for various inborn error of metabolism. A persistent metabolic acidosis suggests an organic acidemia.
- **Neuroimaging:** these investigations can detect neonatal strokes, structural abnormalities, intraventricular hemorrhage and neuronal migration defects. It includes skull X ray, ultrasound, CT scan and MRI. The choice of neuroimaging is frequently debated [25]. *Skull X ray* is of limited value but can shows intracranial classification in suspected TORCH infection. *Cranial ultrasound* is the test of choice when the patient is in critical condition and he or she suspected to have intracranial pathology. The advantages are that it is readily available in most centers, can be done at bedside and in most of the time there is no need for anesthesia but it is limited by its low resolution and its ability to assess cerebral cortex. *CT scan* is very helpful to exclude intracranial hemorrhage, infarction, structural abnormalities of the brain and hydrocephaly. *MRI* is indicated when other tests not revealed the underlying pathology and the seizures is refectory to antiepileptic drugs. It can be diagnostic in Lissencephaly, cerebral dysgenesis, neuronal migration defects and it's the study of choice for pattern of hypoxic ischemic brain injury [25]. For symptomatic seizures cause by HIE, abnormal T2, fluid attenuated inversion recovery, and diffusion signals can be used to pinpoint regional injury and severity [79]. Some studies revealed that magnetic resonance spectroscopy can be used to predict the severity and prognosis in those patients [80, 81].
- **Electroencephalography:** It should be done in all neonates with seizures requiring anticonvulsant therapy. It has both diagnostic and prognostic value. The EEG definitions vary, but paroxysms are considered to be seizures if they last more than 10 seconds [82]. The typical duration of the electrographic neonatal seizures is 2-3 minutes [83] but many seizures is shorter particularly in preterm infants [84]. Although focal sharp

waves may be present interictally in the neonatal EEG, they are not considered epileptiform. Some focal sharp waves are normal features of the neonatal EEG, such as frontal sharp transients and some temporal sharp waves [85]. On the other hand, not all neonatal seizures have abnormal EEG pattern, because of immaturity of the brain and interictal scalp recording may fail to pickup seizures activity especially those originated at subcortical level and are not propagated to surface electrodes [86] or some subtle and tonic seizures might not be epileptic but are primitive brain stem and spinal motor phenomena [76]. There is often poor correlation between the electrographic and clinical manifestations of neonatal seizures [87]. The background EEG activity can provide information concerning degree of associated central nervous system dysfunction, potential risk of seizures and prognosis. The degree of abnormality of the interictal background activity may suggest the extent and type of CNS dysfunction associated with seizures. The nature of the interictal background activity may also indicate the potential risk the individual infants have in experiencing a seizure [85, 88]. Video EEG monitoring has proved to be a powerful tool in diagnosis and management of neonatal seizures and as well as in clinical research. It is now becoming more available at many centers for routine use and more widely employed in neonatal intensive care units [85].

7. Diagnosis

Diagnostic evaluation for neonates with seizures should be performed in a stepwise manner starting with exclusion of conditions that might simulate seizures. *Jitteriness* is the most common neonatal movement that might mistaken for seizures. It is due to cerebral excitability and usually mimics clonic seizures. Common causes include hypocalcemia, hypoglycemia, hypoxic ischemic encephalopathy; infant of diabetic mother, polycythemia, drug withdrawal or idiopathic were no cause can be identified. It consist of fast tremor of one or more extremities that can be easily differentiated from seizures by the facts that it can be provocated by stimulation of the infant or stretching of a joint, terminated by holding or passive flexion of the limb, absence of eye signs, absence of autonomic changes especially tachycardia and finely by absence of EEG correlate. *Benign neonatal sleep myoclonus* is more commonly occur in preterm. The mechanism is unknown but might be related to a transient dysmaturity of the brain stem reticular activating system [87]. It present in the first week of life, always in sleep during rapid transmission from wakefulness to REM sleep or from REM to quite sleep. It might be induced by stimulation associated, commonly associated with sucking or stretching activities and can be rapidly abolished by arousal. The EEG is normal. *Apnea* especially if occur alone in preterm infant might be due to causes other than neonatal seizures. It usually associated with bradycardia in contrast with seizures where tachycardia is common. *Opisthotonos* consist of prolong arching of the back, might be mistaken for tonic seizures but absence of abnormal eye movement is useful for differentiation. Common causes include meningitis, intracranial hemorrhage and kernicterus. *Neonatal hyperekplexia* also known as startle disease, hyperekplexia is a rare disorder characterized by generalized muscle rigidity in the neonate, nocturnal myoclonus and an exaggerated startle reaction to auditory, tactile and visual stimuli. The startle reaction is a normal response to stimuli that consists of facial grimace and blinking followed by flexion of the trunk. The startle response is exaggerated when it interferes with normal activities, and causes apnea and frequent falls [89].

8. Treatment

The most important factor in determining the treatment in neonatal seizures is the recognition of underlying cause of the seizure. Some cases require only correction of the associated metabolic disturbances like hypocalcemia or hypoglycemia without the need for anticonvulsant drugs. On the other hand, some refractory cases require multiple anticonvulsant therapy in combination. Some causes of neonatal seizures may have more than one mechanism in producing seizures as in cases of hypoxic ischemic encephalopathy were brain injury and metabolic disturbance might play a role in producing seizures. This fact should be taken in consideration while managing a neonate with seizure.

There is a great debate whether a clinical – electrographic correlation is necessary to start vigorous treatment with anticonvulsant medication. Animal data indicate that both clinical and electrographic seizures may have long term behavioral and cognitive consequences on the immature brain. This may indicate aggressive anticonvulsant treatment for all seizures. Treatment of newborn with seizure involves:

1. **General supportive measures**: basic medical emergency principles should be applied to establish airway and breathing and to maintain circulation. Oxygen should be given if the seizures are prolonged and an intravenous line access should be secured for administrations of drugs and drawing blood for baseline investigations.
2. **Treatment of associated metabolic disturbances**:

2.1 **Hypocalcemia**: should be treated by slow intravenous infusion of 2ml/kg of 10% Ca gluconate at a rate of 1 ml/minute under strict monitoring heart rate. The dose can be repeated in 10 minutes if no response occurs. If ionized calcium level is suggestive of hypocalcemia, the Ca gluconate should continue for 3 days at a rate of 8 ml/kg/day. If despite of correction of serum calcium the neonate continue to have seizures, 0.2 ml/kg of 50% magnesium sulphate (50 mg/kg) should be given intramuscularly. The dose can be repeated every 12 hours until normalization of serum magnesium is achieved.

2.2 **Hypoglycemia:** animal studies revealed that glucose administration just before seizures prevents the decrease in brain glucose level that occurs with status epilepticus and markedly decrease mortality and neuronal cell loss [90]. Blood glucose should be obtained immediately and if there is hypoglycemia, 2 ml/kg bolus of 10% glucose in water should be given followed by continuous infusion of glucose at a rate of 6-8 mg/kg/minute. It is important to avoid hyperglycemia by frequent checking of blood glucose.

2.3 **Pyridoxine dependency:** dramatic response to intravenous 100 mg of pyridoxine used empirically in refractory seizures is highly suggestive of pyridoxine dependency this can be confirmed by continuous EEG monitoring.

2.4 **Anticonvulsant:** if the seizures persist or are recurrent, anticonvulsant drugs should be started. The most widely used drug for neonatal seizures is phenobarbitone which together with benzodiazepines (diazepam and lorazepam) and phenytoin (or Fosphenytoin) regarded as first line therapy (table 2).

Phenobarbitone: is the drug of choice for neonatal seizures by most centers. It is given as initial intravenous loading dose of 20 mg/ kg. If the seizure is persist after completions the loading dose, repeated doses of 5-10 mg/ kg every 20-30 minute until a clinical response or maximum dose of 40 mg / kg has been given. The highest therapeutic serum level of 180 μmol/L should not be exceeded. The maintenance dose is 3 – 5 mg/kg/day in 1-2 divided doses, started 12 hours after the loading dose. Careful monitoring of cardiac and respiratory

function is necessary. Some studies, using continuous video EEG monitoring reveals a clinical control in only 30-40% [91, 92]. The reminder might experienced a reduction in the electro-clinical seizures but increased the number of electrographic seizures [92, 93]. The use of phenobarbitone as prophylactic for neonatal seizures in birth asphyxia is debatable. One study reveals a better neurodevelopmental outcome at 3 years of age after 40 mg/kg phenobarbitone used as prophylactic in a term neonates with perinatal asphyxia [94]. Another study revealed immediate adverse effects to phenobarbital used as prophylactic therapy in term newborn with perinatal asphyxia at a dose of 10 mg/kg [95]. The phenobarbitone should be used for the shortest possible period of time because of the possibility of phenobarbital induced neurodegeneration, inhibition of brain growth and impaired cognition and behavior [96, 97].

Drug	Rout	Dose
First line drugs		
• Phenobarbitone	IV	Loading 20 mg/kg Maintenance 3 – 5 mg/kg/day
• Phenytoin	IV infusion	Loading 20 mg/kg Maintenance 2 – 3 mg kg/day
• Benzodiazepines Diazepam	IV injection , infusion or rectal	0.3 mg /kg bolus followed by o.3 mg/kg/hour infusion 0.5 mg/kg rectally
Lorazepam	IV injection	0.05 – 1 mg/kg
midazolam	IV injection and infusion	Loading 0.15 mg/kg followed by infusion 0.1 – 1.4 mg/kg/hour
Second line drugs		
• Lidocaine	IV infusion	Loading 2 mg/kg followed by 4 – 6 mg/kg/hour
• Levetiracetam	Oral Intravenous	Initial dose 10 mg/kg increased to 30 mg/kg
• Carbamazepine	Oral	10 mg/kg initially followed by 15 – 20 mg/kg/day
• Valproic acid	intravenous , rectal	Loading 20 – 25 mg/kg/day followed by 5 – 10 mg/kg/12 hourly
• Vigabatrin	Oral	50 mg /kg/day

Table 2. Anticonvulsant drugs used in neonatal period.

Phenytoin: is the second most commonly used drug as first line therapy for neonatal seizures. It is given as a loading dose of 20 mg/kg by slow intravenous infusion, not more than 1 mg / kg / minute followed by maintenance dose of 2-3 mg/kg/day intravenously in 2-4 divided doses. The drug should not be dissolved in dextrose as it precipitated in it and the intravenous line should be washed with normal saline before given the medication if the neonate receiving glucose water. There should be a close monitoring of the cardiovascular system for arrhythmia and hypotension. One study compared the effectiveness of phenytoin and phenobarbitone in controlling neonatal seizures found no significant difference between

the two drugs [98]. Another double blind prospective study shows phenytoin as effective in controlling neonatal seizures in 43% when use alone as first line drug and the efficacy is increased to 63% when combined with phenobarbitone [92]. Furthermore, another study revealed that 30% of neonates continued to have electrographic seizures despite full loading doses of both phenytoin and phenobarbitone [99]. Fosphenytoin is a prodrug of phenytoin has the advantages higher water solubility and lower pH, which, in addition to the lack of toxic vehicles required for its formulation, reduce local irritation of skin and blood vessel at the site of infusion, this will also avoid purple glove syndrome which represent the soft tissue necrosis and injury which occur with highly alkaline poorly soluble intravenous phenytoin [100]. Fosphenytoin is converted to phenytoin by plasma phosphatase enzyme and it does not cause cardiac arrhythmia and hypotension to the same degree as phenytoin. Dose is calculated as equivalent to phenytoin and 1.5 mg/kg of Fosphenytoin is equal to 1 mg/ kg of phenytoin.

Benzodiazepines: some centers use acute administration of repeated doses of short acting benzodiazepines (diazepam, lorazepam and midazolam) as first line anticonvulsant therapy in a neonates with seizures because of their rapid onset of action but most centers use it as second or third line therapy because of their short half life, narrow therapeutic index and immediate cardiac respiratory and central nervous system depressive effect. These drugs are given intravenously (or rectally in case of diazepam) and diazepam and midazolam are more effective when given by continuous intravenous infusion at which time the neonate should be monitored closely for cardio respiratory and CNS depression. Lorazepam is preferred over diazepam because of its longer duration of action and wider therapeutic index. Dose of diazepam is 0.3 mg/kg intravenously and 0.3 mg /kg/hour infusion rate when used by continuous infusion. Rectal rout might be used in a dose of 0.5 mg/kg. lorazepam is given by intravenous injection at a dose of 0.05 – 1 mg/kg over 2 – 5 minute while midazolam given as an initial loading dose of 0.15 mg/kg followed by continuous intravenous infusion at a rate of 0.1 – 1.4 mg/kg/hour.

Alternative anticonvulsant therapy for refractory seizures: the majority of neonatal seizures will respond to the above mention drugs. Less than 10% are refractory to treatment and another group of anticonvulsant drugs are needed. *Lidocaine* may be effective in refractory seizures but its use is hampered by potential cardiac toxicity [101]. Lidocaine drip given in an initial loading dose of 2 mg/kg given over 10 – 20 minutes followed by 4 – 6 mg /kg/hour in continuous drip. The drug has narrow therapeutic range and adverse effects include arrhythmia, hypotension and seizures if given in high doses. One study reports 4.8% incidence of cardiac arrhythmia, all of which is respond to Lidocaine discontinuation [102]. *Levetiracetam* may also be effective in controlling neonatal seizures but there is little pediatric experience on its use in neonatal period, although a recent survey among pediatric neurologist suggests quite widespread off label use of Levetiracetam for refractory neonatal seizures despite lack of evidence on the safety, pharmacokinetics and efficacy of its use in neonates [103]. Recent study use mean initial dose is 16 ± 6 mg/kg and the mean maximum dose is 45 ± 19 mg/kg/day. No respiratory or cardiovascular adverse effects were reported or detected. Levetiracetam was associated with a greater than 50% seizure reduction in 35% [104].

Other drugs that have been used orally as an adjunctive anticonvulsant therapy for controlling seizures in refractory cases include *carbamazepine* in a dose of 10 mg/kg initially

followed by 15 – 20 mg/kg/day. Also *valproic acid* can be used per rectally for acute condition and orally for maintenance therapy. Intravenous preparation of valproic acid is recently available. The dose is 20 -25 mg/kg/day followed by 5 – 10 mg/kg 12 hourly. The major risk of hepatotoxicity is more common in this age group which might occur at a rate of 1/500[42]. Other drugs include *primidone*, *felbamate*, *lamotrigine* and *vigabatrin*. The efficacies of the above mention drugs can be difficult to assess since they are seldomly used as sole therapy for neonatal seizures and are usually given in conjunction with other anticonvulsant drugs. One study shows significant reduction in mean seizures duration and frequency following treatment of intractable multifocal neonatal seizures with the diuretic *bumetainde* with no associated clinical side effect or metabolic imbalance [105]. Another study found bumetainde to enhance the anticonvulsant action of phenobarbitone in immature brain by alteration of Cl- transport. Seizures were abolished in 70% and significantly reduced the frequency, duration and power of seizures in the remaining 30% when both drugs used in conjunction [106].

Maintenance therapy: there are no consensuses guideline exist regarding the duration of keeping an infant on anticonvulsant therapy after a neonatal seizures [107, 108, 109]. The principle is to keep the infant for the shortest possible time on anticonvulsant therapy. The duration is variable according to the underlying etiology, neurological examination and EEG changes. The most widely accepted drug for maintenance therapy is phenobarbitone in a dose of 3 – 5 mg/kg/day in one or two divided doses with monitoring serum level. Phenytoin is an alternative therapy. Volpe [110] adopt a protocol recommend discontinuation of all medication at discharge if the neonate is neurologically normal, regardless the etiology and EEG findings. If the neurological examination is abnormal on discharge, the neonate kept on anticonvulsant therapy and reassessed at one month age. At the age of one month, if the neurological examination is normal and the infant has no further seizures, the phenobarbitone is weaned over two weeks. If the neurological assessment is abnormal, an EEG is obtained. If the EEG is normal, the drug is tapered and stopped but if the EEG is abnormal, the infant continue on his anticonvulsant and reassess every 3 months till the age of one year in the same manner. Another protocol recommends drug withdrawal 2 weeks after the infant last seizures [111] after doing EEG to exclude subclinical seizures.

9. Prognosis

Seizures in early life may results in permanent anatomical and functional alteration and enhance epileptogenicity [112, 113]. The long term outcome of neonatal seizures is determined by many factors including the underlying etiology of the seizure, seizure type and duration and the EEG findings. Hypocalcemia and benign familial neonatal seizures are associated with excellent prognosis regarding survival and long term sequel in contrast to symptomatic hypoglycemia, intracranial hemorrhage, meningitis and hypoxic ischemic encephalopathy which are associated with high mortality rate and high incidence of long term complication as epilepsy, mental retardation, and various neurological disorders. Short lived, easily controlled seizures are associated with favorable outcome probably because they may reflect transient benign CNS disorder while sustained refractory seizures, on the other hand, reflects more severe brain disorder. Focal clonic and focal tonic seizures where associated with a relatively good outcome, while generalized tonic posturing and motor automatisms where associated with a poor out come. This probably reflects the underlying etiology and the extent of brain dysfunction [85, 114]. A relationship has been shown in infants with neonatal seizures, associated with perinatal asphyxia, between a great amount of

electrographic seizures activity and subsequent relative increased morbidity and mortality [115, 116]. Many studies shows a mortality rate ranging from 7 to 30% , variable percentage of mental retardation and neurological abnormalities of different severity and post neonatal epilepsies in up to 56% in infants with severe brain injury[116-120]. In a population based study by Ronen between 1990 and 1994, a 62 term and 26 preterm newborn with neonatal seizures where followed comprehensively. Only 35% were a live and without disability. Twenty four percent of children died and of the survival, 41% had one of epilepsy, mental retardation, cerebral palsy or learning disability [121]. A scoring system to predict the neurological outcome at the onset of neonatal seizures was tested on 106 newborn with neonatal seizures between 1999 and 2004. This system used 6 variables including birth weight, Apgar score at one minute, neurological examination at the onset of the seizures, cerebral ultrasound, efficacy of anticonvulsant therapy and the presence of neonatal status epilepticus. This system found to be an easy, rapid and reliable prognostic indicator of neurological outcome after the onset of neonatal seizures [122].

10. References

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4

Epileptic Encephalopathy Syndromes in Infancy

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1. Introduction

A diagnostic scheme for people with epileptic seizures and with epilepsy proposed by ILAE Commission (2001) (Engel, Jr. et al, 2001) newly adopted the concept of "epileptic encephalopathy" as one of new key terms. It is defined as a condition in which epileptiform abnormalities are believed to contribute to the progressive disturbance in cerebral function, but this definition may be ambiguous.

The proposal include 8 syndromes; early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, myoclonic status in non-progressive encephalopathies, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, epilepsy with continuous spike-waves during slow-wave sleep. To these syndromes, the migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci (Yamatogi et al, 2006) may be reasonably added. In this chapter, we will concentrate on the epileptic encephalopathies that occur only in infancy.

Earlier-onset epilepsy may potentially have a greater impact on a child's development than later-onset epilepsy. Age of epilepsy onset also varies and depends upon the underlying etiology. Seizures and cognitive function may vary over time, depending on the developmental stage of the child. Seizures may eventually remit in many children over time, but behavioral and cognitive problems may persist into adulthood.

"Catastrophic epilepsy" is also a collective term for types of childhood epilepsy that take a highly unfavorable course despite intensive treatment, often with polypharmacy (Kramer, 2005). This is understood almost synonymous with epileptic encephalopathy.

A common feature is that these disorders are usually refractory to standard antiepileptic drugs (AEDs). As a result, more aggressive use of AEDs considered effective in suppressing interictal epileptiform discharges (eg benzodiazepines, valproic acid, lamotrigine), immunomodulatory therapies (eg, corticosteroids, intravenous immunoglobulin [IVIG], plasmapheresis), ketogenic diet, and surgical options are often considered

In this review, epileptic encephalopathies will be dealt in the following concept: a particular group of usually age-related and extremely intractable epilepsies with characteristic generalized minor seizures and massive epileptic EEG abnormalities, both of which cause stagnation/deterioration in mental and cognitive functions in addition to the pre-existing developmental deficit due to organic brain damage.

2. Pathophysiology

The underlying mechanisms of these disorders are still poorly understood. Identifiable factors that may influence the course and degree of cognitive and behavioral impairment in

these disorders includes underlying etiology, age of onset of epilepsy, seizure frequency and severity, interictal epileptiform activity severity, treatment-related adverse effects, cumulative detrimental effects of severe chronic epilepsy, and genetic factors.It remains unclear how much electrical dysfunction contributes to the neuropsychological impairments seen in these disorders. In 1957, Landau and Kleffner suggested that "persistent convulsive discharges in brain tissue largely concerned with language communication" may be responsible for the deficits seen in LKS. This represents the basic concept that frequent seizures and/or interictal discharges may significantly disrupt the function of neuronal networks involved in language, learning, memory, behavioral regulation, and other higher cortical functions, resulting in either transient or permanent deficits. For example, continuous abnormal discharges during sleep may cause disruption of hippocampal function and interfere with learning and memory while awake and memory consolidation in sleep (Coppola G, 1995. Moruzzi G, 1995).
The duration of electrical dysfunction may in part determine the severity of the disorder. Impairment at the exact moment of an interictal discharge has been described and is termed transient cognitive impairment (Shewmon DA, 1989. Shewmon DA, 1988. Kasteleijn-Nolst, 1995. Aarts JH, 1989. Binnie, 2003. Binnie, 1993. Binnie, 1987). Although challenging to demonstrate, this appears to be due to a temporary disruption of a cortical network involved in a particular function at the time of an interictal epileptiform discharge.

3. Genetics

The epileptic encephalopathies of infancy and childhood are a collection of epilepsy disorders characterized by refractory, severe seizures and poor neurological outcome, in which the mechanism of disease is poorly understood.
There are only some reported cases where the disease locus were identified such as, a disease locus at chromosome 2q35-37, which enabled identification of the causative mutation in the gene SLC19A3 in four Japanese patients in a Japanese pedigree who presented with epileptic spasms in early infancy, severe psychomotor retardation, and characteristic brain MRI findings of progressive brain atrophy and bilateral thalami and basal ganglia lesions (Yamada, 2010). In a recent report, the clinical presentation and evolution of epileptic encephalopathy in a patient, associated with a loss-of-function mutation in the phospholipase C-β 1gene. The discovery of a phospholipase C-β 1 mutation allows us to propose a novel potential underlying mechanism in early-onset epileptic encephalopathy (Kurian, 2010).
A genetic variants in the MC4R promoter are associated with the development of infantile spasms. The rs11872992 polymorphism influences ACTH treatment responses in patients with infantile spasms (Liu ZL, 2007).

4. Epileptic encephalopathy syndromes in infancy

4.1 Early infantile epileptic encephalopathy (Ohtahara syndrome)

Ohtahara Syndrome is the earliest form of the age dependant neo-natal epileptic encephalopathies and was first described by Dr. Ohtahara and colleagues in 1976. It is often defined as "Early Infantile Epileptic Encephalopathy (EIEE) with Burst-Suppression" or "Early Myoclonic Encephalopathy (EME)" (Aicardi, 2002. Clarke, 1987).
Often little is know about the exact causes of Ohtahara, and it is important to remember that it is a syndrome with a definition as opposed to a disease in itself. Although children

suffering from Ohtahara may initially have very similar symptoms, developmental problems and clinical test results, the underlying causes of their illness may differ considerably, and in many cases these causes may never be known (Commission, 1985 &1989).

4.2 Symptoms

- Symptoms appear within the first 3 months of birth and usually within first 10 days. Often symptoms will appear with first few hours after birth, and in some cases mothers have felt possible seizures activity in utero. Onset is acute is previously normal children (Donat, 1992. du Plessis, 1993).
- Initial symptoms include poor suck reflex and general floppiness, followed by epileptic seizures.
- Main seizure pattern is tonic spasms; Other patterns include tonic/clonic, clonic, myoclonic, atonic, absences, partial, complex partial (with or without secondary generalisation), gelastics and Jacksonians. Seizures can appear in clusters or singly and patterns are likely to change with time. It is not uncommon for patterns to reappear at a later stage (Donat, 1992. Engel, 2001).
- EEG pattern is characterised as Burst-Suppression during both waking and sleeping states. This means the EEG (electroencephalogram) tends to show periods of very little electrical brain activity followed by a burst of high spiky activity before returning to very low activity again. Sometimes, one side of the brain seems to be affected more than the other (Fusco, 2001).
- Seizures are intractable, although in some cases can be improved through with treatment (Komaki,1999).
- Further symptoms may include breathing difficulties, apnoeas, poor swallow reflex and reflux. In some cases these can further give rise to other complications such as chest infections (Donat, 1992).
- OS thought to be a progressive, neuro-degenerative disorder with increasing frequency of seizures and with severe retardation of psychomotor development and learning difficulties (Miller, 1998).
- This deterioration may slow with time, although setbacks should be expected along the way. Development skills can be assessed after approximately ten months of age (Murakami, 1993 & Ogihara, 1993).
- Some research has shown boys can be affected more than girls.

4.3 Prognosis

- Prognosis is poor with severe psychomotor retardation and significant learning difficulties.
- The seizures are very often intractable and resistant to antiepileptic therapy making control difficult.
- Frequently cases will progress to West syndrome or partial epilepsy (usually during infancy). Later a much smaller number progress to Lennox-Gastaut syndrome. Psychomotor development may be slightly better if the infants do not develop West or Lennox-Gastaut syndrome
- Half of the children are likely to die in infancy or childhood.
- Some children who survive early children will often see a general improvement beyond initial expectations and increased life expectancy (Murakami, 1993 & Ogihara, 1993).

4.4 Etiology

Research has shown many different causes (polyetiology), however most are linked to some form malformative pathologies (structural brain damage). In most children there has been a significant underdevelopment of part or indeed all of the cerebral hemispheres. After some months Magnetic Resonance Imaging (MRI) can be used to detect such structural malformations.

Very occasionally, babies may suffer from a metabolic disorder where an important part of the body's biochemistry is affected. To rule out this possibility, doctors will carry out a number of specialised metabolic tests, and in most cases no abnormalities will be found. If, however, a metabolic disorder is discovered (at which point the Ohtahara diagnosis will be replaced), the geneticist will discuss a course of potential treatments. At times, in spite of adequate treatment, babies with metabolic diseases can deteriorate (Komaki, 1999, Murakami, 1993, Tominaga, 1993, Williams, 1998).

4.5 Treatments

Although the disorder in incurable, much can be done to improve the lives not only of the children but also the families. Seizure control is the main aim and will be attempted either through optimised dosages of anticonvulsants such as Vigabattrin (Topamax), Dillantin, Zonegran, Phenobarbitone, or through steroid therapies using ACTH and Prednisone. Anticonvulsants or AIDS (AED's antiepileptic drugs) can be taken in either mono or poly therapies. The quest for seizure control can be a slow and frustrating process.

There is also the possibility of utilizing such treatments as the Ketogenic Diet, the VNS (link) or more invasive surgery, such as a partial resection or complete hemispherectomy.

Physiotherapy and Occupational Therapies can help improve motor skills, while Hippotherapy can help improve general mobility, strength and endurance (Komaki, 1999, Ohno, 2000 & Pedespan, 1995).

5. Risk of reoccurrence in future pregnancies

Due to lack of research it is hard for specialists to give an accurate risk of reoccurrence in future pregnancies. However many doctors will site an approximate figure of 5% although this appears to be based on a generic risk for all epileptic disorders. This support group knows of only 4 families around the world with OS siblings, and so this 5% figure is not implausible.

Cases caused by a metabolic disorder will carry a higher risk. Single gene metabolic disorders have a 25% reoccurrence risk. But as mentioned above these cases are rare among Ohtahara children (Donat, 1992).

6. Early myoclonic encephalopathy

Early myoclonic encephalopathy, an epileptic syndrome with onset either in the neonatal period or first months of life, is characterized by erratic, fragmentary, or massive myoclonus, partial seizures, and late tonic spasms. The prognosis is severe. Early myoclonic encephalopathy with the Ohtahara syndrome make the entity of severe neonatal epilepsies with suppression burst pattern.

Since 1978, numerous papers have been published that describe an epileptic syndrome with onset either neonatally or in the first months of life and characterized by erratic,

fragmentary myoclonus, massive myoclonus, partial seizures, late tonic spasms, and EEG signs such as suppression-burst pattern. Various terms have been used: neonatal myoclonic encephalopathy (Aicardi, 1978). In 1989, the ILAE Commission of Classification and Terminology recognized this syndrome with the term "early myoclonic encephalopathy" and classified it under "symptomatic generalized epilepsies and syndromes with non-specific etiology". The same Commission distinguished this syndrome from similar clinical pictures, such as "early infantile epileptic encephalopathy with suppression-burst" or Ohtahara syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

6.1 Symptoms

Early myoclonic encephalopathy is characterized clinically by the onset of erratic or fragmentary myoclonus. Other types of seizures, including simple partial seizures, massive myoclonia, and tonic spasms can also occur. Erratic, partial myoclonus usually appears as the first seizure, even as early as a few hours after birth. The myoclonus usually involves the face or extremities and may be restricted to an eyebrow, a single limb, or a finger. The jerks occur when infants are awake or asleep, and they are often described as "erratic" because they shift typically from one part of the body to another in a random, asynchronous fashion. Frequency varies from occasional to almost continuous. In addition to limited partial myoclonus, generalized myoclonus may also be observed occasionally in some cases. Partial seizures are frequent and occur shortly after erratic myoclonus. The semiology of partial seizures is subtle, consisting, for instance, of eye deviation or autonomic phenomena such as apnea or flushing of the face (Dalla Bernardina, 1983). Tonic seizures are reported frequently and can occur in the first month of life or afterwards; they may occur both in sleep and wakefulness. From a clinical standpoint, the child presents a diffuse tonic contraction, usually extending to the extremities. Real epileptic spasms are rare and generally appear later.

Neurologic abnormalities are constant: very severe delay in psychomotor acquisitions, marked hypotonia, and disturbed alertness, sometimes with vegetative state. Dalla Bernardina and colleagues reported deterioration in the patients, this characteristic is difficult to confirm because the onset of the disease is very early. Signs of peripheral neuropathy may also occur in rare cases (Aicardi, 2002 & Dalla Bernardina, 1983).

6.2 Etiology

No obstetrical complications or other perinatal problems were observed in the reported cases. Consequently, early myoclonic encephalopathy is believed to have various prenatal etiologies that often remain unknown. Siblings have been affected in a few instances (Aicardi, 2002 & Dalla Bernardina, 1983). The parents were believed to be healthy and no consanguinity was recognized. Autosomal recessive inheritance appears likely but has not been proved.

Some conditions, such as inborn error of metabolism, can produce the clinical and EEG picture typical of early myoclonic encephalopathy such as: nonketotic hyperglycinemia, D-glyceric acidemia , propionic acidemia , molybdenum cofactor deficiency, and methylmalonic acidemia . Some reports of patients with a clinical picture of early myoclonic encephalopathy and an atypical suppression-burst pattern, with full recovery after administration of pyridoxine. Some malformative disorders can also cause early myoclonic

encephalopathy, but more often they produce Ohtahara syndrome (Lombroso, 1990, Martin, 1981, Vigevano,2002 & Wang, 1998).

6.3 Pathogenesis and pathophysiology

The lack of consistent neuropathologic features suggests that etiology may vary from case to case. Pathologic findings include a drop-out of cortical neurons and astrocytic proliferation, severe multifocal spongy changes in the white matter, perivascular concentric bodies, demyelination in cerebral hemispheres, imperfect lamination of the deeper cortical layers, and unilateral enlargement of cerebral hemisphere with astrocytic proliferation. On the other hand, absence of pathologic abnormality was reported in 2 affected cases. Others proposed the hypothesis of the presence of numerous large spiny neurons dispersed in the white matter along the axons of the cortical gyri has been interpreted as an abnormal persistence of interstitial cells (Dalla Bernardina, 1983, Aicardi, 1985 & Spreafico, 1993).

6.4 Epidemiology

Early myoclonic encephalopathy is very rare. An epidemiologic study on childhood epilepsy carried out in Okayama Prefecture, Japan, detected 4 cases of early myoclonic encephalopathy (0.168%) among 2378 epileptic patients younger than 10 years of age on the prevalence day of December 31, 1980. The prevalence of early myoclonic encephalopathy was higher than Ohtahara syndrome (0.04%), but much lower than West syndrome (1.68%). Similar results were obtained more recently in the same region (Oka E, 2002).

6.5 Prevention

No information is available. Genetic counseling might be helpful.

6.6 Differential diagnosis

Early myoclonic encephalopathy and Ohtahara syndrome share common clinical and EEG characteristics, such as onset in the first few months of life and suppression-burst pattern on EEG, but there are several features that distinguish these 2 entities.

The presence of erratic myoclonus and the absence of tonic spasms distinguish early myoclonic encephalopathy from Ohtahara syndrome.

In Ohtahara syndrome, the suppression-burst pattern is characterized by longer paroxysmal bursts and shorter periods of suppression. Etiologically, Ohtahara syndrome is mainly due to structural abnormalities; in the early myoclonic encephalopathy case series we found metabolic disorders and a high proportion of cryptogenic cases. The prognosis is more severe in early myoclonic encephalopathy.

The EEG pattern of "burst- suppression" with long suppression periods, without variations between different vigilance stages, distinguishes early myoclonic encephalopathy from other conditions that produce a neonatal "burst-suppression" picture, such as hypoxic-ischemic encephalopathy and neonatal convulsions (Aicardi, 2002 & Ohtahara S, 2003).

6.7 Diagnostic workup

In early myoclonic encephalopathy, EEG is characterized by a "burst-suppression" pattern with bursts of spikes, sharp waves, and slow waves, which are irregularly intermingled and separated by periods of electrical silence. The EEG paroxysms may be either synchronous or asynchronous over both hemispheres. There is no normal background activity. The burst-

suppression pattern usually evolves into atypical hypsarrhythmia or into multifocal paroxysms after 3 to 5 months of life.
Erratic myoclonus does not generally have an ictal EEG counterpart. Partial seizures have EEG characteristics similar to those of neonatal fits. The CT and MR findings vary and are related to etiology. The brain may be either grossly normal or have asymmetrical enlargement of 1 hemisphere, dilatation of the corresponding lateral ventricle, or cortical and periventricular atrophy.
Considering the inborn error of metabolism reported above, the serum levels of amino acids should be determined, especially glycine and glycerol metabolites, and organic acids, as well as the amino acids in the cerebrospinal fluid (Aicardi, 2002).

6.8 Prognosis
The prognosis for early myoclonic encephalopathy is poor. The patients reported either died before 1 or 2 years of life, with a mortality rate of 50% or greater, or survived in a persistent vegetative state. Early myoclonic encephalopathy can persist into childhood or evolve into severe partial epilepsy.

6.9 Management
There is no effective therapy for early myoclonic encephalopathy. Antiepileptic drugs as well as adrenocorticotropic hormone or corticosteroids cannot alter the poor prognosis. In nonketotic hyperglycinemia, pyridoxine and benzoate can normalize the levels of glycine in the blood and improve the EEG picture, but without improvements in prognosis. Trying pyridoxine is always justified in cases of early myoclonic encephalopathy.

6.10 Infantile spasms (West syndrome)
West syndrome usually occurs in the first year of life and consists of the triad of infantile spasms, developmental deterioration, and a hypsarrhthymia pattern on EEG.

6.11 Symptoms
The epileptic spasms are brief, generalized seizures involving extension and/or flexion axially and of the extremities. An individual spasm lasts seconds, often longer than typical myoclonic seizures, though not as long as most tonic seizures. The spasms may be subtle and may be isolated at onset, typically clustering later in the course. Several clusters per day, particularly in drowsiness, are characteristic.

6.12 Diagnosis
Hypsarrhythmia, the typical interictal EEG finding, consists of a disorganized pattern with asynchronous, very high amplitude slowing and frequent multifocal spike and sharp wave discharges. The ictal EEG typically reveals a generalized slow wave followed by diffuse voltage attenuation (electro-decrement), which may associated with a spasm or be only electrographic (without clinical correlate).

6.13 Etiology
No clear etiology is found in approximately 40% of cases (Hrachovy, 2008 & Vigevano, 1992). There is a broad range of potential causes, including cerebral malformations, infection, hemorrhage, hypoxic-ischemic injury, metabolic disorders, and genetic conditions, such as Down syndrome.

6.14 Treatment

- Variation in study methodologies prohibits a clear recommendation for first-linetreatment; however, ACTH and vigabatrin are usually used in practice.
- Corticosteroids may be less efficacious than ACTH, although they are effective. Vigabatrin may be more efficacious in tuberous sclerosis. Other agents that are efficacious include valproate, levetiracetam, topiramate, zonisamide, lamotriginen and benzodiazepines.
- The ketogenic diet is helpful in most cases. Focal cortical resection or hemispherectomy may be considered for cases that are lesional and medically intractable (M.T. Mackay, 2004).

6.15 Prognosis

Development remains unaffected only in a minority. Most children experience slowing, plateauing, or regression of their developmental trajectory. The developmental prognosis partially depends on the etiology. No specific AED has been shown to affect long-term developmental outcome. An extensive literature review revealed that 16% had normal development, and 47% had continued seizures at an average follow-up of 31 months (Hrachovy, 2008). When classified by etiology, normal development was described in 51% of cryptogenic cases versus only 6% of symptomatic cases. Approximately 17% of cases evolved into Lennox-Gastaut syndrome.

7. Malignant epilepsy with migrating partial seizures in infancy

7.1 Symptoms

- Onset of this rare syndrome occurs in the first year of life and may occur in the neonatal period. It is characterized by frequent partial seizures of multifocal onset, with autonomic or motor involvement. The seizures increase in frequency and may become near-continuous.
- Lateral deviation of the head and eyes, lateral eye jerks, fixed sight, clonic twitches of the eyelids, increased tone or clonic jerks of one or both limbs on one side, chewing movements, apnea, flushing of the face, salivation, mastication, secondary tonic-clonic generalization.

7.2 Diagnosis

- The interictal EEG reveals multifocal epileptiform activity and slowing. Diffuse slowing of the background activity. Few patients may have a normal EEG.
- Then the EEG background activity became slow with fluctuating asymmetry between different recordings. Initially sleep-waking cycle can be identified, spindles are rare and asymmetric
- The ictal EEG confirms multifocal onsets, which may shift from seizure to seizure.

7.3 Etiology

In most cases, there is no clear etiology or structural problems, suggesting genetic factors may be causative or contributory.

7.4 Treatment

Seizures are often difficult to control with standard AEDs. Bromides, stiripentol, and clonazepam may be helpful in some cases.

7.5 Prognosis

Developmental regression is common, and death has been reported in infancy and childhood in severe cases (Coppola G, 2009).

8. Myoclonic status in non-progressive encephalopathies

This rarely reported disorder has onset in infancy or early childhood, with onset usually during the first year of life (Dalla Bernardina B, 1999).

8.1 Symptoms

Seizures typically begin with partial motor seizures, although myoclonic status may occur at onset. Myoclonic absences, massive myoclonias, and rarely generalized or hemiclonic seizures may occur. Myoclonias may be multifocal and occur with startles. Myoclonic status epilepticus may be recurrent. Motor abnormalities and movement disorders are common.

8.2 Diagnosis

The interictal EEG consists of multifocal epileptiform discharges and background slowing. Epileptiform discharges are potentiated in sleep, in some cases similar to an ESES pattern. Ictal EEG recording may demonstrate generalized slow spike and wave, or an absence pattern, depending on the seizure type.

8.3 Etiology

A genetic cause is identifiable in approximately half of children, including Angelman syndrome and 4p- syndrome (46). Other reported causes include hypoxic-ischemic injury and cortical dysplasia.

8.4 Treatment

Episodes of myoclonic status may respond to benzodiazepines. AEDs that may be efficacious include valproate with ethosuximide or clobazam.

8.5 Prognosis

Children have a poor prognosis, experiencing developmental regression, and eventual severe mental retardation. The repeated episodes of myoclonic status may contribute to cognitive deterioration (Dalla Bernardina B, 1999)

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5

The Lessons from Angelman Syndrome for Research and Management

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1. Introduction

Interest in monogenic disorders with epilepsy has provided significant insights into the pathophysiology of epilepsy. Among these disorders, Angelman syndrome has attracted particular attention because of its complex genetics. Angelman syndrome is characterized by developmental delay, absence of speech, motor impairment, epilepsy and a peculiar behavioral phenotype with apparent happy demeanor. It is caused by the lack of expression of the *UBE3A* gene, which can result from various abnormalities of chromosome 15q11-q13 if they concern the chromosome inherited from the mother (illustrating the phenomenon of genomic imprinting). In most case, Angelman syndrome is due to a de novo 15q11-q13 deletion. Rarely, patients have inherited both copies of chromosome 15 from the father and none from the mother, i.e. paternal uniparental disomy. As a result, no functional copy of the UBE3A gene is inherited from the mother. Patients with uniparental disomy have a statistically less severe phenotype than those with a deletion. Another small group of patients have an imprinting defect resulting in a lack of the typical maternal pattern of DNA methylation. Statistically, the phenotype of patients with an imprinting defect is indistinguishable form that of patients with uniparental disomy. In some patients, a mutation in the maternal *UBE3A* gene can be detected, and in about 10% of typical cases, no cytogenetic or molecular abnormality can currently be found. Patients with Angelman syndrome have a remarkably high risk of epilepsy compared to many other neurodevelopmental disorders. In particular, early-childhood onset of refractory epilepsy with atypical absences and myoclonic seizures with predisposition to developing non-convulsive status epilepticus is a common presentation. In recent years, there has been increasing awareness of epilepsy in adults. The neurocognitive effects of seizures are difficult to evaluate. Propensity to develop epilepsy may be due to hypersynchronous neuronal activity, which might be related to abnormal GABA-mediated transmission due to lack of UBE3A expression, or other factors. Recent findings in animal models demonstrated altered dendritic spine formation as well as both synaptic [$GABA_A$ and NMDA transmission] and nonsynaptic (including gap junction) influences in various brain regions, including hippocampus and cerebellar cortex. Much research is still required to fully understand the functional links between lack of UBE3A expression and clinical manifestations of Angelman syndrome. Studies of regulation of *UBE3A* expression, including imprinting-related methylation, may point to possibilities of therapeutic

upregulation. Understanding relevant roles of the gene product might lead to targeted intervention. Further documentation of brain network dynamics, with particular emphasis on hippocampus, thalamocortical, and cerebellar networks is needed, including in a developmental perspective. There is also a need for further clinical research for improving management of problems such as epilepsy, behavior, communication, learning, motor impairment, and sleep disturbances.

2. Clinical features

The clinical picture of Angelman syndrome has been broadly documented, principally in children, but with an increasing emphasis on adolescents and adults. Clinical diagnosis is based on a set of physical (Fig. 1) and behavioral features (Williams et al., 2006) (Table 1). All patients have developmental delay with severely impaired cognitive skills. They show specific speech impairment; about one-third of patients speak no words at all, and the others rarely use more than five words. This contrasts with better receptive verbal communication and communication skills based on spontaneous or learned signs. Behavior is characteristically overactive, exuberant, sociable, and happy, with frequent smiling and laughing (Pelc et al., 2008a). Developmental motor impairment includes mild to moderate axial hypotonia, present from birth, and eventual spastic hypertonia of the limbs that may become apparent during the first year of life (Dan & Cheron, 2008). Despite varying degrees of ataxia, most patients develop independent walking. Gait is distinctive, with a wide support base, extension and lateral rotation of the lower limb, elbow flexion, and wrist supination. About 90% of patients have epileptic seizures. Seizure onset is often between 1 and 3 years. Many seizure types, both generalized and focal, have been reported, including epileptic spasms, myoclonic absences, myoclonic, atonic, tonic, and tonic–clonic seizures, but atypical absence and myoclonic seizures have been particularly emphasized. As in other developmental conditions with epilepsy, the seizure disorder often improves in late childhood, although epilepsy can persist or reappear in adulthood, and be difficult to

Fig. 1. Facial characteristics of a child with Angelman syndrome. Visual contact, fair eyes, midface hypoplasia, wide smiling mouth.

A. Consistent features (100%)
Developmental delay, functionally severe.
Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotor behavior
Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

B. Frequent features (more than 80%)
Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (-2 standard deviations of normal head circumference) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions
Seizures, onset usually before 3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood
Abnormal electroencephalogram, with a characteristic pattern (Dan and Boyd 2003). The electroencephalographic abnormalities can occur in the first 2 years of life, can precede clinical features, and are often not correlated to clinical seizure events

C. Associated features (20%–80%)
Flat occiput
Occipital groove
Protruding tongue
Tongue thrusting; suck/swallowing disorders
Feeding problems and/or truncal hypotonia during infancy
Prognathia
Wide mouth, wide-spaced teeth
Frequent drooling
Excessive chewing/mouthing behaviors
Strabismus
Hypopigmented skin, light hair, and eye color compared to family, seen only in deletion cases
Hyperactive lower extremity deep tendon reflexes
Uplifted, flexed arm position especially during ambulation
Wide-based gait with pronated or valgus-positioned ankles
Increased sensitivity to heat
Abnormal sleep-wake cycles and diminished need for sleep
Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
Abnormal food related behaviors
Obesity (in the older child)
Scoliosis
Constipation

Table 1. Clinical diagnostic criteria for Angelman syndrome. (Adapted from Williams et al 2006)

control. Both convulsive and non-convulsive status epilepticus may occur. The latter isparticularly common during childhood, but it can occur in infancy and adulthood. In adolescents and adults, particularly, prolonged disabling tremor has been ascribed to cortical myoclonus (Guerrini et al., 1996) or myoclonic status (Ogawa et al., 1996; Elia, 2009). Piracetam, levetiracetam, topiramate and other antiepileptic drugs can be tried with variable results. The underlying mechanism remains unclear. It seems to be non-epileptic at least in some cases, where response to levodopa (Harbord, 2001) or reserpine (Stecker & Myers, 2003) has been documented. Sleep problems commonly reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid eye movement (REM) sleep, and periodic leg movements.

3. Natural history of the seizure disorder

Onset of seizures is often before 3 years of age, mostly between 1 and 3 years (Buntinx et al., 1995; Buoni et al., 1999; Clayton-Smith, 1993; Saitoh et al., 1994). Whereas epilepsy is often a prominent clinical problem in childhood, seizure onset occurs during infancy in a minority of patients. If seizures do occur in infants, they tend to do so in a febrile context. In a high proportion of patients, the onset of epilepsy precedes the diagnosis of Angelman syndrome (Valente et al., 2006). Seizure types may evolve with age (Matsumoto et al., 1992; Uemura et al., 2005). As in other developmental conditions with epilepsy, the seizure disorder often improves in late childhood. Sustained seizure-freedom following epilepsy in childhood has been found in four of five patients with a 15q11-q13 deletion followed up longitudinally until the age of 30 years or more (Uemura et al., 2005). Other studies, however, have shown that epilepsy can persist or reappear in adulthood (Moncla et al., 1999; Thomson et al., 2006).

4. Seizure types

Many different types of seizures have been reported, both generalized and focal. They include myoclonic absences, myoclonic, atonic, tonic and tonic—clonic seizures (Cersósimo et al., 2003; Elia et al., 1998; Galván-Manso et al., 2002; Laan et al., 1997; Matsumoto et al., 1992; Minassian et al., 1998; Viani et al., 1995). Atypical absence and myoclonic seizures have been particularly emphasized. Multiple seizure types occur in about half of the patients with a 15q11-q13 deletion (Valente et al., 2006). Patterns of seizures, including type, age of onset, other clinical features and electroencephalographic features of patients with Angelman syndrome may show some resemblance with defined epileptic syndromes. In this context, it is important to characterise their epilepsy correctly given implications for both management and prognosis. Although epileptic spasms are the typical seizure type of West syndrome or infantile spasms (in association with hypsarrhythmic electrencephalogram and 'developmental arrest'), this epileptic syndrome has rarely been documented convincingly in Angelman syndrome. In the vast majority of cases, the electrencephalographic patterns seen in Angelman syndrome can be differentiated easily from hypsarrhythmia (Dan & Boyd, 2003). The most commonly identified of these typical patterns consists of runs of rhythmic 2—3/s activity of high amplitude often exceeding 300 mV seen mainly over the frontal regions (Boyd et al., 1988, 1997; Korff et al., 2005; Laan et al., 1997; Valente et al., 2003) i.e. Pattern I in Dan and Boyd's classification (Dan & Boyd, 2003). Although tonic seizures and complex absences can occur in Angelman syndrome, confusion with Lennox-Gastaut syndrome can be avoided without much difficulty in many cases. Confusion with the

electroencephalographic features of Lennox- Gastaut syndrome has also arisen in some reports, although the runs of slow spike—wave complexes seen in Angelman syndrome are usually rhythmic and signal non-convulsive status epilepticus (which has no specific features and is indeed indistinguishable from that seen in Lennox-Gastaut). In contrast, another epileptic syndrome, referred to as myoclonic status in non-progressive encephalopathies, has been appropriately recognised in a number of patients with Angelman syndrome (Dalla Bernardina et al., 1995). This syndrome is characterised by recurrent episodes of myoclonic status in patients who have pre-existing non-progressive neurological deficits including severe intellectual disability, axial hypotonia and ataxia (Dalla Bernardina et al., as cited in Roger et al., 1983) It also occurs in Wolff-Hirschhorn syndrome (4p-syndrome), neonatal encephalopathy and metabolic disorders such as non-ketotic hyperglycinaemia. Another condition, which is not an epileptic syndrome stricto sensu in the absence of seizures, is electric status epilepticus during sleep, also known as continuous spike—wave discharges during sleep. The electroencephalographic features consists of generalised slow (usually around 2/s) spike—wave complexes, sometimes with a frontal emphasis, occupying more than 85% of slow-wave sleep, while this activity is exceedingly rare in rapid eye movement sleep. When the triad of electroencephalographic continuous spike—wave discharges during sleep, seizures (all types can occur except for tonic seizures) and impairment of neuropsychological and motor (e.g. ataxia) function is present, the condition can be regarded as an epileptic syndrome termed 'epilepsy with continuous spike—wave discharges during sleep'. This syndrome has rarely been documented in Angelman syndrome (Rubin et al., 1997). The lack of clinical alteration concomitant to the electrographic epileptiform activity excludes it from the context of non-convulsive status epilepticus (Dan & Boyd, 2005). Both convulsive and non-convulsive status epilepticus may occur. Compared to other conditions with epilepsy, the latter is relatively common, including in cases that are not due to 15q11-q13 deletion (Boyd et al., 1997; Laan et al., 1997; Uemura et al., 2005; Viani et al., 1995). Although non-convulsive status epilepticus appears to be more common during childhood, it can occur in infancy (Ogawa et al., 1996) and adulthood (Espay et al., 2005). Electroencephalogram shows continuous epileptic discharges which are distinct from the typical rhythmic electroencephalographic features of Angelman syndrome (Dan & Boyd, 2003). The distinction between generalised and complex partial non-convulsive status epilepticus is often difficult to make. The term 'dialeptic status epilepticus', which refers to seizure phenomenology with alteration of consciousness as main ictal feature without any reference to the origin, might appear more appropriate in this context (Dan & Boyd 2005). Frequent or prolonged episodes of dialeptic status epilepticus may contribute to a poor cognitive outcome, as suggested in other conditions with epilepsy (Hoffmann-Riem et al., 2000). In some cases, prolonged disabling tremor has been ascribed to cortical myoclonus (Guerrini et al., 1996) or myoclonic status (Ogawa et al., 1996). Such disabling resting tremor may appear in day-long clusters, particularly in adolescents or adults (Clayton-Smith, 2001; Van Buggenhout et al., 2000). When severe, it may result in loss of ability to eat or walk independently during episodes. The aetiology of this tremor remains unclear. It seems to be non-epileptic in a number of cases. In one report of two adult patients, associated cogwheel-type rigidity and bradykinesia suggested Parkinsonism and tremor improved dramatically on levodopa (Harbord, 2001). In another young adult, episodes of generalised shaking predominating in the upper extremities were correlated with 4—10/s electromyographic bursts but no ictal electroencephalographic changes (Stecker & Myers, 2003). The

electromyographic features were similar to the postural bursting activity described in children with Angelman syndrome (Dan & Cheron, 2004) although the latter was not associated with actual tremor. The muscle activity associated with the movements was so intense that it induced hyperthermia and rhabdomyolysis. The movements were effectively controlled by reserpine in association with topiramate. This prominent, quasi-clonic activity may be difficult to distinguish from myoclonus. In a few other cases, fast-bursting myoclonus has been correlated with electroencephalographic activity of similar frequency or at subharmonics, suggesting cortical myoclonus (Guerrini et al., 1996; Ogawa et al., 1996) similar to findings in Rett syndrome (Guerrini et al., 1998). Finally, it must be noted that absence of electroencephalographic discharges correlated with bouts of laughter suggests that they do not correspond to gelastic seizures. Other possibly challenging spells include stereotyped movements, tremors, staring episodes, eye rolling, motor/behavioural manifestations of gastro-oesophageal reflux (Sandifer syndrome) and self-gratification episodes ('masturbation').

5. Management

Seizures may be difficult to control with pharmacological treatment, particularly in childhood. Surveys of antiepileptic drugs used in patients with Angelman syndrome have suggested that sodium valproate is the most commonly used (Ruggieri & McShane, 1998). The use of clonazepam has also been reported in a number of cases. These drugs have been recommended on the basis of early reports of retrospective, open studies of limited patient series. The effectiveness of other benzodiazepines, such as nitrazepam and clobazam, seems to be similar to that of clonazepam in patients with Angelman syndrome (Østergaard & Balslev, 2001). However, in the majority of patients, the use of benzodiazepines does not appear to be justified as a first-line treatment. Phenobarbitone can be both effective and well tolerated in infants. Because of sedative or cognitive side effects, it is less used in children and older patients. However, Clayton-Smith and Laan have suggested that it may be a good option in adults (Clayton-Smith & Laan, 2003). Levetiracetam, topiramate, ethosuximide and lamotrigine have been successfully used in many cases, but there is a lack of controlled studies. It is noteworthy that although lamotrigine drug has no direct effect on GABAA receptors (Gibbs et al., 2002) it might promote GABRB3 gene expression in hippocampal cells (Dan et al, 2007). Some antiepileptic drugs may be paradoxically detrimental through increase in the risk of seizures, facilitation of the development of other seizure types or precipitation of non-convulsive status epilepticus. These drugs include carbamazepine (Minassian et al., 1998; Valente et al., 2006; Laan et al., 1996) oxcarbazepine (Valente et al., 2006) vigabatrin (Kuenzle et al., 1998; Østergaard & Balslev, 2001; Valente et al., 2006) tiagabine and probably gabapentin. However, this observation does not imply absolute contraindication of these drugs, which may prove useful in some patients. This aggravation due to antiepileptic drugs is not specific to Angelman syndrome, where it appears to be more marginal than in some epileptic syndrome, notably idiopathic generalised epilepsies. Response of non-convulsive status epilepticus to treatment is variable and management may be difficult. Oral benzodiazepines, corticosteroids and ketamine (Mewasingh et al., 2003) may be early options, but there has been a marked lack of well-designed studies. Morbidity associated with aggressive treatment mayoutweigh the risk of therapeutic abstention. In contrast, convulsive status epilepticus requires early effective treatment according to common treatment protocols. Non-pharmacological management is rarely

considered, despite the relatively high prevalence of drug resistance. Ketogenic diet was effective in four patients with refractory epilepsy in Valente et al.'s series (Valente et al., 2006).

6. Neurophysiologic features

The contribution of EEG to diagnosis of Angelman syndrome has been recognized in both children (Boyd et al., 1988; Korff et al., 2005; Rubin et al., 1997) and adults (Sandanam et al., 1997; Van Buggenhout et al., 2000), and particularly highlighted in infants (Van Lierde et al., 1990). In contrast to the paucity of physiologic rhythms, interictal EEG shows three distinctive high-amplitude rhythmic patterns (Dan & Boyd, 2003), which can reinforce the clinical diagnosis (Williams et al., 2006). The most commonly identified EEG abnormality (pattern I) consists of runs of high amplitude rhythmic 2–3 Hz (delta) activity, seen mainly over the frontal regions (Fig. 2A). A variant composed of sharp slow waves (Fig. 2B) has been characterized as ''triphasic'' (Laan et al., 1997), ''triphasic-like'' (Valente et al., 2003), ''polyphasic slow waves'' (Minassian et al., 1998), ''pattern IB'' (Dan & Boyd, 2003), or ''notched delta'' (Korff et al., 2005). Another pattern consisting of prolonged runs of rhythmic 4–6 Hz (theta) activity with centrotemporal emphasis (pattern II, Fig. 2C) is common in young children (Rubin et al., 1997), but tends to disappear after 5 (Boyd et al.,

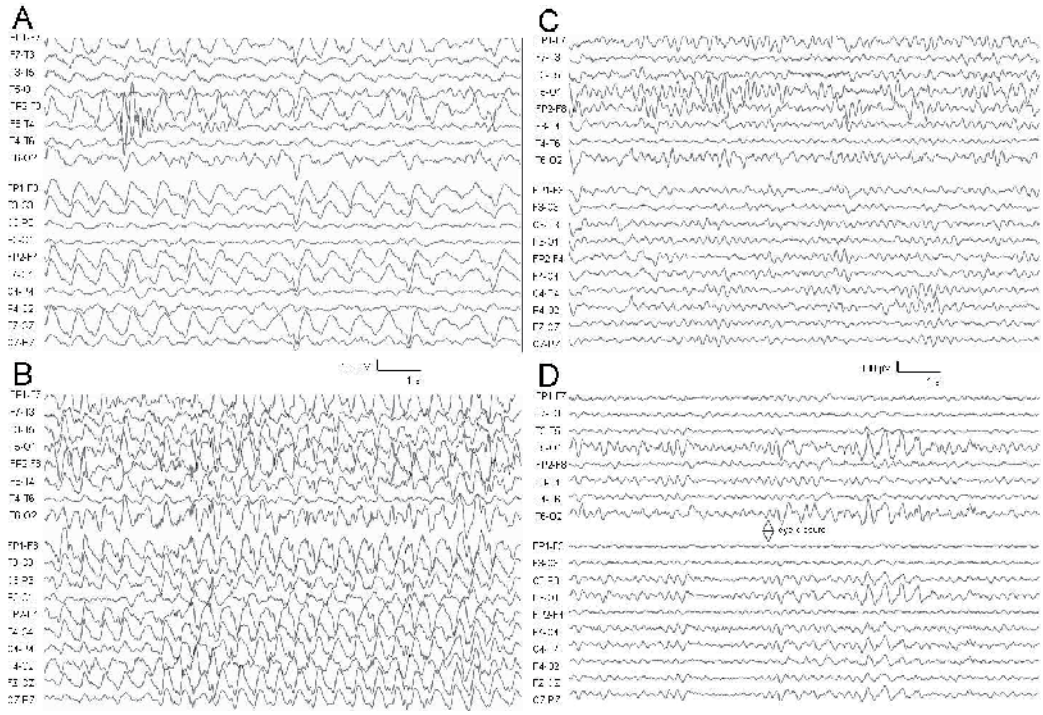

Fig. 2. Typical rhythmic electroencephalographic patterns. A, B. Pattern I: run of high-amplitude delta activity mixedwith spikes predominating in the anterior regions without clinical correlation. C. Pattern II: run of diffuse moderate-amplitude theta activity. D. Pattern III: high amplitude delta activity mixed with spikes in the posterior regions on eye closure.

1988) to 12 (Laan et al., 1997) years of age. Pattern III consists of high amplitude 3–6/s rhythmic activity sometimes containing small spikes, predominating over posterior regions (Fig. 2D). Eye closure facilitates its occurrence (Boyd et al., 1988; Rubin et al., 1997; Viani et al., 1995). In addition to these characteristic rhythmic activities, electroencephalography (EEG) may show epileptic discharges. Interictal nonspecific discharges including spikes, spike-waves, polyspike-wave, and more rarely bursts of fast sharp activity (Cersósimo et al., 2003) may show focal or generalized distribution. A few patients show prolonged runs of 2–3 Hz spike-wave complexes without any clinical correlation (Dan et al., 2000; Matsumoto et al., 1992; Uemura et al., 2005).

7. Genetic aspects

In more than 90% of patients with a clinical diagnosis of Angelman syndrome, genetic testing can demonstrate a molecular mechanism causing lack of expression of the UBE3A gene. This gene is imprinted in (at least) some brain cells (Rougeulle et al., 1997), being expressed only from the chromosome 15 that is inherited from the mother. In about 70% of patients with Angelman syndrome, lack of UBE3A expression is due to microdeletion of the 15q11-q13 region on the maternally inherited chromosome 15. Similar abnormalities affecting the paternally inherited chromosome 15 result in Prader-Willi syndrome, a clinically distinct condition (Knoll et al., 1989). This illustrates genomic imprinting, where expression of imprinted genes is effectively monoallelic and depends on the paternal or maternal origin. This nonmendelian type of inheritance in human disease also prevails in Huntington disease, Beckwith-Wiedemann syndrome, and Silver- Russell syndrome. Other genes are implicated in the deletion, possibly resulting in a contiguous gene syndrome. The ATP10C gene is expressed preferentially from the maternal chromosome only; lack of its expression may underlie eventual obesity (Meguro et al., 2001). ''Pinkeyed dilution'' or P gene has been implicated in hypopigmentation that is seen in patients with a 15q11-13 microdeletion, characterized by light skin, reduced retinal pigment, low hair bulb tyrosinase activity, and incomplete melanosome melanization (King et al., 1993). Absence of a copy of the GABRB3, GABRG3, and GABRA5 genes, which code for subunits of GABAA receptor, has tentatively been related to abnormalities in GABAergic neurotransmission (Olsen & Avoli, 1997). There is a mutation in the maternal UBE3A gene (Kishino et al., 1997; Matsuura et al., 1997) in another 5–10% of patients (Lossie et al., 2001; Malzac et al., 1998). About 3–5% of patients have an imprinting defect resulting in lack of the typical maternal pattern of DNA methylation required for UBE3A expression (Buiting et al., 1995). Approximately 2–3% of patients inherited both copies of chromosome 15 from the father and none from the mother, that is, paternal uniparental disomy (Malcolm et al., 1991); as a result, no functional copy of the UBE3A gene is inherited from the mother. Finally, 1–2% of patients have complex structural chromosome abnormalities leading to inactivation of the maternal UBE3A gene (Chan et al., 1993). To some extent, these molecular categories can be linked to two phenotypic pictures. One is more severe and seen in association with 15q11-q13 microdeletion or UBE3A mutation, that is, with only one intact copy of the UBE3A gene, which does not bear a maternal methylation pattern. Patients in those groups tend to have more severe microcephaly, greater delay in developmental milestones, more severely impaired communication skills, more severe seizures, and show hypopigmentation (Bürger et al., 1996; Lossie et al., 2001; Minassian et al., 1998; Moncla et al., 1999). The other phenotypic picture is relatively less severe, with low incidence of microcephaly, of hypopigmentation, less severe seizures, and more words, although speech is extremely

limited and not used as a main communication tool. It is seen in association with uniparental disomy or imprinting defect, that is, with two intact copies of the UBE3A gene, none of which bear a maternal methylation pattern. However, the core phenotypic features, including the rhythmic EEG patterns described earlier, are shared, and there is much overlap in their severity across patients in all molecular classes. Genetic testing, therefore, has confirmatory rather than prognostic value. Nevertheless, obtaining a precise genetic diagnosis is essential in view of the complexity of genetic counseling.

8. Animal models

Molecular characterization of Angelman syndrome has allowed the development of animal models of the different mechanisms underlying the syndrome. Such models provide important insights into the pathophysiologic mechanisms involved in various aspects of Angelman syndrome. A mouse model of maternal microdeletion including the Ube3a gene did not result in obvious phenotypic abnormalities, but fine phenotypic aspects, such as motor control, learning skills, or neurophysiological features, have not been studied (Gabriel et al., 1999). This model is potentially very interesting, as it would represent the most prevalent situation in the human condition. The absence of a drastic phenotype, however, contrasts with Angelman syndrome. A model of Angelman syndrome due to paternal uniparental disomy showed high incidence of failure to thrive for the first 4–5 weeks and spontaneous death in the first month (Cattanach et al., 1997). Survivors developed obesity, hyperactive behavior, and gait described as ''ataxic.'' Electrocorticographic recordings showed bilateral prolonged runs of high-amplitude delta rhythmic activity. The phenotype of proposed models of imprinting defect (Wu et al., 2006) has not been studied in detail, but mice showed a marked decrease in Ube3a (the gene product) in both the cerebral cortex and cerebellum. Mice with selective maternal Ube3a gene inactivation, providing models of Angelman syndrome due to maternally-inherited UBE3A gene mutation, showed no obvious phenotypic abnormality, but fine testing revealed impaired motor coordination and learning (Jiang et al., 1998; Miura et al., 2002). One of these models showed context-dependent learning impairment and deficits in hippocampal long-term potentiation (Weeber et al., 2003). These abnormalities have been related to diminished calcium/ calmodulin–dependent protein kinase II activity, which was secondary to altered autophosphorylation. More recently, van Woerden et al. demonstrated that loss of this self-inhibition resulted in improvement of both learning defects and synaptic plasticity (van Woerden et al., 2007). This mouse model also showed abnormal dendritic spine development in hippocampal
pyramidal neurons (Dindot et al., 2008). Electrocorticographic recordings showed almost continuous runs of rhythmic 3/s activity mixed with polyspikes and slow waves (Jiang et al., 1998). In another mouse model with targeted inactivation of maternal Ube3a (Miura
et al., 2002), hippocampal electrocorticographic recordings showed runs of high amplitude 4-5/s spike–waves. Intracerebellar recordings in alert mice showed local field potential high frequency (ca. 160 Hz) oscillation correlating with increased Purkinje cell firing rate and rhythmicity (Cheron et al., 2005, 2008).This oscillation was inhibited by gap junction, NMDA, or GABAA receptor blockers. In sleep, these mice showed reduced proportions of slowwave sleep (Colas et al., 2005). Among mouse models that do not involve Ube3a expression, the most relevant seems to be provided by mice that are deficient in the Gabrb3 gene (Homanics et al., 1997). Surviving homozygous knockout mice had seizures, hyperactive behavior, coordination and learning impairment (DeLorey et al., 1998;

Homanics et al., 1997), reduced benzodiazepine binding to GABAA receptors in the cortex (Sinkkonen et al., 2003), and developmental changes in electrocorticographic recordings consisting of progressive slowing and subsequent appearance of highamplitude irregular slow and sharp waves, and generalized clonic seizures associated with spiking (DeLorey et al., 1998). In vitro electrophysiologic study suggested loss of reciprocal GABAergic inhibition between thalamic reticular neurons (Huntsman et al., 1999). Heterozygotes tended to show behaviors intermediate between wild-type and homozygous null mutants, with significant abnormalities in electrocorticography, seizures, and rest–activity patterns (DeLorey et al., 1998). This model shows interesting similarities with several phenotypic aspects of Angelman syndrome, mostly epilepsy. It has been particularly well studied from the neurophysiologic point of view. Recently, genetically engineered Drosophila with null Dube3a (UBE3A homolog) has been suggested as a model for Angelman syndrome (Wu et al., 2008). Mutants showed abnormal climbing behavior, impaired olfactory associative memory, and altered free-running circadian activity, which the authors tentatively related (in a somewhat far-fetched leap) with abnormal motor coordination, cognitive impairment, and sleep problems in patients with Angelman syndrome. Dube3a-null mutant flies also showed reduced dendritic branching of sensory neurons in the peripheral nervous system and altered growth of terminal dendritic processes (Lu et al., 2009).

9. Pathophysiology

Although the causative gene was identified more than 12 years ago (Kishino et al., 1997; Matsuura et al., 1997), underlying pathophysiology is still a matter of speculation. The gene product, UBE3A, acts as an E3 ubiquitin–protein ligase along the ubiquitin pathway. The best-characterized function of ubiquitination is to mark target proteins for specific proteolysis by proteasomes. Cytoplasmic accumulation of the p53 oncoprotein was found in Purkinje cells and in a subset of hippocampal neurons maternal Ube3a-deficient mice (Jiang et al., 1998). Because this protein is specifically ubiquitinated by UBE3A, the authors suggested that failure of Ube3a to ubiquitinate target proteins and promote their degradation could be a key aspect of the pathogenesis of Angelman syndrome. However, these findings have not been replicated in other models. Ubiquitin-mediated proteolysis may be important in a number of neuronal processes, including synaptogenesis and mechanisms of long-term memory. The ubiquitin pathway may also be involved in regulating abundance of postsynaptic receptors (Burbea et al., 2002). Functional absence of UBE3A might thus impair the regulation of GABAA receptors (Dan &Boyd, 2003). In this hypothesis, altered regulation of b3 subunit–containing GABAA receptors would lead to ''compensation'' involving isoforms of the GABAA receptor that do not contain the b3 subunit, possibly changing the receptors' kinetics and desensitization properties. Although these changes are expected to be subtle, they may have extensive—but yet undocumented—effects during brain maturation as well as through the patient's life. In patients with the common 15q11-q13 microdeletion, hemizygosity of GABAA receptor subunits a5, b3, and c3 has been suggested to underlie deficits in GABA-related neural synchrony mechanisms (Egawa et al., 2008). This could explain the propensity for more severe neurologic impairment in patients with 15q11-q13 microdeletion. Based on data from human patients and animal models, a model of thalamocortical dysfunction resulting from dysregulation of synaptic GABAergic neurotransmission has been proposed to account for the typical rhythmic EEG features (Dan & Boyd, 2003). In this model, excessive neuronal synchrony precludes the generation complex spontaneous activity in neuronal networks and interferes

with neuronal responsiveness. Synchronous network activity disrupts processing of inputs and, therefore, representation of information. Emergence of cerebellar oscillation in maternal Ube3a-deficient mice (Cheron et al., 2005) is consistent with a network mechanism implicating gap junctions and GABAA transmission (Dan et al., 2004; Traub et al., 2008). This oscillation shows similarities with various mouse models with altered calcium signaling (Cheron et al., 2008) and also involves NMDA transmission (Cheron et al., 2005). Hippocampal NMDA-dependent long-term potentiation abnormalities have also been documented in another model with inactivated maternal Ube3a (Weeber et al., 2003). In sum, formation of dendritic spines as well as both synaptic (including GABAA and NMDA transmission) and nonsynaptic (including gap junction) influences appear to be specifically altered in various brain regions (including hippocampus and cerebellar cortex). But much research is still required to fully understand the functional links between lack of UBE3A expression and the clinical manifestations of Angelman syndrome.

10. Perspectives

Despite the gaps that still preclude comprehensive understanding of Angelman syndrome, this condition potentially offers a powerful paradigm for both clinical and basic investigation of the complexity of brain maturation and motor, cognitive, and behavioral development (Scheiffele & Beg, 2010). Most studies conducted until now have been retrospective and based on questionnaires. Such studies have mostly focused on issues relating to epilepsy, sleep, behavior, communication, or general health. Although large surveys are not expected to provide insights into mechanisms that lead to these manifestations, more studies are still required in these areas in order to add to the current body of knowledge and to refine the notions that have emerged. Given the trend for differences in severity of various phenotypic features between groups of patients from the different molecular classes, it would appear critical to carefully record the underlying genetic cause when constructing cohorts of patients. This might lead to the delineation of a typology of Angelman syndrome with multidimensional classification that could accommodate both milder and more severe atypical phenotypes. Studies of more homogenous categories thus defined would provide much-needed information about the natural history of specific subgroups. They would also make intervention– outcome studies more pertinent. Another key issue that has been overlooked in many previous surveys is the relationship between phenotypic expression and development. It is essential to take the dynamic aspects of development into account. Furthermore, it will become increasingly relevant to gather information about aging in Angelman syndrome. Relevant contextual factors need to be recognized. Quality-of-life issues need to be addressed. This should also encompass the psychological burden on both patients and caregivers, as well as coping strategies. Clinical studies could be considerably enhanced if a carefully designed large-scale database could be set up with open access available to professionals. In this context, cross-study evaluation of various features, and their prevalence and natural history could be performed reliably. This would also allow assessment of the effect of management approaches. In connection with the neurology of Angelman syndrome, epilepsy has been the most studied subject. Controlled studies of treatment are still very much needed. Other neurologic features would also deserve special attention. With respect to motor control, for example, dysfunctions of various components of the motor system, including the motor cortex, cerebellum, and basal ganglia, have been hypothesized (Beckung et al., 2004; Dan et al., 2001, 2004; Harbord, 2001), but more studies are required to test the hypotheses. It is also

important to further investigate cognition. Neuropsychological studies of well-defined subgroups of patients are necessary to shed more light on cognitive processing and learning strategies. This might have implications on the design of appropriate pedagogic approaches. Studies that are more pragmatic are also required, such as those that have assessed training programs (Didden et al., 2001). Almost all electrophysiologic studies conducted to date were limited to EEG, a number of them entertaining confusion between epileptic and nonepileptic changes. Recent methods analyzing brain dynamics and how it modulates neural processing can probably yield invaluable information. The typical rhythmic EEG activities likely reflect dynamic states of neural circuits. Experimental paradigms could be designed to analyze how these network activities are modulated by parameters such as attention or sensory inputs. Evoked-potential techniques (Egawa et al., 2008), and, in particular, ''event-related potentials'' will likely provide important information on specific aspects of brain functioning. Studies of processing of verbal language will be of special interest. Neuroimaging should also provide more insights into Angelman syndrome (Dan et al., 2009). The recent development of new analysis paradigms of MRI is likely to have implications in the documentation of alternative brain maturation in Angelman syndrome. Functional imaging can address a number of highly relevant issues, also including speech processing. There is also a great need for neuropathologic studies, as only two autopsies have been published. A large number of current studies concern molecular biology, including investigation of the mechanisms of imprinting and the possible roles of UBE3A. These studies are extremely important for achieving a better understanding of the involved processes. Based on this understanding, appropriate modulation might be proposed in order to improve neurologic functioning in patients with Angelman syndrome. Molecular biology studies must take into account possible differences between studied species. Among the most pressing questions that are yet to be solved, it will be crucial to discover the functions of UBE3A that are relevant to Angelman syndrome. This might open the way toward possible (partial) compensation for the virtual absence of UBE3A where and when it is needed. However, confusion may arise in association with the use of terms such as ''cure'' to characterize reversal of selected abnormalities in rescue genetically engineered animal models (Elgersma, 2007). ''Cure'' implies recovery from an illness, which is deceptive in this context. Brain development heavily relies on orderly processes that start in the embryo, drawing developmental trajectories. Although the issue of neuronal development has been poorly addressed in Angelman syndrome, it is likely to be altered given documented impairment in neuronal functioning in patients and animal models. Diagnosis is always made relatively late in the brain developmental history: late infancy at best and later childhood in most cases. Current research does not aim at discovering a cure but rather at improving management in order to optimize development, ameliorate symptoms, and improve of quality of life of children and adults with Angelman syndrome. In this context, it is important to consider that the effects of lack of UBE3A gene expression may represent an emergent property of developmental interactions among a number of brain regions and functions at the network level rather than a singular, localized dysfunction in otherwise normally developing central nervous system. Given the phenotypic variability even within a molecular class, it may prove important to dedicate attention to individuals' genetic, environmental, and/or developmental context as potential modulating factors. Another central question concerns the regulation of UBE3A gene expression in the hope that it can be enhanced. The phenotypic differences between patients who have one virtually nonfunctional copy of the UBE3A gene (i.e., patients with 15q11-q13 microdeletion or UBE3A inactivating mutation) and those who have two virtually nonfunctional copies (in case of uniparental

disomy or imprinting defect) suggest that there is residual expression when the gene is intact, even in the absence of a functional methylation pattern. Although a dietary supplementation study did not bring about any clear clinical changes (Bacino et al., 2003), more topical intervention might prove useful. Another important question relates to determinants of the deleterious effect of absence of other genes in the 15q11-q13 region. This might explain phenotypic modulation in cases that are caused by a deletion. It might also point to requirements for compensation of lack of gene function. As suggested earlier, the putative roles played by GABRB3 may prove to be directly relevant to the function of UBE3A. Some studies concentrate on the possible relationship between genes implicated in Angelman syndrome and other conditions, such as Rett syndrome, autism, or epileptic syndromes. In particular, there seems to be some crucial interactions in the regulation of MECP2 and UBE3A expression (Samaco et al., 2005). There have been recent advances in this domain, which remain controversial (Jordan & Francke, 2006). If the interactions are confirmed, there are likely to be found at multiple levels, perhaps including downstream effects on the regulation of the number of neurons, neuronal and synaptic structure or neurotransmission. Therefore, these interactions would potentially induce fundamental alterations in network properties of the central nervous system. This may also have therapeutic implications.

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Part 3

Therapy of Epilepsy: Medicamentous and Surgical Approach

6

Novel Neuroprotective Strategies and Targets of Intervention in Epilepsy

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1. Introduction

Epilepsy is a debilitating disorder that affects over 50 million people worldwide, resulting in $15.5 billion in medical expenses and lost income/worker productivity in the United States every year (Patel, 2004). Epilepsy, also known as *status epilepticus* (SE), is described as the unregulated over stimulation of neurons throughout various regions of the brain. SE is characterized by seizures lasting for 30 or more minutes accompanied by a loss of consciousness. This disorder has been associated with significant rates of morbidity and mortality, possibly induced by neuronal damage and dysfunction (Sleven, et al., 2006). It is thought to be the result of an imbalance of excitatory and inhibitory input in a subset of neurons, which is then propagated to other regions of the brain, causing improper activation of multiple brain regions and uncontrolled cortical output (Rho, et al., 2004). Most patients are either under the age of 20 or over 65 years old, with a greater prevalence being in younger patients. While development of SE has a wide range of possible etiologies, whether spontaneously, as the direct result of trauma, brain tumors, metabolic abnormalities, or due to genetic predisposition, the exact mechanism(s) of the development of SE is poorly understood (Pellock, et al., 2001, Rho, et al., 2004).

Oxidative stress has been associated with SE; however, it continues to be somewhat controversial whether it plays a causal role in the development of epilepsy or if it is simply the consequence of prolonged excitation (Patel, 2004). This increased excitation exerts high metabolic demands on cellular systems, such as Na^+/K^+ pumps and other ATP dependent mechanisms, required for maintaining normal cellular homeostasis. Mitochondria are the main source of ATP in neurons and mitochondrial dysfunction has been linked to many acute and chronic neurological disorders including Parkinson's disease, traumatic brain injury, stroke/ischemia, and Alzheimer's disease.

Mitochondrial dysfunction is known to increase oxidative damage via increased mitochondrial reactive oxygen species (ROS) production, which has been shown to be a critical side effect of prolonged epileptic seizure and may cause increased susceptibility to subsequent seizures (Patel, 2002). It has also been shown that after prolonged seizure activity there is significant oxidative damage to mitochondrial DNA (mtDNA), which is responsible for encoding key proteins of the electron transport chain (ETC) required for oxidative phosphorylation and normal mitochondrial function (Patel and Li, 2003). Disruption of ATP production can cause impaired mitochondrial and plasma membrane transporter function, initiation of necrotic

pathways, alteration of neurotransmitter metabolism, and opening of the mitochondrial permeability transition pore (mPTP), ultimately leading to cellular destruction/dysfunction (Patel and Li, 2003, Sullivan, et al., 2005).

2. GABA

Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the brain, activates Cl^- and HCO_3^- ($GABA_A$) or K^+ ($GABA_B$) permeable receptor ligand-gated channels by binding to specific GABAergic receptors on cellular membranes of neurons, thereby hyperpolarizing the cell and rendering it unable to fire rapid sequential action potentials (Czapinski, et al., 2005, Kwan, et al., 2001, Rho, et al., 2004). Deficiencies in these receptors are believed to play an important role in the development of epilepsy, as studies using various models of epilepsy indicate that modulation associated with subunits of the $GABA_A$ receptor cause a decreased ability to inhibit neuronal activity and cause promotion of neuronal hyperexcitability (Brooks-Kayal, et al., 1998, Rho, et al., 2004). There is also some evidence that the developmental roles of these receptor subtypes are not solely associated with the inhibition of neurons and, in the case of $GABA_A$ receptors, they can also act as excitatory inputs via GABA activation in immature neuronal networks.

$GABA_B$ receptors are believed to be responsible for primary inhibitory effects at this early stage of development, although they may not be able to compensate for increases in excitation (Pellock, et al., 2001). The loss of GABAergic neurons and the subsequent improper neuronal compensatory reorganization for the lost inhibitory input or the loss of key GABA regulatory enzymes could alter the excitatory/inhibitory balance and lead to inappropriate excitatory signal propagation initiating SE (Rho, et al., 2004). Improper potassium regulation has also been suggested to be a potential cause of the increased excitability in young neurons due to its decreased clearance from the extracellular environment evoking repetitive neuronal discharges (Pellock, et al., 2001). Studies using calcium chelators (i.e. BAPTA) suggest that the loss of inhibitory neurons is due to their inability to properly buffer calcium, rendering these neurons unable to maintain adequate membrane potential, which could implicate mitochondrial involvement (Rho, et al., 2004).

However, calcium has also been suggested to have age-specific effects on NMDA receptors by acting as the regulatory ion, rather than magnesium (Mg^{2+}), due to its increased influence on the development of neuronal networks in the developing brain, and increased levels of intracellular calcium may interfere with the ability of immature neurons to make appropriate inhibitory connections during this critical period (Pellock, et al., 2001). This aberrant Ca^{2+} cycling effect highlights the importance of mitochondrial homeostasis due to their function of Ca^{2+} sequestration, which regulates the cytosolic concentrations in order to maintain proper cellular function.

3. Excitotoxicity

Recent studies have shown seizures to be associated with neuronal loss in various regions of the brain, including age-dependent damage to hippocampal regions; and it has been suggested that this damage is a result of prolonged excitation by excitatory amino acid (EAA)-induced excitotoxicity (Pellock, et al., 2001, Sullivan, 2005) (Fig. 1). During seizures neurons become depolarized for a prolonged period of time resulting in an increase in Na^+ influx through voltage-dependent channels, and this prolonged increase in Na^+ perpetuates neuronal depolarization. This increased and sustained depolarization causes the voltage

dependent Mg^{2+} block to be removed from NMDA channels, allowing them to be activated by glutamate thus facilitating the influx of Ca^{2+} and a loss of neuronal Ca^{2+} homeostasis (Pellock, et al., 2001, Rajasekaran, 2005, Sullivan, 2005).
Whether oxidative stress is the cause or consequence of prolonged activation by EAA has been controversial. Studies suggest that chronic seizures result in increased oxidative stress, upregulation of neurotrophic factor genes, and structural rearrangement, all of which can contribute to increased susceptibility by inducing a chronic state of hyper-excitability (Liang and Patel, 2004, Patel, 2002). Key glial transporters (GLT-1 and GLAST) responsible for the uptake of exogenous glutamate from the extracellular environment can also be damaged by oxidative stress, resulting in the propagation and extension of activation by this EAA (Liang and Patel, 2004).

4. Mitochondria

Mitochondria function primarily as the major source of the energy production for the cell and are responsible for maintaining calcium homeostasis by sequestering excess calcium from the cytosol. The mitochondria perform these vital functions by shuttling electrons down a series of complexes in the inner mitochondrial membrane called the electron transport chain (ETC) and subsequently pump protons across the inner membrane from the matrix creating a membrane potential ($\Delta\Psi$) within the inner membrane space (Figure 2).
This membrane potential can be used to sequester calcium through membrane channels and to carry out oxidative phosphorylation by complex V (ATP synthase) to produce ATP (Brookes, et al., 2004, Nicholls and Budd, 2000, Sullivan, et al., 2002, Sullivan, et al., 1998). A normal byproduct of oxidative phosphorylation is the production of ROS, which under normal physiological circumstances is scavenged by endogenous antioxidant systems such as MnSOD, Cu/ZnSOD, and glutathione (GSH) (Ilhan, et al., 2005). However, during trauma or prolonged epileptic seizure the production of ROS can overwhelm the endogenous antioxidant defense systems and cause damage to lipids, proteins, and DNA resulting in cellular dysfunction and subsequent neuronal loss.
The brain is both rich in mitochondria and substantially more sensitive to insult and oxidative stress than any other tissue in the body because of its high metabolic demand for oxygen and glucose, its large amount of peroxidizable membranous polyunsaturated fatty acids (PUFA), poor repair/regenerative mechanisms, and high iron content (Patel, 2002, Rho, et al., 2004). In addition to epilepsy there has been an association between both oxidative damage and mitochondrial dysfunction with the development of many cognitive disorders, including Parkinson's and Alzheimer's disease (Ilhan, et al., 2005, Patel, 2002, Sullivan, et al., 2004). Studies showing that oxidative damage precedes seizure initiation and studies implementing strategies to limit free radical formation and several antioxidant therapies have indicated that oxidative mechanisms are involved a causal role of seizure induced neuronal loss. However, studies have also detected oxidative damage to mitochondrial complex I, as well as some integral citric acid cycle proteins, up to 44 hours after SE, suggesting that oxidative damage is the result of prolonged seizure activity (Gibbs, et al., 2006, Jung, et al., 2001, Patel and Li, 2003, Patel, 2002, Rong, et al., 1999).

5. Antioxidative mechanisms

Superoxide dismutase (SOD), a major component of the endogenous antioxidant system of the cell, has three isoforms which each have distinct localizations within the cell.

Cu/ZnSOD (SOD1) is primarily found in the cytosol, MnSOD (SOD2) is found in the mitochondria, and EC-SOD (SOD3) is found in the extracellular space (Patel and Li, 2003). These enzymes catalyze the dismutation of superoxide into hydrogen peroxide (H_2O_2) and oxygen (O_2) at a rate very close to its diffusion rate (Ilhan, et al., 2005, Patel and Li, 2003). Glutathione peroxidase (GPx) and glutathione (GSH), another major component of the endogenous antioxidant system, catalyze H_2O_2 into water preventing the formation of hydroxyl radicals, rendering the previously dangerous superoxide species harmless to cellular structures (Ilhan, et al., 2005, Rho, et al., 2004).

Glutathione levels were shown, *in vitro* and *in vivo*, to decrease as early as 4 hours after SE, which highlights its importance in influencing mitochondrial /cellular damage outcome after SE (Gibbs, et al., 2006, Sleven, et al., 2006). Studies conducted by modulating the level of SOD in a mouse model of epilepsy have given us insights into the role of antioxidant systems in the prevention of oxidative stress and a seemingly causal role of oxidative damage in seizure. Homozygous MnSOD -/- knockout mice are embryonic lethal, which highlights its vital function in physiological function and developmental processes. Using heterozygously expressing (-/+) or transgenic overexpressing MnSOD mice have allowed for the investigation of the consequences of diminished or overabundant (respectively) antioxidant capacity on seizure development and hippocampal damage. It has been shown that overexpression of MnSOD, 0.5-2 fold, can attenuate kainate induced seizures, however animals with diminished MnSOD levels showed an exacerbation of kainate-induced seizure and hippocampal damage, which was attenuated with antioxidant treatment (Patel, 2002). Overexpression of MnSOD also produces lower amounts of inactive aconitase and 8-hydroxy-2-deoxyguanosine (8-OHdG), measures of oxidative protein and DNA (most likely mtDNA) damage, indicating a role in the preservation of mitochondrial function (Gonzalez, et al., 2005, Patel, 2002, Sleven, et al., 2006).

Damage to mitochondrial complex I, α-keto-glutarate dehydrogenase, citrate synthase, aconitase, and GSH can be detected at time points well after the end of an epileptic episode, and damage to these cellular components can induce cell death cascades and increase the likelihood of future seizures (Gibbs, et al., 2006). Highlighting the importance of this oxidative damage in epileptogenic pathologies is the specific defect of complex I activity found in the hippocampal CA3 region of patients suffering from hippocampal sclerosis and intractable seizures, which was found to be sufficient enough to affect ATP production in this region, possibly accounting for the pathology of seizure development in these patients (Gibbs, et al., 2006, Kunz, et al., 2000).

6. Antiepileptic drugs

AEDs have been in use for the attenuation of seizures since the early part of the 20th century (Fig. 2). Since their inception, many pharmacological interventions have been examined for their efficacy in attenuating the development of epileptic seizures, however, out of the thousands of compounds that have been screened for their ability to treat seizure, only a handful of antiepileptic drugs have been approved for clinical use. It was believed that early AEDs, such as benzodiazepines, phenobarbital, and valproate decreased seizure prevalence by increasing GABA inhibition of aberrant neuronal excitation, where as newer AEDs affect a much broader set of cellular systems, which can increase the complexity of pharmacological effect (Czapinski, et al., 2005, Kwan, et al., 2001). In addition to the potential detrimental effect, most of these interventions focus on the prevention of future

seizures rather than preventing neuronal damage resulting from prolonged or multiple seizures. Alternative targets at the cellular level to modulate seizure incidence and, perhaps more importantly, attenuate neuronal damage must be developed in order to create a more substantial and permanent treatment for epilepsy.

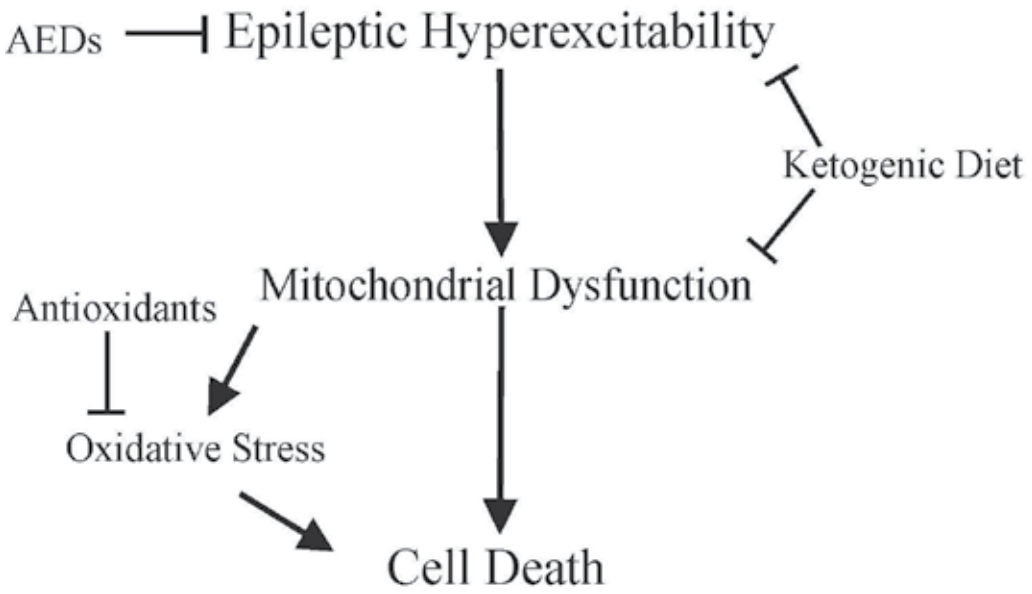

Fig. 1. Hypothetical sites of neuroprotective actions of epileptic therapeutic strategies. Following seizure mitochondria buffer rises in intracellular Ca^{2+}. Excessive mitochondrial Ca^{2+} cycling results in an increase in ROS production and in the initiation of cell death. AEDs target hyperexcitability by two mechanisms; I.) increasing inhibitory neurotransmission or II.) decreasing excitatory neurotransmission. The ketogenic diet alters neurotransmitter metabolism which decreases neuronal excitability. Additionally, the ketogenic diet has been shown to increase uncoupling protein activity and in-turn reduces oxidative stress. Antioxidants act to decrease oxidative stress and prevent cell death.

6.1 GABA modulators

AEDs that modulate the action of GABA in order to increase the inhibitory effect of this neurotransmitter have been widely used as the first line of treatment therapies for SE (Gibbs, et al., 2006). These drugs include Phenobarbital (PB), Benzodiazepines (BZD), Vigabatrin (VGB), and Tiagabine (TGB). PB, perhaps the oldest and most studied member of the barbiturate family has been used since the turn of the 20th century for its properties as an anticonvulsant and sedative, confers anticonvulsant protection to animals subjected to various experimental seizure models (Kwan, et al., 2001). This type of GABA modulators include that also includes Methylphenobarbital, Pentobarbital, and Primidone. In addition to increasing the affinity of GABA for its respective receptor and the activation of chloride channels, PB extends the time of chloride channel opening, without affecting frequency of opening or channel conductance (Czapinski, et al., 2005, Kwan, et al., 2001). PB has also been shown to elicit their antiepileptic effect by directly blocking high-voltage-activated Ca^{2+}

channels and inhibiting AMPA/kainate receptors, preventing depolarization of neurons, propagation of the aberrant signals, and the cascade of damaging secondary events within the cell (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001, Sullivan, 2005). This AED is unique due to its ability to activate $GABA_A$ receptors in the absence of exogenous GABA, and that this augmentation of GABA-mediated inhibition and inhibition of glutamate-mediated excitation is selective for the postsynaptic terminal (Kwan, et al., 2001, Pellock, et al., 2001). It has also been suggested that PB locks Na^+ channels, together with its modulation of GABA receptors it induces its anticonvulsive action by inhibition of glutamate activation (Pellock, et al., 2001, Rho, et al., 2004, Sullivan, 2005, Trojnar, et al., 2002). PB has showed great efficacy in attenuating seizure and is generally a safe medication with a prolonged treatment duration of action, however, there are still cognitive and behavioral side effects, as well as increased hepatic enzyme activation effecting the concomitant administration of additional AEDs, limiting its use in some situations (Gibbs, et al., 2006, Pellock, et al., 2001). There have been conflicting studies describing PB as both neuroprotective and neurodegenerative after SE, however its neurodegenerative effect may be isolated to the developing brain where mitochondrial degeneration, deficits in hippocampal based behavior measurements, and myelin degradation have been found with PB administration early in life (Sankar and Holmes, 2004, Trojnar, et al., 2002).

Along with PB, Benzodiazepines, which have more than 50 distinct family members including Diazepam, Loarazapam, Midazolam, and Clonazepam, represent the first line treatments for SE and have abroad spectrum of clinical activity used mainly for partial and idiopathic generalized epilepsies, complex seizures, secondary generalized motor seizures, and acute SE (Gibbs, et al., 2006, Pellock, et al., 2001). This class of drugs also bind to the $GABA_A$ receptor subtype at the allosteric binding site on the α-subunit inducing an increase in the frequency of Cl^- channel opening, however they are unable to activate these receptors in the absence of endogenous GABA (Czapinski, et al., 2005, Gibbs, et al., 2006, Granja, et al., 1997, Pellock, et al., 2001). It has also been shown that BZDs can also block Na^+ channels at high concentrations encountered during intensive treatment of acute SE (Czapinski, et al., 2005).They work to lower seizure threshold in order to decrease the duration of erroneous discharges thereby limiting the spread of the aberrant excitation to adjacent brain regions. This type of AED is marked for its consistency in efficacy, however they are susceptible to tolerance development and have been shown to exacerbate neuronal damage in some experimental models, limiting their use in chronic seizure disorder patients (Gibbs, et al., 2006, Pellock, et al., 2001). Much like the action of PB, these drugs seem to have an altered neuroprotective function depending on neuronal development, where as in mature animals BZDs have been shown to be neuroprotective, in immature animals these same compounds show a dose-dependent induction of apoptotic cell death (Sankar and Holmes, 2004, Sullivan, 2005, Trojnar, et al., 2002).

Vigabatrin and Tiagabine were designed as a new generation of novel AED intended to regulate GABA metabolism by either acting as an irreversible inhibitor of (GABA-T) GABA transaminase (VGB) or inhibiting glial/neuronal uptake of GABA (TGB) both resulting in increased and prolonged duration of GABA signaling (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001, Trojnar, et al., 2002). VGB, a structural GABA analogue, actually uses GABA-T to enzymaticly transform in to its active metabolite, which then irreversibly binds to GABA-T and acts to inhibit its ability to degrade GABA, causing a prolonged increase in GABA levels throughout the brain, without manipulating any other GABA

synthesis or metabolic enzymes (Kwan, et al., 2001). TGB inhibits GABA reuptake from the synaptic cleft by selectively blocking the GAT-1, a GABA transporter, without affecting GAT-2, GAT-3, or GBT-1; allowing its affects to be localized primarily to the cerebral cortex and the hippocampus (Kwan, et al., 2001). Both TGB and VGB were designer drugs targeted at specific aspects of the GABAergic system and have been shown to be protective against seizure and neurodegeneration; however, like PB and BDZ there is also evidence that they are detrimental to the developing nervous system (Kwan, et al., 2001, Pellock, et al., 2001, Trojnar, et al., 2002). VGB administration for refractory epilepsy in children and infantile spasms has presented a pronounced prevalence (~40%) retinal toxicity and development of visual field defects, and as a result its use has declined worldwide in younger patients (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001).

With any AEDs whose primary action is prolonging the duration of inhibition by the GABAergic system, symptoms such as, drowsiness, dizziness, agitation, amnesia, fatigue, depression, weight gain, ataxia, and nystagmus are prevalent in patients with prolonged use. These drugs have been shown to be efficacious in attenuating seizures and have shown potential in promoting neuroprotection; however, the key to their effectiveness will be the regulation of their administration to children due to their age specific effects on the developing brain.

6.2 Ion channel modulators

Recently developed AEDs have been designed to modulate specific ion channels to prevent aberrant and prolonged excitation. Na^+ channels blockers such as Phenytoin (PHT) and Carbamazepine (CBZ), Ca^{2+} blockers such as Ethosuximide (ESM), or Na^+/Ca^{2+} (L-Type) channel blockers such as Lamotrigine (LTG), Oxcarbazepine (OXC), and Zonisamide (ZNS), were introduced to replace the sedative GABAergic modulating AEDs (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001, Sullivan, 2005). Blockage of Na^+ channels reduces the ability of neurons to undergo multiple rapid excitations resulting in increased instances of prolonged depolarization propagated by the activation of voltage-dependent Na^+ channels, and increased cellular swelling via Cl^- influx, ultimately leading to cellular damage and dysfunction (Kwan, et al., 2001, Sullivan, 2005). Increased Ca^{2+} influx is also a result of prolonged excitation, which causes increased excitatory amino acid (EAA) release from the presynaptic membrane into the synaptic cleft, resulting in further dissemination the aberrant excitatory activation to surrounding brain regions, inducing cellular damage via secondary signaling cascades (Brookes, et al., 2004, Kwan, et al., 2001, Nicholls and Budd, 2000, Nicholls and Ferguson, 2002, Pellock, et al., 2001).

PHT and CBZ share the selective mechanism of Na^+ channel inhibition, which decreases the frequency of depolarization, thereby decreasing the amount of irregular signal transmissions. In the case of PHT, it is the most effective when there is a high frequency of depolarization, which is an important feature of this mechanism; instead of completely inhibiting activation it works to minimize only excessive neuronal activity (Kwan, et al., 2001). Also, PHT is generally the most well tolerated AED, side effects are common due to its unique non-linear elimination kinetics, but these symptoms can normally be attenuated with proper dose adjustments (Pellock, et al., 2001). There are also a few reports suggesting that PHT functions by blocking high voltage Ca^{2+} channels and may be involved in GABAergic modulation, however this evidence has yet to be fully substantiated (Granger, et al., 1995, Kwan, et al., 2001, Rowley, et al., 1995). CBZ, which is effective in focal (partial)

and grand mal (tonic-clonic) seizures and exclusively blocks Na^+ channels, seems to be less effective as a neuroprotective agent than other anticonvulsant compounds in treating SE, but was shown to have increased protection for ischemia/traumatic insult (Czapinski, et al., 2005, Pellock, et al., 2001). Neurotoxicity of CBZ, like PHT, was only found when the administrated dose was at supra-therapeutic concentrations (Czapinski, et al., 2005, Pellock, et al., 2001, Sullivan, 2005).

OXC is a structural analogue of CBZ, however due to modifications designed to prevent the production of the 10,11-epoxide metabolite, it is more easily tolerated by the patient and shows a decreased level of side effects compared to CBZ (Kwan, et al., 2001, Pellock, et al., 2001). It has the ability to block both Na^+ and L-type Ca^{2+} channels, and has an additional possibly unique function of increasing K^+ channel conductance, all of which leads to decreased excitation and excitotoxic signaling cascades (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001). Retigabine (RTB) functions as an anticonvulsant by decreasing the activation threshold of neurons via activation of K^+ channels and increasing GABA-mediated Cl^- currents (Czapinski, et al., 2005). ZNS, which is one of the only drugs specifically evaluated for the pediatric patient population, also blocks both Na^+ and Ca^{2+} channels, GABA receptor linked Cl^- channels, enhances dopaminergic/serotonergic neurotransmission, and inhibits glutamate-induced excitation (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001). In addition to its antiepileptic and anticonvulsant effects, ZNS also decreases the production of exogenous nitric oxide and free radicals, giving it a unique neuroprotective quality against oxidative stress resulting from prolonged SE (Czapinski, et al., 2005). LTG is a novel AED, effective in blocking both Na^+ (primarily slow inactivated state) and L-type Ca^{2+} channels, which is efficacious in treating partial, absence, myoclonic and tonic-clonic seizures (Kwan, et al., 2001, Pellock, et al., 2001, Trojnar, et al., 2002). ESM is unique from other ion channel modulators in that it is specific for T-type Ca^{2+} channel blockage, and does not have any other known mechanism (Kwan, et al., 2001). It has been used for many years for generalized absence seizures, due to its ability to prevent the characteristic T-type Ca^{2+} channel induced synchronized 3-Hz spike-and-wave discharge (Kwan, et al., 2001).

6.3 Multi-mechanistic AEDs

There have been many AEDs developed with multiple mechanisms of action to attenuate seizure activity. One of the most studied and widely used multi-mechanistic AED is valproic acid (VPA), however, the exact mechanism of its anticonvulsant action is still debated, and in fact may be a number of different mechanisms (Kwan, et al., 2001, Pellock, et al., 2001). It has proven to be effective in treating a range of disorders in addition to epilepsy, including bipolar effective disorder and migraine headaches (Schulpis, et al., 2006). The possible mechanisms include, the modulation of the GABAergic system by modulation of either inhibition of GABA-T and succinic semialdehyde dehydrogensase or the increase of glutamic acid dehydrogenase, which work to either inhibit GABA breakdown or elevate GABA synthesis (respectively), however the later is thought unlikely to be the primary mechanism (Czapinski, et al., 2005, Pellock, et al., 2001). VPA has also been shown to block voltage-dependent Na^+ channels, thereby reducing sustained repetitive firing of neurons, however it does not exert an effect on the recovery of Na^+ channels from the inactivated state (Kwan, et al., 2001, Pellock, et al., 2001). This AED also has similar effects on T-type Ca^{2+} channels as does ESM, which may account for its efficacy in specifically treating

absence seizures (Kwan, et al., 2001, Trojnar, et al., 2002). However, recent studies have shown that chronic VP administration can cause some side effects including increased free radical formation (ROS) and oxidative DNA damage, impairment of liver mitochondrial function, hepatotoxicity, and increased serum lipids, lipoproteins and Apo lipoproteins increasing the risk of cardiovascular problems (Karikas, et al., 2006, Schulpis, et al., 2001, Schulpis, et al., 2006).

GBP is a structural analogue of GABA designed to be a blood brain barrier permeable mimetic of GABA activation of GABA receptors inducing an increase in the activation of the GABAergic system. However, studies using binding assays show that there is not affinity for GBP for either $GABA_A$ or $GABA_B$ receptors; instead there is evidence that GBP acts through interactions with the L-amino acid transport system, reducing high frequency action potential firing via Na^+ channel blockage, possible modulation of GABA metabolism, and blockage of L-type voltage dependent Ca^{2+} channels (Czapinski, et al., 2005, Kwan, et al., 2001, Pellock, et al., 2001). Both Felbamate (FBM) and Topiramate (TPM), also multi-mechanistic AEDs, can inhibit neuronal activation by the EAA glutamate (Czapinski, et al., 2005). FBM, which is used clinically to treat a wide variety of seizure disorders, can have dual actions on excitatory and inhibitory neuronal mechanisms, as highlighted by the conflicting studies showing the lack of ligand binding to the GABA receptor and increases in GABA-mediated responses, as well as the inhibition of NMDA-linked excitation (Pellock, et al., 2001). TPM, however, has clearly been shown to block Na^+ channels, increase GABAergic-mediated inhibition, and antagonize glutamate activation of both NMDA and AMPA/kainate receptors (Pellock, et al., 2001). Both FBM and TPM have good clinical efficacy in reducing seizure and have a low incidence of tolerance development, which makes these AEDs more ideal for the treatment of chronic epileptic disorders.

6.4 Unknown mechanism

There are still more compounds being investigated for their potential antiepileptic properties, however the mechanism of some of these AEDs have not fully been elucidated. One such compound, Levetiracetam (LEV), is an analogue of piracetam and has been used and has shown great promise as an anticonvulsant pharmacological therapy; however, its exact mechanism of conferring this anticonvulsant action is currently known. Studies have shown that LEV has little to no effect on increasing the inhibitory effect of the GABAergic system, and it has been inferred that it has a completely unique activity profile that is unlike any of the AEDs mechanisms that have come before it, including Na^+ and Ca^{2+}channel blockage, K^+ channel activation, and GABA/glutamate system modulation (Gibbs, et al., 2006, Kwan, et al., 2001, Pellock, et al., 2001). Perhaps the most interesting property of LEV is that it has exhibited neuroprotective effects after experimentally induced SE; and has been shown to attenuate seizure severity. In addition to this attenuation, decrease damage to many vital mitochondrial proteins, such as α-keto-glutarate dehydrogenase, complex I, Aconitase, citrate synthase, and GSH has been shown with LEV treatment; which seems indicate an ability to attenuate oxidative damage and mitochondria dysfunction resulting from prolonged seizure induced excitation (Kwan, et al., 2001, Mazarati, et al., 1998). This suggests that LEV acts to not only prevent the damaging epileptic episode, but also to promote intracellular/intramitochondrial reparative mechanisms. The elucidation of this mechanism of anticonvulsive neuroprotection is could result in a wider administration of LEV, and has the potential to lead to the development of an entirely new class of AEDs with similar neuroprotective effects.

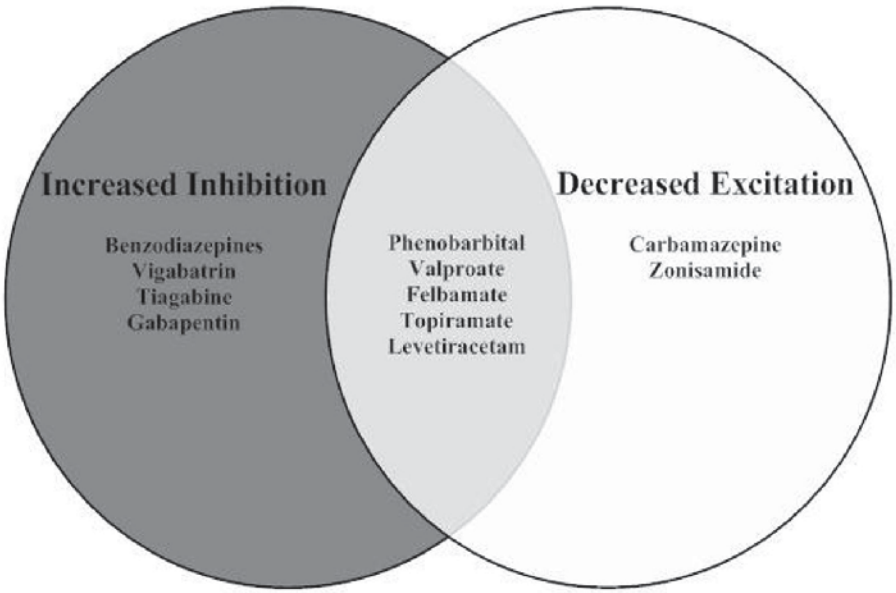

Fig. 2. Effects of commonly used AEDs.

7. Antioxidants

Antioxidant therapy following seizure has been shown to be beneficial (Acharya, et al., 2008). Resveratrol is a naturally occurring antioxidant and has been shown to decrease hippocampal neuronal cell death and decrease mossy fiber sprouting following kainite-induced temporal lobe epilepsy (Wu, et al., 2009). Other antioxidants, such as ascorbic acid and α-tocopherol, have been shown to decrease neuronal cell death following seizure induced with pilocarpine (Tome Ada, et al., 2010). Additionally, the naturally occurring antioxidant melatonin has been shown to be neuroprotective in human epilepsy (Molina-Carballo, et al., 1997). Thus, oxidative stress is one potential target for neuroprotective intervention following seizure.

8. Alternative non-pharmacological treatments

An alternative to pharmacological interventions is the implementation of the ketogenic diet (KD), originally designed physiological effects that occur as a result of fasting, such as ketosis, in order to mimic its protective outcomes. Fasting, which has been used for centuries as an unproven method for controlling seizure disorders, primarily results in increased levels of ketone bodies and causes the body begin using stored fat as the primary energy source as opposed to glucose (Thiele, 2003, Ziegler, et al., 2003). The KD was developed as way to mimic both the increase in ketone bodies and shift of metabolic utilization without depriving patients of essential nutrients and energy. The regime requires a shift in the ratio of fat: carbohydrate consumption from roughly 1:2 to 4:1 (Rho, et al., 2004, Thiele, 2003). Many versions of the ketogenic diet have been examined for efficacy in attenuating seizure, of which the program shown to have the best efficacy is a reduced calorie regime combined with the increased fat: carbohydrate ratio (Rho, et al., 2004).

Although, the mechanism of the KD is not fully understood; it has been shown to increase antioxidant enzymes, such as glutathione peroxidase (GPx), as well as upregulate specialized mitochondrial uncoupling proteins (fig. 3) thereby reducing ROS and oxidative damage by supporting the endogenous antioxidant system as well as decreasing the amount of ROS actually produced. (Sullivan, et al., 2004). The reduction of ROS and oxidative damage, coupled with preferential utilization of an efficient energy source (ketone bodies), in neuronal tissue could explain how this treatment proves to be an effective therapy for epileptic seizure, however, the rigorous constraints on caloric intake has been a stumbling block for its wide spread implementation, most patients opting for an alternative pharmacological treatment (Rho, et al., 2004)

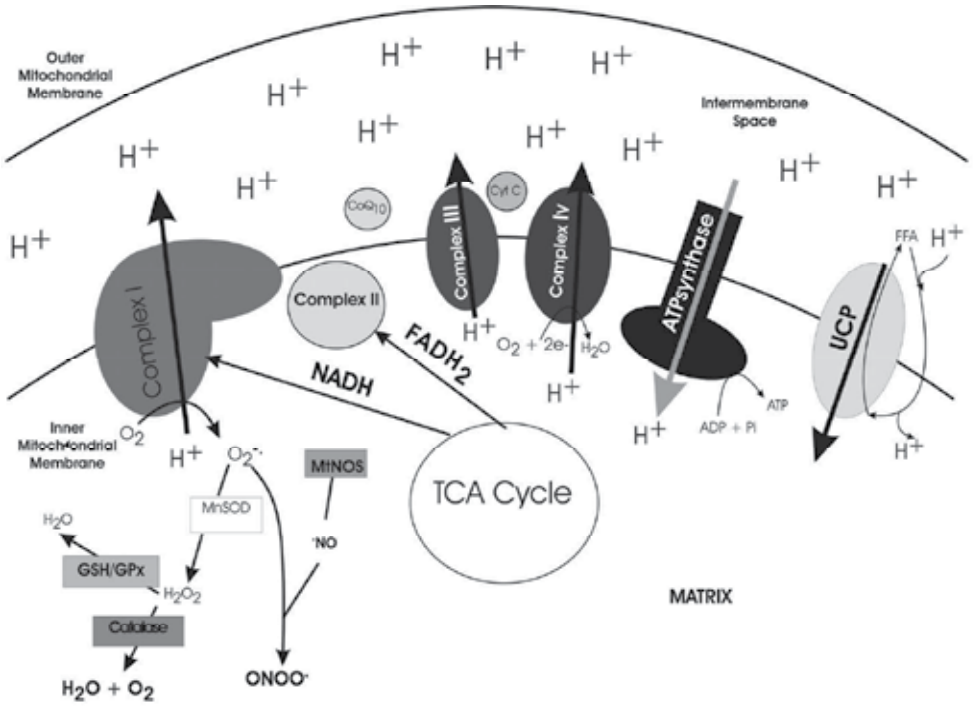

Fig. 3. This is a schematic of the mitochondrial electron transport chain (ETC). Electrons are donated by reducing agents (NADH and FADHH) which flow down the ETC causing the pumping of protons (H+) into the intermembrane space, thereby creating a proton gradient (separation of charge). It is by this mechanism that the cell is able to produce energy in the form of ATP by utilizing this proton gradient to phosphorylate ADP to ATP via Complex V (ATPsynthase). Oxidative phosphorylation produces reactive oxygen species (ROS) as a normal byproduct of physiological function. ROS is mostly produced at Complex I; however it can be produced at Complex III/IV (via the same mechanism pictured at Complex I) as well. Endogenous antioxidant systems such as GSH and MnSOD prevent the formation of peroxynitrite ($ONOO^{\cdot}$) which can lead to mitochondrial and cellular damage/dysfunction. Uncoupling Proteins (UCP) can dissipate the proton gradient by translocating protons from the intermembrane space to the mitochondrial matrix in response to activation by free fatty acids (FFA).

9. Conclusion

Most of the AEDs discussed in this chapter are effective treatments for a wide range of seizure disorders; however each has their distinct pros and cons. There are some AEDs that are better to administer in a pediatric setting, where as others will work better for patients with chronic seizure disorders. Most, if not all, depend on the proper dosing to achieve their optimum treatment effect. Only when the therapeutic dose is surpassed is there an increased risk of potential side effects that may terminate that avenue of treatment options.

It has been shown that there is a correlation between seizure development and oxidative damage, which in turn causes a state of hyper-excitability causing the initiation of future seizures due to the increased sensitivity to excitation. It has become apparent that mitochondria are intimately involved in this mechanism due to the involvement of mitochondrial superoxide dismutase (MnSOD) in the attenuation of seizure induced oxidative damage (Liang and Patel, 2004). The attenuation of this oxidative damage could lead to a decrease in the initiation of prolonged seizures and further oxidative damage, thereby ending this vicious cycle. Therapeutic interventions and AEDs designed to attenuate oxidative damage and decrease the total level of excitation to reduce the incidence of seizure and the amount of subsequent damage will be the most beneficial. AEDs that provide neuroprotection, in addition to their anticonvulsant properties, are currently in use and should be further studied so that other treatments may be developed with neuroprotection, not only attenuation of SE, in mind.

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7

Zonisamide – An Overview

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1. Introduction

Zonisamide, a 1,2 benzisoxazole derivative is a structurally novel antiepileptic drug (AED) with a broad spectrum of antiseizure activity. [1,2]Zonisamide has been available in Japan since 1989, where it is widely used both as monotherapy and adjunctive therapy (i.e. as Add on) for various seizure types and syndromes in adults and children.[3,4]

In the United States, clinical trials of zonisamide began in the early1980s. These studies provided clear evidence of zonisamide's promise as an effective adjunctive therapy for refractory partial seizures. Leppik et al. observed a 52% reduction in seizure frequency in a historical-control, open-label, multicenter study. However, development of kidney stones in 3.7% of patients enrolled in this study led to the temporary termination of US development efforts. Testing resumed in the 1990s, and zonisamide was approved by the US Food and Drug Administration (FDA) in March 2000 as adjunctive treatment for refractory partial-onset seizures in adults(aged>16years).[5]

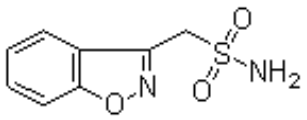
Results from placebo-controlled, short-term studies, as well as baseline- or historical-controlled, long-term studies, demonstrate that zonisamide is an effective adjunctive treatment for refractory partial- onset seizures. Zonisamide efficacy did not decline over time, suggesting that most patients do not develop tolerance to the anticonvulsant effects of zonisamide. Findings from one of the long-term studies indicate that, for some patients, zonisamide can be effective as monotherapy.[7]

Zonisamide was well-tolerated; most adverse events were mild to moderate, and their incidence declined as treatment continued. The few serious adverse events were all reversible with zonisamide dose reduction or discontinuation or the passage of time. US clinical trials show that zonisamide is a safe and effective AED for the treatment of refractory partial-onset seizures. Further studies are needed to establish monotherapy efficacy in epilepsy.

The potential use of zonisamide in non epileptic conditions like neuropathic pain, migraine prophylaxis [2] and Parkinsonism [6] are briefly touched in this review.

2. Basic structure and chemistry[58]

1-(1, 2-Benzoxazol-3-yl) methanesulphonamide

Molecular Structure	
Molecular Formula	C8H8N2O3S
Molecular Weight	212.23
Appearance	White powder
pKa	10.2
Solubility	moderately soluble in water (0.80 mg/mL)
Melting point	161-163 oC
Isoelectric Point	10.2

Phase 1. Metabolising Enzyme (1-st Step of Metabolism) CYP3A4

3. Overview of pharmacodynamic properties

A brief overview of pharmacodynamic properties including mechanism of action is discussed here.[1,3, 6]

Mechanism of action: The precise mechanism is still unclear[5] but various proposed mechanisms based on various animal and cellular studies are listed below.

A. Membrane stabilisation through,

1. Blockade of voltage-dependent T-type calcium channels and
2. Blockade of voltage-sensitive sodium channels.

B. Neuro modulation by

1. Blockade of potassium-evoked glutamate response
2. Reduction of glutamate-mediated synaptic excitation
3. Increased γ -amino butyric acid (GABA) release and
4. Facilitation of Dopaminergic and serotonergic transmission and

C. Neuroprotection By free radical scavenging.[2,3,6]

Despite the presence of a sulphamoyl group in its chemical structure, zonisamide is only a weak inhibitor of carbonic anhydrase [3]and it is 100–200 times less potent than acetazolamide[5,8].In contrast to acetazolamide, this effect does not contribute to the antiepileptic activity of zonisamide.[8]

4. Overview of pharmacokinetic properties

The pharmaco kinetic profile is extensively studied from healthy volunteers from U.S, Japan and Europe. The data are published in various reviews [1,3,7.9-12] as well as in conference abstracts.[13-16]

Zonisamide is absorbed relatively rapidly from the gastrointestinal (GI) tract; a peak plasma concentration (Cmax) of 3 micrograms/mL was reached 4–5 hours after a 200mg dose in healthy volunteers in Japan[17,18].In contrast, Cmax values ranging from 2.3 micrograms/mL after a 200mg dose to 12.5 micrograms/mL after an 800mg dose were reached within 2.4–3.6

hours in healthy volunteers in the United States.[20].The oral bioavailability of zonisamide is 100%[19].Food consumption does not influence the extent of zonisamide absorption, although the time to Cmax is delayed, occurring at 4–6 hours.[5]

Zonisamide steady-state plasma concentrations are achieved within 14 days.[5]In patients with epilepsy in Japan, zonisamide steady-state plasma concentrations increased linearly with increasing dose in the zonisamide dosages of up to 13 mg/kg/day in children and 18.6 mg/kg/day in adults.[22] On the other hand, zonisamide appeared to demonstrate non linear pharmacokinetics in healthy volunteers[20] and patients with epilepsy in the US.[23-25]

Zonisamide is distributed relatively evenly throughout the whole body; the apparent volume of distribution is 1.45 L/kg following a 400mg oral dose[5].The drug is not highly bound to plasma proteins (40–60%).However, zonisamide has a high affinity for erythrocytes, with concentrations in these cells exceeding those in plasma by 4- to 9-fold in healthy volunteers in Japan.[7,18]

Zonisamide undergoes hepatic metabolism and is primary route of excretion is by the kidneys.[5]After oral administration, inactive zonisamide metabolites identified in the urine, but not in the plasma, include *N*-acetyl-zonisamide and the glucuronide conjugate of the open isoxazole ring metabolite 2-sulphamoylacetyl phenol (SMAP). Acetylation of zonisamide is mediated by *N*-acetyltransferase,[9] while reduction to SMAP is mediated by the cytochrome P450 isoenzyme 3A4.[5]

Zonisamide has a long terminal elimination half- life (50–68 hours in plasma and 105 hours in erythrocytes) after administration of single oral 200–800mg doses in healthy volunteers in Japan and/or the US .Overall, 62% of the administered dose was recovered in the urine and 3% in the faeces. The pharmacokinetics of zonisamide were not altered to a clinically significant extent when compared in young (mean age 28 years) and elderly (mean age 69 years) healthy volunteers suggesting that dosage adjustment is not necessary in patients of advanced age.

Dosing data from a meta-analysis of 1008 patients in Japan (403 children and 605 adults) suggest that zonisamide clearance is moderately higher in children than in adults.[57] In a single-dose study, the renal clearance of zonisamide decreased with decreasing renal function; marked renal impairment was associated with a 35% increase in the zonisamide area under plasma concentration curve. The US manufacturers' prescribing information recommends caution, but not dosage adjustment, in patients with hepatic or renal disease.

5. Therapeutic efficacy

5.1 Add-on therapy in adults

A Randomized, Double-blind, Placebo-controlled Study in Patients with Refractory Partial Seizures-Martin J. Brodie et al states that ZNS provides dose-dependent, effective, and generally well-tolerated adjunctive therapy in patients with partial seizures [26]

Review of United States and European clinical trials of zonisamide in the treatment of refractory partial-onset seizures done by Edward Faught et al [27]: Results from placebo-controlled, short-term studies, as well as baseline- or historical-controlled, long-term studies, demonstrate that zonisamide is an effective adjunctive treatment for refractory partial- onset seizures. Zonisamide efficacy did not decline over time, suggesting that most patients do not develop tolerance to the anticonvulsant effects of zonisamide. Findings from one of the long-term studies indicate that, for some patients, zonisamide can be effective as monotherapy. Zonisamide was well-tolerated; most adverse events were mild to moderate, and their incidence declined as treatment continued. The few serious adverse events were

all reversible with zonisamide dose reduction or discontinuation or the passage of time. US clinical trials show that zonisamide is a safe and effective AED for the treatment of refractory partial-onset seizures. Further studies are needed to establish monotherapy efficacy.

Practical prescribing and long-term efficacy and safety of zonisamide by Ilo E. Leppik et al [28]: A range of clinical studies and extensive clinical experience have demonstrated the long-term efficacy and tolerability of zonisamide in the treatment of refractory partial seizures. Substantial patient benefit is maintained during continued administration of zonisamide, including sustained decreases in seizure frequency for many patients and attainment of seizure freedom for a substantial number of individuals. Careful patient management can optimise these benefits whilst minimising risks of any AEs. Clinical experience in the US indicates that the benefits of zonisamide may extend across a range of seizure types. These observations suggest that zonisamide is an efficacious and well tolerated treatment option for the long-term management of many types of epilepsy.

Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide - William A. Tosches et al[29]: In this study, zonisamide, when used as monotherapy or concomitant therapy, proved effective as an anticonvulsant and was well tolerated over time.

According to a Cochrane data base review done in 2005[30], Zonisamide has efficacy as an add-on treatment in people with drug-resistant partial epilepsy. Minimum effective and maximum tolerated doses cannot be identified. The trials reviewed were of 12 week duration and results cannot be used to confirm longer periods of effectiveness in seizure control. The results cannot be extrapolated to monotherapy or to people with other seizure types or epilepsy syndromes.

In four short-term (24 weeks), placebo-controlled trials conducted in the US or Europe (n = 138–351), once- or twice-daily administration of zonisamide at dosages of >300 mg/day was mostly effective in the treatment of patients with medically refractory partial seizures, with or without secondary generalisation to tonic-clonic seizures, based on significantly greater reductions in median seizure frequency for all partial seizures, for complex partial seizures only and for all seizure types. The corresponding responder rates (i.e. patients achieving a >50% reduction from baseline in seizure frequency) in zonisamide >400 mg/day recipients were generally significantly greater than with placebo. When assessed in two of the above-mentioned trials, twice-daily administration of zonisamide 100 or 200 mg/day was mostly effective in one study, whereas 100 mg/day was not effective in the other.

Longer term, the antiepileptic efficacy of zonisamide was maintained in patients who continued therapy for up to 2 years, with no evidence of tachyphylaxis or pharmacological tolerance.

The efficacy of zonisamide at mean dosages of 5.9–8.8 mg/kg/day was demonstrated in a total of 1008 adults or children in Japan with various types of epilepsy mainly refractory to treatment who were recruited to a series of predominantly non-comparative clinical trials. In the only active comparator-controlled study performed to date, zonisamide (mean dosage 330 mg/day) was judged to be as effective as carbamazepine (mean dosage 600 mg/day) in Japanese patients with predominantly partial epilepsies.

5.2 Add-on therapy in children

There has been extensive clinical trial and clinical practice experience with zonisamide therapy in Japanese children. Open-label data from pediatric clinical trials conducted in Japan suggest that zonisamide is well tolerated and effective against partial- and

generalized-onset seizures in children. Despite this wealth of open-label data, no formal pharmacokinetic studies and only one well-controlled trial of zonisamide's efficacy and safety in Japanese children have been completed to date. No controlled clinical trials of zonisamide in children have been completed in the United States or Europe[31]

5.3 Monotherapy in children

Tohru Sekia32 did a study on seventy-seven children with epilepsy (ages 8 months–15 years) who were treated with zonisamide. Nine patients were withdrawn early because of side effects; these patients were included in side effect but not efficacy analyses. Zonisamide dosages were initiated at approximately 2 mg/kg per day and adjusted for each patient individually to a maximum of 12 mg/kg per day. Among 44 patients with cryptogenic/symptomatic partial epilepsy, 36 (82%) became seizure free; 4 (9%) had a ≥50% reduction in seizure frequency; and 4 (9%) had no change in seizures with zonisamide treatment. Of 11 patients with cryptogenic/symptomatic generalized epilepsy, 10 (91%) became seizure free, and 1 experienced no change with zonisamide treatment. Similarly, 4 patients (100%) with idiopathic partial epilepsy, and 8 of 9 patients (89%) with idiopathic generalized epilepsy became seizure free with zonisamide treatment; in the last group, 1 experienced no change. Thirty patients (39%) reported side effects, including somnolence (11.7%), decreased spontaneity (7.8%), anorexia (6.5%), and rash (6.5%). Thus, zonisamide is effective for partial seizures with or without secondarily generalized seizures in children and should be considered a broad-spectrum antiepilepsy agent.

There has been extensive clinical trial and clinical practice experience with zonisamide therapy in Japanese children. Open-label data from paediatric clinical trials conducted in Japan suggest that zonisamide is well tolerated and effective against partial- and generalized-onset seizures in children. Despite this wealth of open-label data, no formal pharmacokinetic studies and only one well-controlled trial of zonisamide's efficacy and safety in Japanese children have been completed to date. No controlled clinical trials of zonisamide in children have been completed in the United States or Europe.

5.4 Monotherapy in adults

Angus A. Wilfong[33] in his several small, open-label studies have indicated that it may be safe and effective as monotherapy. This present chart review study was conducted to evaluate the safety and effectiveness of zonisamide monotherapy in a paediatric and young adult patient group. Patient records at the Blue Bird Circle Clinic for Paediatric Neurology were reviewed to identify patients receiving zonisamide monotherapy. Efficacy was assessed from seizure diaries and patients' subjective evaluations. Safety and tolerability were evaluated by analysis of adverse events and change in body weight. The study included 131 patients aged 1 to 21.8 years with a broad spectrum of seizure types and epilepsy syndromes. A total of 101 patients (77.1%) achieved a 50% or greater decrease in seizure frequency, including 39 patients who achieved seizure freedom. Zonisamide monotherapy was well tolerated, with three patients (2.3%) discontinuing for adverse events. These results support open-label studies from Japan reporting that zonisamide monotherapy is safe and effective in paediatric and young adult patients.

Pooled analyses of open-label studies[34] specifically in young adults and/or children showed zonisamide to be effective as adjunctive therapy for refractory partial seizures (dosage of 2.0–18.6 mg/kg/day) and as monotherapy for newly diagnosed or refractory partial seizures (dosage of 1–12 mg/kg/day).

6. Specific categories of seizures

1. Post-operative seizures - Zonisamide, an agent with antiepileptogenic, free radical scavenging and neuroprotective actions in experimental animals, showed promising effects against postoperative epilepsy in a randomized double blind controlled trial.[36]
2. Myoclonic epilepsy - zonisamide may be useful in the treatment of patients with PME. Studies have found it to be useful in Unverricht-lundborg disease[37].
3. West syndrome
4. Brain tumour related epilepsy[38]

7. Tolerability and adverse effects

Zonisamide was generally well tolerated as adjunctive therapy in patients (n = 499) with refractory partial seizures enrolled in placebo-controlled trials conducted in the US and Europe[35], and as adjunctive therapy or monotherapy in adults or children in Japan (n = 1008) with various types of epilepsy recruited in predominantly non-comparative clinical trials. The most frequently occurring adverse events common to these studies were somnolence, anorexia, ataxia, gastrointestinal discomfort/abdominal pain, mental slowing, weight loss and skin rash/itch.

Adverse events usually occurred early during treatment (within 4 weeks), were generally of mild-to-moderate intensity, and decreased with time in the US and European studies. Patient tolerability of zonisamide was optimised during slow titration from low initial dosages to therapeutic dosages over 4–8 weeks.

The tolerability profile of zonisamide in a Japanese study was generally similar to that of carbamazepine, although anorexia occurred more frequently with zonisamide, and ataxia was noted more frequently with carbamazepine.

Patients mainly in the US and Europe appear to be at increased risk of developing kidney stones (incidence equivalent to 18 cases per 1000 patient-years of exposure), while paediatric patients, in particular, appear to be at increased risk of zonisamide-associated oligohidrosis/hyperthermia (estimated reporting rate 1–2 cases per 10 000 patient-years of exposure).

7.1 Adverse effects

All seizure medicines affect the amount of activity by brain cells, and carry dose-related risks of:

- fatigue/somnolence (usually within the first month of treatment and at higher doses)
- psychiatric symptoms
- depression
- psychosis
- cognitive symptoms
- impaired concentration
- speech problems (especially word-finding difficulties)
- psychomotor slowing

7.2 Allergy and hypersensitivity

Zonisamide is a sulfonamide medication. Life-threatening allergies to sulfonamide medications can occur, including

- Stevens-Johnson syndrome

- toxic epidermal necrolysis
- aplastic anaemia
- agranulocytosis
- other blood dyscrasias
- fulminant hepatic necrosis

Zonisamide should be discontinued immediately in any patient with signs of hypersensitivity reaction. Any rash that develops during zonisamide treatment should be monitored carefully, and discontinuation should be strongly considered. Deaths due to serious rashes have been reported. Rash is most common in the first 2-16 weeks of treatment.

7.3 Metabolic acidosis

The FDA identified that zonisamide can cause metabolic acidosis in some patients. The acidosis is characterized by:

- Elevated serum chloride and reduced serum bicarbonate
- Greater apparent risk early in treatment (but it can arise later)
- Greater risk with increased dose (but acidosis has been observed with doses as low as 25 mg daily)
- Children are at greater risk of acidosis than adults.

Risk factors include

- Kidney disease
- Severe respiratory disorders
- Diarrhoea
- Ketogenic diet
- Drug interactions

Metabolic acidosis may be asymptomatic, but can be accompanied by symptoms of:

- Hyperventilation
- Fatigue
- Anorexia
- Cardiac arrhythmias

Identification and treatment of metabolic acidosis is important, because it can increase the risk of:

- Kidney stones
- Nephrocalcinosis
- Bone abnormalities (with increased risk of fracture)
- Growth delay
- Abnormal foetal development.

The FDA recommends treatment of acidosis if it occurs:

- Consider either reducing the dose or discontinuing the drug and modifying the patient's anti-epileptic treatment
- If a patient with metabolic acidosis is to continue on zonisamide, consider treatment with alkali.

7.4 Oligohydrosis/hyperthermia

Oligohydrosis, characterised by decreased sweating and elevation in body temperature above normal, has been noted in rare cases. Risk factors appear to be the paediatric age group, a high level of physical activity and a high ambient temperature. The occurrence of oligohydrosis during treatment may be related to weak inhibition of carbonic anhydrase by

zonisamide as similar effects have been described following treatment with topiramate and acetazolamide, which are known to possess this mechanism. Cautioning parents of this rare effect, combined with monitoring in warm climates or hot weather, and ensuring that patients remain cool and well hydrated, should help to minimise the risk of oligohydrosis

7.5 Kidney stones

The rate of new kidney stones is approximately 18 per 1000 patient-years; with a relative risk five to nine times that of the general population. The risk of renal stones appears to be greater with higher doses and longer duration of treatment. Increased fluid intake is likely to reduce the risk of renal stones through limitation of tubular precipitation and aiding passage of any calculi, and fluid intake should be encouraged to get specific gravity to 1.010.

7.6 Appetite/weight loss

Mean weight loss was <1.7 kg and the majority of weight decreases are <5 kg in pivotal studies. The changes in body weight did not appear to be progressive in the clinical trial population, and remain stable over periods of up to 2 years. Weight loss has been confirmed by clinical experience with women losing more weight than men. Weight loss has been observed even when zonisamide is used in conjunction with valproate

7.7 Suicide

The FDA has issued a general warning regarding anticonvulsants and suicide, which applies to zonisamide. Children (especially adolescents and young adults) taking zonisamide should be monitored closely by their parents for any notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression

7.8 Teratogenicity

Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of foetal abnormalities, including cardiovascular defects, and embryo-foetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of Zonisamide Capsules during pregnancy in humans may present a significant risk to the foetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

8. Dosage and administration[39]

8.1 Infants and children

Initial: 1-2 mg/kg/day given in two divided doses/day (although in more urgent settings, up to 4 mg/kg/d to start may be tolerated)
Increase by 0.5-1 mg/kg/day every 2 weeks
Goal dose: 5-8 mg/kg/day
Max dose: ~12 mg/kg/day
(Glauser 2002; Leppik, 1999; Oommen, 1999)

8.2 Adolescents and adults

Initial: 100 mg once daily for 1 week, then 200mg once daily
Titration: Increase in increments of 100 mg/day if needed for seizure control, with a minimum of 2 weeks between adjustments
Usual effective dose: 100-600 mg/day
There is no evidence of increased benefit with doses >400 mg/day
Once vs. twice daily dosing:
Once daily dosing keeps steady-state serum concentrations within 27%
Twice daily dosing keeps concentrations within 14%
Patient with an effective dose which is near the maximum tolerated dose may benefit from twice daily dosing

8.3 Dosage adjustment in renal/hepatic disease

Slower dosage titration and more frequent monitoring are recommended in patients with renal or hepatic disease. It should be used with extreme caution if creatinine clearance is less than 50 mL/minute.

8.4 Levels

Plasma concentrations may be useful; with therapeutic levels usually between: 10-20 mcg/mL. Higher levels (up to 30 mcg/mL), may improve control, but are associated with adverse effects (Oommen, 1999 and Leppik, 1999).

8.5 Monitoring

Due to the risk of asymptomatic metabolic acidosis, the FDA recommends measuring serum bicarbonate before starting zonisamide and periodically thereafter (even in the absence of symptoms)

9. Current role of ZNS in the therapy of epilepsy

Zonisamide was approved by the US Food and Drug Administration (FDA) in March 2000 as adjunctive treatment for partial-onset seizures in adult. In Japan, it is approved for use as monotherapy and as adjunctive therapy for children and adults with both generalized and partial seizures

10. Use in non-epileptic indications

- The drug has recently hypothesized to be useful in autism[40].
- Zonisamide-induces long-lasting recovery of dopaminergic neurons from MPTP-toxicity. It has been found to be useful in managing impulse control disorders in Parkinson's disease[41].
- Zonisamide can be used for migraine prophylaxis in topiramate-intolerant patients. It is also used in the preventive treatment of migraine[42,43]
- SUNCT syndrome has been found to show response to zonisamide[44]
- It is found to be effective in the treatment of alcohol dependence. It reduced ethanol self-administration by risky drinkers.[45,46]
- Zonisamide ameliorates symptoms of secondary paroxysmal dystonia.[48]
- It is used in the treatment of extrapyramidal and psychotic symptoms in patients suffering from dementia with lewy bodies[50]

- Zonisamide Combined with Cognitive Behavioural Therapy has been useful in the treatment of Binge Eating Disorder[53]
- Idiopathic hemifacial spasm has been found to be responsive to zonisamide[54]
- Zonisamide is used in the treatment of neuropsychiatric disorders[55].
- Zonisamide suppresses pain symptoms of formalin-induced inflammatory and streptozotocin-induced diabetic neuropathy[56].

11. Conclusion

In conclusion, the new-generation AED zonisamide, either as adjunctive therapy or as monotherapy, effectively reduces the frequency of partial seizures, with or without secondary generalisation to tonic-clonic seizures, in adults and children with epilepsy. The drug is generally well tolerated and, additionally, has a favourable pharmacokinetic profile permitting once- or twice-daily administration. Direct head-to-head comparisons with other AEDs would be beneficial in fully defining the place of zonisamide in therapy. In the meantime, adjunctive therapy or monotherapy with zonisamide is a convenient, useful option for the management of partial seizures, including those refractory to other AEDs.

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8

Practical Use of the Ketogenic Diet in Childhood Epilepsy

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1. Introduction

The ketogenic diet (KD) is a high fat, low carbohydrate diet that has been used for intractable childhood epilepsy since the early 1920s. After the resurgence of the ketogenic diet in the mid 1990s, it has been used worldwide for the treatment of refractory pediatric epilepsy. Thus the ketogenic diet is an established, effective nonpharmacologic treatment for intractable childhood epilepsy. Over the past decade the role of the ketogenic diet in the treatment of intractable epilepsy has became evident from the explosion of interest and publications available, as well as the increased number of epilepsy centers that offer the ketogenic diet. However, the ketogenic diet is not yet a convenient therapy, especially because the customary diets of Asian countries contain substantially less fat than the traditional Western diets. Therefore, recent research endeavor to achieve a safer and more convenient dietary treatment for refractory pediatric epilepsy.

Recent consensus of ketogenic diet by expert's opinion provided guideline in using the diet. Suggested protocols, which include changes to the applicable ages, seizure types, and etiologies, the initiation of the diet, changes in the ratio of constituents to reduce the fat content, the duration of the diet, and revised formulae, such as ketogenic milk or the all-liquid ketogenic diet, have attempted to extend the indications of the ketogenic diet and increase its tolerability. Physicians should also be aware of the various complications of the diet. Less restrictive ketogenic diet including a modified Atkins and low-glycemic-index diets have also been clinically tried with comparable efficacies.

This chapter will provide practical recommendations to guide the management of the ketogenic diet in childhood epilepsy and give a review on the current state of ketogenic diet.

2. Background

Epilepsy is the most common serious neurological condition in the world, with an estimated prevalence of 1% of the population. Traditional epilepsy management includes pharmacological treatment, epilepsy surgery, and vagal nerve stimulation. Despite these therapies, 25% of children continue to have uncontrolled seizures. The ketogenic diet, which has been in use since 1921, is a treatment option for many of these children. The original

classical ketogenic diet is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1. Protein is kept to minimum requirements for growth, and carbohydrate sources are mostly limited to small portions of vegetables or fruit. The classic diet is calculated using a ratio of the weight of fat to the sum of protein and carbohydrate. Protein is provided to meet dietary reference intake, which is approximately 1 g per kilogram of body weight. Carbohydrate completes the remaining allowance of the ratio. Although it is a "ketogenic diet," one nutrient class (carbohydrates) is depleted, while providing an alternative fuel source for the brain with another substrate (ketones), which may be anticonvulsant.

Ketogenic diets are categorized as either long-chain fatty acid based or medium-chain fatty acid based. The classical ketogenic diet uses long-chain triglycerides (LCT). Medium-chain triglycerides (MCT) are more ketogenic than LCTs, as octanoic and decanoic acids are more easily transported into the cell (Huttenlocher, 1976). Since it is more ketogenic, the MCT ketogenic diet (MCT-KD) allows for a lower overall fat content and subsequent greater inclusion of protein and carbohydrate in the daily intake (Sinha & Kossoff, 2005). Clinically, there does not appear to be a difference in efficacy between the MCT and the LCT diets (Huttenlocher et al., 1971; Schwartz et al., 1989). Patients on the MCT diet are more likely to experience abdominal bloating and diarrhea than those on the LCT diet, which is believed by some, in return, to be less palatable than the MCT diet. In addition, patients on the LCT diet are more prone to constipation than those consuming an MCT diet (Hartman & Vining , 2007). Other options have been devised for using the diet in particular situations, such as in patients fed through a gastrostomy tube or in infants. These diets include ketogenic diet formulas of the Nutricia's (MD, USA) KetoCal®, Solace Nutrition's (MD, USA) KetoVolve® and Ketonia™ in South Korea. The availability of these formulas for infants, particularly those with gastrostomy tubes, makes palatability less of a problem in this patient population (Sinha & Kossoff, 2005). For infants with epileptic encephalopathy and infantile spasms, a short-term trial of the diet for about 6-12 months, including a 2-4 month tapering-off period, can be considered (Kang et al., 2011).

The ketogenic diet is an effective treatment for medically refractory epilepsy, and is characterized by elevations in ketone bodies and fatty acids in both blood and brain. While a detailed understanding of the anticonvulsant mechanisms of action of the ketogenic diet has remained elusive, recent investigations have suggested that a global shift from glycolysis to fatty acid oxidation is necessary to achieve the desired clinical effects. Moreover, there are growing data indicating that the ketogenic diet – whether through ketone bodies or PUFAs – can exert neuroprotective actions, most likely by enhancing ATP production and decreasing ROS production, both of which help to preserve mitochondrial integrity. Also there is growing evidence that the ketogenic diet alters the fundamental biochemistry of neurons in a manner that not only inhibits neuronal hyperexcitability but also induces a protective effect (Kim do & Rho, 2008).

3. The history of the ketogenic diet

Fasting has been used in the treatment of epilepsy since Biblical times (Matthew 17:5-21). To mimic the metabolism of fasting, the ketogenic diet was introduced by modern physicians as a treatment for epilepsy in the 1920s (Geyelin, 1921). Wilder (Wilder, 1921) postulated that the antiepileptic effect of the diet was related to the production of ketones and not to starvation. He proposed that increasing the fat content in the diet while reducing the

carbohydrate would lead to reduction in seizure frequency. In the following decades, the use of the ketogenic diet were eclipsed as phenytoin, and then other anticonvulsants, became available in the late 1930s. With the development of newer antiepileptic drugs with improved efficacy and convenience, there was a significant decrease in the use of the ketogenic diet. However, the varied adverse effects of such medications should be considered, especially since more than 25% of epilepsy remains intractable, despite the development of new anticonvulsants (Kwan & Brodie, 2000).

The diet regained widespread recognition as a viable treatment option beginning in 1992 due to the efforts of parent advocate groups. This changed dramatically when the ketogenic diet received national media attention via NBC-TV's *Dateline* program on the treatment. This television program was based on the true story of Charlie, a 2-year-old boy with intractable generalized seizures, who presented out of desperation to Johns Hopkins Hospital for treatment. He was seen by Dr. Freeman and Ms. Millicent Kelly (the same dietitian who had worked with Dr. Livingston) and initiated on the ketogenic diet. He quickly became seizure-free and the Charlie Foundation was formed by his father. He made videos for parents, physicians, and dietitians about the ketogenic diet. In addition, he directed the movie *First Do No Harm*, starring Meryl Streep, in 1997, which presented the ketogenic diet as a miracle cure for epilepsy. This exposure to the diet in the popular media contributed to a movement led by patients and their families to expand use of the treatment (Bailey et al., 2005). The Foundation also supported the first multicenter prospective study of the efficacy of the ketogenic diet (Vining et al., 1998). There has been an explosion in both the use, and scientific interest in the ketogenic diet. The ketogenic diet has experienced a reemergence in recent years and modern clinical studies have established the treatment as significantly effective (Freeman et al., 1998). The ketogenic diet is now available in over 45 countries (Kossoff & McGrogan, 2005).

4. Efficacy and complications of the ketogenic diet

To establish the efficacy of the ketogenic diet, this procedure requires the development of a blinded prospective study using a well-defined cohort and sufficient sample size (i.e., Class One Evidence). To date, no studies met the criteria for Class One Evidence for efficacy in the use of ketogenic diet in children with refractory epilepsy. The development of a blinded prospective trial of the ketogenic diet in children would be difficult to design (Thiele, 2003). Finding a placebo with similar metabolic responses to the diet both at the time of initiation (i.e., acidosis, lethargy, hypoglycemia) and during the maintenance phase (presence of ketones) that does not have antiepileptic properties would be difficult. Therefore, the diet's efficacy has been established primarily through large case series. Many reports on the efficacy of the ketogenic diet have shown similar outcomes. After 12 months on the ketogenic diet, about 50% of patients remained on the diet, 30%-70% of patients showed a reduction in seizure frequency of more than 50%, and 10%-20% were seizure-free(Kang et al., 2005). Recent papers (Keene, 2006) reported an overall reduction of seizure frequency greater than 50% in approximately one third of children initiated on the diet. The duration the child remained on the diet was variable, with over half the children discontinuing the diet between 6 months and a year after the treatment onset. Although the efficacy of the ketogenic diet is not maintained in all patients after they discontinue the diet, beneficial effects persist in most patients relative to their symptoms prior to diet initiation(Hemingway et al., 2001; Kang et al., 2005). Because of the variation in study designs and in the

description of the clinical variables (such as seizure type, electroencephalographic findings, duration of treatment), it was not possible to assess which child might benefit most from the diet (Keene, 2006). The widespread acceptance of the ketogenic diet has ended the debate about its efficacy.

The ketogenic diet predisposes to nutritional deficits in energy, proteins, minerals, and vitamins and excess in lipids, saturated fat, and cholesterol. Use of such an unbalanced diet requires particular attention regarding its implementation and monitoring, particularly in children. Some adverse events may occur within a few days or a month of commencing the diet, although others may occur after several months (table 1)(Freeman et al., 2006; Kang et al., 2004; Lyczkowski et al., 2005). The potentially serious complications should also be considered. Rare, life-threatening complications, such as cardiomyopathy, serious infections, or aspiration pneumonia leading to respiratory distress, should be carefully monitored for during follow-up (Kang et al., 2004). Especially in patients with cardiac arrhythmias such as prolonged QT interval (Best et al., 2000), and in patients with underlying metabolic disorders or those taking zonisamide, topiramate, or acetazolamide (Kossoff et al., 2002; Takeoka et al., 2002), the use of the diet might be associated with a higher risk of adverse events. However, most events are transient or can be controlled with regularly scheduled assessments (table 2) and conservative management.

Early- and late-onset	**Late-onset**
Gastrointestinal disturbances*	Growth retardation
Dehydration†	Hepatic failure
Infectious disease‡	Exacerbation of gastro-esophageal reflux
Sepsis	Mineral deficiencies
Lipoid aspiration pneumonia	Vitamin deficiencies
Hepatitis	Osteopenia
Acute pancreatitis	Renal stone
Biochemical disturbances	Cardiomyopathy
Abnormal lipid profiles§	Prolonged Q-T interval
Symptomatic hypoglycemia¶	Iron deficiency anemia
Persistent metabolic acidosis	2nary hypocarnitinemia
Hypoproteinemia	Optic neuropathy
Repeated hyponatremia	Basal ganglia injury
Hyperuricemia	

(*) Nausea/vomiting, diarrhea, constipation, loss of appetite. (†) A body weight reduction of over 5% of the baseline and marked dry skin or mucous turgor with increased urine specific gravity of over 1.020. (‡) Pneumonia, cystitis, nonspecific febrile illness. (§) High triglyceridemia, high cholesterolemia, low high density lipoproteinemina. (P) <40 mg% of blood sugar with nausea, lethargy, perspiration, dizziness, tachycardia and pale appearance. (Adapted from Dr. Kang HC).

Table 1. Early- and late-onset complications of the ketogenic diet.

5. Protocol of the classic ketogenic diet

While the Hopkins protocol has been the basic model, the general protocol has evolved over time, as new advances have been made in how the diet is administered and followed (Kang & Kim, 2006). Prior to introducing the ketogenic diet, patients are screened by history and

exam (as well as supporting laboratory studies, if indicated) for metabolic disorders that may affect their ability to generate adequate amounts of ketones. A brief hospitalization for 3-7 days was also recommended to give parents and children extensive instructions on how to calculate and prepare the diet, identify potential sources of glucose, and address other possible sources of error in administering the diet. On the first day of feeding, the patient is given 1/3 of the planned total caloric intake; on the second day, 2/3 of the total calories are administered, and on day 3, the full (previously calculated) caloric intake is administered. While on the diet, patients should also receive recommended daily intakes of vitamins and minerals (in sugar-free formulations), as well as calcium supplementation, as the ketogenic diet is not nutritionally complete. During the diet's initiation, blood glucose, urine ketones, and vital signs are monitorred. The outpatient phase of the ketogenic diet consists of routine clinic visits (3, 6, 12, 18, and 24 months after starting the diet) with the staff and laboratory measurements, along with frequent contact with the nutritionist (table 2).

Pre-diet
Metabolic workups* (lactate, urine organic acid and plasma amino acid assay, plasma acylcarnitine profiles) urine ALA and PBG†
0,1,2,3,4 days and monthly
Blood ketone, blood sugar (every 12 hours for 4 days)
0,3 days and 1,3,6,12,18,24 months
CBC with platelets, BUN/creatinine, liver profiles‡, electrolytes with tCO2, calcium/phosphorus/alkaline phosphatase, magnesium, uric acid, lipid profiles§, urinalysis, PT/PTT, urine ca/urine creatinine
0,6,12,24 months
Blood AED levels, abdominal ultrasonography, echocardiography
plain X-ray on wrist, if needed, bone densitometry, bone enzyme profilesΠ
Intermittently
Urine ketone¶

ALA = d-aminolevulinic acid; PBG = porphobilinogen; CBC = complete blood count; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time; AED = antiepileptic drug. (*) In children with associated developmental delay of unknown etiology, hypotonia, exercise intolerance, cyclic vomiting, fatigability, hepatomegaly, cardiomyopathy, pigmentary retinitis, hypoacusia, metabolic acidosis, hypoglycemia, hyperammonemia or unexpected ketonuria. (†) Especially in nationalities that have high incidence of acute intermittent porphyria. (‡) Total protein/albumin, total bilirubin, aspartate aminotransferase and alanine aminotransferase. (§) Cholesterol, high density lipoprotein-cholesterol, triglyceride. (P) Parathyroid hormone, 25(OH) vitamin D3, 1.25(OH)2 vitaminD3, osteocalcin. (¶) Recommend measurement of urine ketones at home, especially when seizures occur or seizure frequencies increase. (Adapted and revised from Dr. Kang HC)

Table 2. Scheduled assessments to screen medical contraindications and evaluate complications of the classic ketogenic diet.

There is the need for standardized protocols and management recommendations for both clinical and research use of the diet, because the ketogenic diet is provided differently throughout the world, with occasionally significant variations in its administration. In December 2006, the Charlie Foundation commissioned an international committee of neurologists and dietitians with expertise in the ketogenic diet. The charge of this consensus group was to provide practical recommendations to guide management of the ketogenic diet (Kossoff et al., 2009). Recommendations are as follows:

Patient selection

The ketogenic diet should be strongly considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies. The ketogenic diet yielded a good response in patients with an immature cerebral cortex due to developmental malformation (Jung et al., 2008b). It can be considered the treatment of choice for two distinct disorders of the brain metabolism, i.e. the GLUT-1 deficiency syndrome and PDHD. In particular epilepsy syndromes, such as the Dravet syndrome, infantile spasms, myoclonic-astatic epilepsy, and tuberous sclerosis complex, the ketogenic diet could be offered earlier. Before starting the ketogenic diet, inborn errors of metabolism that could lead to a severe metabolic crisis should be ruled out. For example, defects in fatty acid oxidation generally are contraindications to starting the ketogenic diet. Absolute contraindications to the ketogenic diet include pyruvate carboxylase deficiency and porphyria.

Medications and the ketogenic diet

There is little evidence of any consistent positive interactions between the ketogenic diet and anticonvulsants. The ketogenic diet may work well in combination with VNS. Conversely, the ketogenic diet is not negatively affected in regards to efficacy or side effects by any particular anticonvulsant. Medications can often be reduced within the first few months if the ketogenic diet is successful, although caution is advised especially when reducing phenobarbital and benzodiazepines.

Maintenance of children receiving the ketogenic diet

Ongoing clinic visits at least every 3 months for the first year, with ready access to experienced advice, are important for the successful management of children receiving the ketogenic diet. More frequent visits may be necessary for infants and other patients at high risk for nutritional deficiency. All children should be seen by experienced pediatric neurologists and dietitians and should have a nutritional assessment, laboratory evaluation, and discussion regarding ketogenic diet and anticonvulsant discontinuation decisions.

Ketogenic diet discontinuation

Consideration should be given to discontinue the ketogenic diet after 3 months if unsuccessful, or after 2 years if completely successful. However, longer diet durations are usually necessary for GLUT-1 and PDHD and may be perfectly appropriate, based on individual responses for intractable epilepsy. Prior to diet discontinuation in seizure-free children, a routine EEG and review of clinical data should be performed to counsel families regarding recurrence risk, which is 20% overall. Children with an epileptiform EEG, abnormal MRI, and tuberous sclerosis complex are at higher risk. During discontinuation, the group generally recommends a gradual wean over 2–3 months, as outlined above, unless an urgent discontinuation of the diet is indicated.

6. Newer versions of the diet

In Asia, even now, the ketogenic diet is still not convenient to use, especially because the customary diets of Asian countries contain substantially less fat than traditional Western diets. Moreover, in adolescents, an unpalatable diet may cause resistance and poor compliance and a lower ability to extract ketones from the blood into the brain can be a barrier to its effectiveness (Williamson, 1985). In addition, there are various complications associated with the diet and they should be carefully considered. Therefore, we require an

alternative diet therapy that is safer and more convenient while maintainging efficacy. In the last decade, variations to the classical ketogenic diet have been utilized. Recently less restrictive ketogenic diet, including a modified Atkins diet and low-glycemic-index treatment, has been suggested to replace the conventional ketogenic diet (Kossoff et al., 2006; Pfeifer & Thiele, 2005). Modified atkins diet (grams of fat: protein and carbohydrate, 1:1 ratio) has several advantages over the traditional ketogenic diet, most notably no restriction on protein, calories, or fluids. This "Modified Atkins Diet" restricts only carbohydrates to 10 g/day (15 g/day in adults) while encouraging high fat foods. The antiepileptic effects of both fasting and the ketogenic diet have been associated with decreased blood glucose and increased blood ketone levels (Owen et al., 1967); however, recent research indicates that ketosis alone cannot account for the anticonvulsant effects of the ketogenic diet (Greene et al., 2003); it suggests that regulation of blood glucose may be at least partly responsible for these effects. The glycemic index describes the tendency of foods to elevate blood glucose (Jenkins et al., 1981). The glycemic index is calculated from the incremental area under the blood glucose curve after feeding, indexed to ingested glucose = 100. Foods with high glycemic index (e.g., most refined carbohydrates) produce substantial increases in blood glucose and insulin levels, whereas foods with a low glycemic index (e.g., meat, dairy, some fruits, some vegetables, and some unprocessed whole-grain foods) induce lower postprandial plasma glucose and insulin profiles. By limiting the quantity of carbohydrates consumed and by restricting sources of carbohydrates to low-glycemic index foods, the low glycemic index treatment (LGIT) is designed to prevent dramatic postprandial increases in the blood glucose (Pfeifer & Thiele, 2005). The low glycemic index treatment, compared to the ketogenic diet, allows for a more liberal total carbohydrate intake but restricts foods to those that produce relatively little elevation in the blood glucose (i.e. glycemic index <50). In conclusion, modification of the ketogenic diet with higher carbohydrate/protein and lower fat than the classic ketogenic diet, such as the modified Atkins diet or the low-glycemic-index treatment, can be used with similar efficacy and better tolerability (Carrette et al., 2008; Ito et al., 2008; Kang et al., 2007; Kossoff et al., 2003; Kossoff et al., 2006; Kossoff et al., 2008; Kossoff et al., 2007; Muzykewicz et al., 2009).

7. How to provide a successful ketogenic diet

As current thinking focuses on making the ketogenic diet safer and more palatable, the original protocol has been modified and has evolved to achieve increased efficacy and tolerability (Kang & Kim, 2006). Improving and maintaining efficacy is a major goal in the use of the ketogenic diet. Comprehensive dietary education and an easy calculation method, using a software program based on accurate food composition analysis, are important to use the ketogenic diet in an optimal fashion. The calculation of a single meal can be tedious, and hence the possibility for errors is significant. Computer applications for calculating ketogenic diet, such as KetoCalculator (Zupec-Kania, 2008), are available and can save time and minimize errors. The presence of well trained dietitians is critical and they should instruct caregivers in both dietary calculation and food composition. The dietitian provides nutrition management and technical manipulation of the diet in order to optimize the seizure control. The dietitian is frequently communication with both the caregivers and the ketogenic diet team, and this necessitates his/her role as coordinator of the ketogenic diet program. Dietary education also plays an important role in increasing the efficacy of the ketogenic diet. Key members of the team managing the patient include physicians, nutritionists familiar with the diet, nursing staff, and, most importantly, patients and their families. Families should be encouraged to

participate in support groups to share information and build strong bonds; this, in turn, will increase the maintenance rate of the diet.

To improve the antiepileptic efficacy of the ketogenic diet, the maintenance of consistent and strong ketosis is important. Furthermore, the lipid:nonlipid ratio affects the efficacy, as seen in many animal studies and one clinical study (Seo et al., 2007). When a child on the ketogenic diet does not show a significant reduction in seizure frequency, physicians should consider every possible way in which ketosis may be breached. It is important to maintain an accurate lipid:nonlipid ratio for each of the patient's meals and to avoid extra carbohydrate consumption derived from prescribed drugs or miscalculation.

Improving tolerability is the other major arm for the successful maintenance of the diet. Although the Johns Hopkins protocol used for the classic ketogenic diet recommends an initial fasting period, a nonfasting protocol provides better tolerance in the initial period of the diet and avoids dehydration from fluid restriction (Bergqvist et al., 2005; Kim et al., 2004). It can also decrease the incidence of early complications, such as acute renal failure, elevation of blood urea nitrogen, and electrolyte imbalance. The nonfasting ketogenic diet has similar antiepileptic efficacy to the conventional fasting ketogenic diet with the additional advantage of fewer days of hospitalization. The careful monitoring of complications and their prevention and management are also valuable ways to improve patient's tolerability during the diet's maintenance. Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or constipation, which are common early complications, may cause both the parents and patients to consider giving up the diet. Temporary use of antiacids or antiemetics can help to relieve the symptoms (Jung et al., 2008a). Psychological support is also critical for families, as is education about complications and their prevention and management. To ensure successful maintenance, care-givers should have a positive attitude about the diet. The positive attitudes of doctors and parents seem to be the most important supporting factor in maintaining the diet. Although the typical ratio of fats to carbohydrates and protein (in terms of grams) is 4:1, lower ratios are used successfully in other parts of the world, such as Asia, where rice is a major dietary staple (Kossoff & McGrogan, 2005). Moreover, breaking with tradition and convincing the physicians and their patients are the most important factors to introduce the diet in Asian countries(Seo & Kim, 2008).

8. Conclusion

The ketogenic diet is a useful therapy for patients with intractable epilepsy, including some of the catastrophic epilepsies in infancy and childhood. This chapter is a review of previous and current papers regarding the proposed practical use of the ketogenic diet in epileptic children. The diet's strictness, lack of palatability, and side effects limit its use and adversely affect both patients' compliance and clinical efficacy. Careful planning and monitoring from a committed and experienced medical team will help ensure a successful ketogenic diet program. We should continue our endeavors to develop a safer and more convenient diet therapy that can be extended to more patients with refractory epilepsy.

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9

Epilepsy Surgery in Children

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1. Introduction

Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book "On The Sacred Disease", in which it refuted the idea that the upheaval was the work of spirits and wisely related to brain. This concept was not fully accepted until modern era (Horsey, 1886). Classically, epilepsy is defined as a chronic disease with recurrent seizures, that affects individuals in all age groups, and affects 1-2% of children (Rasmussen, 1983). In childhood, epilepsy is more common in the first year of life, and its incidence decreases progressively with increasing age, affecting approximately 100 children per 100,000 births in the first year of life, 40 children for every 100,000 births in subsequent years, and approximately 20 individuals per 100,000 adolescents (Obeid et al, 2009a). In 75% of these cases, seizures are well controlled with antiepileptic drugs and in the remaining 25%, epilepsy is refractory to pharmacological treatment and surgical approach should be considered (Terra-Bustamante et al, 2005).

The definition of intractability is not easy and many factors such as age of epilepsy onset, classical evolution of the specific epileptic syndrome, seizure frequency and epilepsy etiology should be considered. The goal of epilepsy surgery is complete resection of the epileptogenic zone, thus allowing patients to a greater chance of cure or disease control, with a better behavioral, cognitive and intellectual development, especially when considering the pediatric group. In these lines, early indication for surgery may allow children have better development and social inclusion (Lippé et al, 2010). It is estimated that 90% of brain growth and maturation occur until five years of age and intense dendritic synaptic connections remained until the age of seven, making this a favorable period for better post-operative recovery. In children the occurrence of neuronal plasticity is maximal and several eloquent cortical areas have great ability to reorganize its circuits, and can be functionally represented in both cerebral hemispheres (Obeid et al, 2009a; Benifla et al, 2009). It is known that the early indication for surgery is the single most important factor in getting good results, and that anti-epileptic drugs do not alter the long-term prognosis of epilepsy drug resistance, therefore, surgical treatment should not be postponed.

When considering epilepsy surgery, some concepts should be established to achieve better seizure control (Obeid et al, 2009b):

- Epileptogenic zone: cortical area responsible for seizure generation, whose removal is sufficient to leave patient seizure free.

- Symptomatogenic zone: cortical area responsible for the symptoms of epileptic seizures, almost always contained or near the epileptogenic zone, but whose removal is not necessary for seizure control.
- Irritative zone: cortical area involved in generating interictal epileptiform discharges.
- Ictal onset zone: area where seizures began detected by the electroencephalogram.
- Epileptogenic lesion: lesion or anatomical area macroscopically visible on imaging studies, which may be responsible for seizures generation, which usually is included in the epileptogenic zone, but may be smaller than it.

Considering these definitions, the gold standard of epilepsy surgery is complete resection of the epileptogenic zone, thus allowing patients to become seizure free. Today are considered preferable candidates for epilepsy surgery patients that have defined refractory epilepsies, with no involvement of eloquent areas and with a well-defined epileptogenic zone. However this is not always possible, especially when considering the pediatric group (Lippé et al, 2010). The first challenge is when define pharmacological refractoriness. Some authors suggest that patient should have been submitted for at least three different drugs, for at least two years, appropriated to the type of seizure and / or epileptic syndrome, at doses related to weight and age, excluding possible idiophatic syndromes of childhood with transitory refractoriness. This controversial definition may have catastrophic meaning when considering small children with more severe forms of epilepsy, where surgery in the first year of life may be essential for neurological and cognitive development (Dunkley et al, 2011). In the same way should be considered the risk of developing post-operative sequelae. In some patients it is acceptable the occurrence of motor deficits considering the severity of the disease.

It is worthwhile to emphasize the differences between epilepsy in children and in adults (Villarejo & Comair, 2000). Although there are many similarities, and much of the knowledge of epilepsy in children is extrapolated from studies in adults, there are relevant differences, which influence pre-operative decisions and surgical techniques. Also, children have a lower threshold to seizures, which results in an increased occurrence of catastrophic epilepsies (and consequent development delay). Regarding the pathological substrate, the epilepsies related to extensive brain lesions are relatively common in the pediatric age group, as opposed to mesial temporal sclerosis, whose incidence is several times higher in adults. Moreover, the seizure semiology and electrophysiological data in pediatric epilepsies are distinct of that observed in adults, with more generalizes symptoms and diffuse electrographic patterns in children even in focal epilepsies (Tsiptsios et al, 2010; Hnojciková et al, 2010).

Unlike epilepsy in adults, childhood mesial temporal sclerosis has a lower incidence, occurring in 39% of children versus 87% in adults (Obeid et al, 2009a). Among the etiological factors, cortical development malformation is overwhelmingly the most frequent, followed by brain tumors, gliosis and finally the mesial temporal sclerosis. Other common etiologies for epilepsies in children are tuberous sclerosis, Sturge-Weber syndrome and Rasmussen encephalitis

Defined the diagnosis of refractory epilepsy, patient need to be referred to an epilepsy surgery center. The pre-surgical evaluation usually include a detailed medical history, a high resolution brain magnetic resonance image (MRI), ictal and interictal video-electroencephalogram (VEEG), neuropsychiatric assessment, psychiatric evaluation and social interview. In this way is preferable that patient is evaluated by a multidisciplinary team. In selected cases, brain computed tomography, single photon emission tomography (SPECT) or positron emission tomography (PET) may be indicated. The analysis of all these

tests will determine the next step to be followed: epilepsy surgery, exams complementation or refuse surgery. Other exams that may also be indicated are functional MRI (mainly for motor and language localization), quantitative MRI and intra-operative electrocorticography (ECoG).

Brain MRI is the test of choice in defining the presence or not of a potential epileptogenic lesion and concordance with video-electroencephalogram findings is crucial for a better prognosis. However, in many children a multifocal interictal pattern or multiple seizure types may be present. In this way it is essential that video-electroencephalogram is analyzed by an experienced neurophysiologist that is able to recognize age related specific syndromes and determined if they have a focal or generalized onset. With the advance of image techniques, syndromes previous considered as generalized are now identified in some cases as localized (Chugani, 1994). The main example is children with West Syndrome with typical spasms and electrographic hypsarrhythmia pattern that may be secondary to focal lesions or focal functional abnormal brain areas. In some of these children, relatively small resections may be sufficient to seizure control (Asano et al, 2001) and surgery should not be refused.

2. Childhood epilepsy syndromes

2.1 West syndrome

West syndrome is a severe epileptic syndrome occurring in 1 in 2000-4000 live births. The syndrome has a triad consisting of development regression with mental retardation, epileptic spasms and EEG hypsarrhythmia. It may be found in previously normal children (probable symptomatic forms) or occur in children with development delay observed before seizure onset, with identifiable brain lesions (symptomatic forms) (Sakakihara, 2011).

Epileptic spasms are brief movements involving both up and lower limbs, usually with arm flexion and lower limbs extension. Other forms of spasms that may be observed are extension of up and lower limbs and asymmetric or lateralized spasms. Ocular movements as circular or lateral nystagmus are frequently observed in seizures. Seizures usually begin in the first year of life and have a poor prognosis progressing with increasing age for more complex epilepsy and other syndromes (mainly the Lennox-Gastaut syndrome or unspecific symptomatic generalized epilepsies).

The electroencephalogram typically shows hypsarrhythmia (chaotic pattern with disruption and attenuation of the background rhythm, combined with slowing and multifocal epileptiform discharges) (Sakakihara, 2011).

Response to pharmacological treatment is generally poor and the classical association of valproic acid and a benzodiazepine is still recommended. Vigabatrin has been considered a better choice especially for patients with tuberous sclerosis complex (Pesaturo et al, 2011). Alternative therapies as the use of steroids or ketogenic diet may contribute do seizure control in some patients. Surgical treatment may be indicated in some cases, particularly in patients with focal brain lesions or functional localized abnormalities detected by PET scan (Obeid et al, 2009a).

2.2 Lennox-Gastaut

One of the most severe epileptic syndrome characterized by atypical absence, axial tonic/atonic seizures, slow spike-wave complex and bursts of fast rhythms at 10 to 20 Hz during sleep on EEG. Mental retardation, behavioral disturbances and others seizure types

are usually present, mainly complex partial, generalized tonic-clonic and myoclonic seizures. Children with this syndrome may develop several seizures per day, with the installation of atypical absence *status epilepticus*. This condition may occur in previously normal children or in patients with signs of brain damage and has major impact on cognitive development. On the other hand, tonic, atonic and myoclonic seizures are frequently associated with repetitive trauma requiring the use of helmets to prevent head injuries. Typical electroencephalographic interictal pattern may be associated with multifocal spikes or sharp waves, with marked background disorganization.
Treatment is primarily pharmacologic and polytherapy is usually indicated. Recently, the use of rufinamida has been associated with great improvement in seizure frequency, but it is not common to have patients that becoming seizure free (Wier et al, 2011). In the same way as West Syndrome, some patients may have benefit of localized cortical resection, but callosotomy or vagus nerve stimulation is frequently the only options (García-March et al, 2008; Benifla et al, 2006) with some authors reporting satisfactory response.

2.3 Landau-Kleffner

Landau-Kleffner syndrome is a rare condition characterized by aphasia, auditory agnosia and epileptic seizures (Obeid et al, 2009a). The main symptom is the regression of language through persistent aphasia in a previously normal child that may develop mutism or autistic regression. Seizures occur in 70-80% of patients, but may be rare, with good response to antiepileptic drugs.
The EEG in wake state may be normal, but with somnolence typically shows bitemporal independent epileptiform discharges, that are activated by sleep involving the rolandic areas. MRI is normal and treatment with corticosteroids, ACTH or immunoglobulin appears to slow the evolution of language deficit (Snead III & Martien, 2001). Surgery with multiple subpial transections may be proposed (Cross et al, 2006) but there are few studies showing some improvement in respect of language evolution. Vagus nerve stimulation may also be tempted to reduce cognitive impairment (Park, 2003).

2.4 Focal epilepsies of childhood

Focal epilepsies in children may be associated with a large number of pathologies, such as abnormalities of cortical development, hypoxic-ischemic lesions, benign tumors, phakomatosis and mesial temporal sclerosis. Extratemporal neocortical epilepsies predominate in most of the described series. As in adults, symptoms of seizures will be related to the lobe involved but age of epilepsy onset may modify this paradigm. In this way, patients with mesial temporal epilepsies secondary to cortical development malformation may present in the firsts years of life with tonic seizures or even with a typical West Syndrome. When epilepsy settles latter, especially if children is older than three to six years, complex partial seizures predominate with simple automatisms. Typical automatisms with dystonic posturing will be present latter on, usually after six years (Mohamed et al, 2001). Extratemporal epilepsies may manifest as in adults with more exuberant symptoms, but auras are less frequently reported although some children may be capable of describe simple visual aura or sensitive symptoms.
Seizure frequency may be high even in temporal lobe epilepsies, with daily seizures. Long term prognosis is variable and in symptomatic cases, a significant proportion of children evolve with refractory forms of epilepsy that may persist true adulthood. In this way, the

option of a surgery should be considered early to avoid cognitive and social impairment secondary to chronic seizures (Mohamed et al, 2001).
Surgery proposed will depend on the etiology and localization of the lesion and one of the most striking factors is the complete lesion resection. Differently from adult epilepsies, here the goal should be permit a better cognitive and motor development, especially when considering the most catastrophic forms of epilepsies. In temporal lobe epilepsies, long term follow up is similar to that observed in adults, with almost 70 to 80% of patients being seizure free.

2.5 Status epilepticus

Refractory status epilepticus occurs when seizures are not controlled with initial benzodiazepine therapy or a subsequent anticonvulsant drug therapy used in a methodological way (Abend & Dlugos, 2008). When seizures persist other options, such as surgery, must be considered (Whelless, 2010). Surgical approaches include focal cortical resections, hemispherectomies, multiple subpial transections, and rarely corpus callosotomy and vagus nerve stimulator implantation. Focal resective surgery is usually indicated in patients with localized brain lesions and electrographic evidence of ictal focal seizure onset (Vendrame & Loddenkemper, 2010). Defining the optimal moment to indicate surgery and which patients may benefit from a cortical resection or a palliative procedure is not easy. There are few series of patients evaluated until now and timing and criteria for intervention need to be stated.

2.6 Cortical development malformation

Cortical development malformation are congenital diseases that are associated with intractable epilepsy in both children and adults, being the most frequent pathology found in pediatric epilepsy in surgery centers (Cepeda et al, 2006). The advances in MR images have increased the number of patients diagnosed with this pathologies and consequently undergoing surgical treatment (Chern et al, 2010). Younger cases are more likely to have multilobar and severe forms of cortical development malfromations compared with older patients with focal and mild lesions (Figure 1).

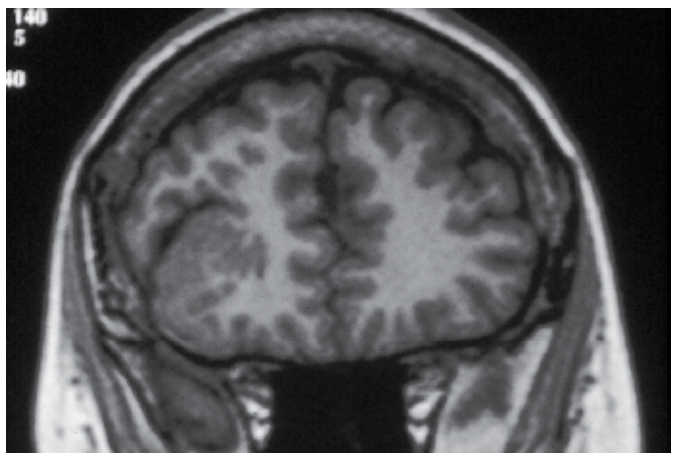

Fig. 1. Magnetic resonance image of a frontal polymicrogyria.

Seizures symptoms are usually related to lesion localization an age of epilepsy onset and MRI is the exam of choice to confirm diagnosis. The best option to treat refractory cases is the complete resection of the lesion and the associated epileptogenic zone (Diaz et al, 2008).

2.7 Tuberous sclerosis

Tuberous sclerosis is a multisystem genetic disease, autosomal dominant, with variable phenotypic expression, with an incidence of 1/58.000 (Connolly et al, 2006). Approximately 80-90% of individuals with tuberous sclerosis will develop epilepsy throughout his life. The syndrome results to two known mutations: one on the gene TSC1 located on chromosome 9 (9q34 region) that encodes the protein hamartin; and the other on the TSC2 gene, localized on chromosome 16 (region 16p13.3) that encodes the expression of tuberin (Connolly et al, 2006). Its features include the presence of pathognomonic cerebral cortical tubers, subependymal nodules, retinal lesions, disseminated sebaceous adenomas (Figure 2), subcutaneous fibrous plaques (especially on the scalp) and renal angiomyolipomas (Connolly et al, 2006). Subependymal giant cell astrocytoma (SEGA) may be present and evolve with obstruction of the ventricular system and hydrocephalus. In some patients, this tumor may have a more malignant evolution and surgery is the treatment of choice.

The EEG is normal in only 12% of cases of tuberous sclerosis. In the remaining cases, localized or multifocal frequent epileptiform discharges are present. West syndrome may be the clinical presentation form, mainly when seizures start in the first year of life.

Treatment should be directed to seizure types and Vigabatrin may be the first option when epileptic spasms are present. Surgery of choice is tuberectomy, and although the great majority of the patients have numerous tubers, in some selected cases it is possible to identify just on tuber as being epileptogenic, with approximately 60% of the patients submitted to tuberectomy being seizure free (Moavero et al, 2010). There is considerable controversy whether the remaining lesions may become epileptogenic or not. The use of intracranial EEG recording with chronically implanted electrodes may contribute to seizure localization. When ressective surgery is not possible, palliative procedures may be proposed as callosotomy or vagus nervous stimulator.

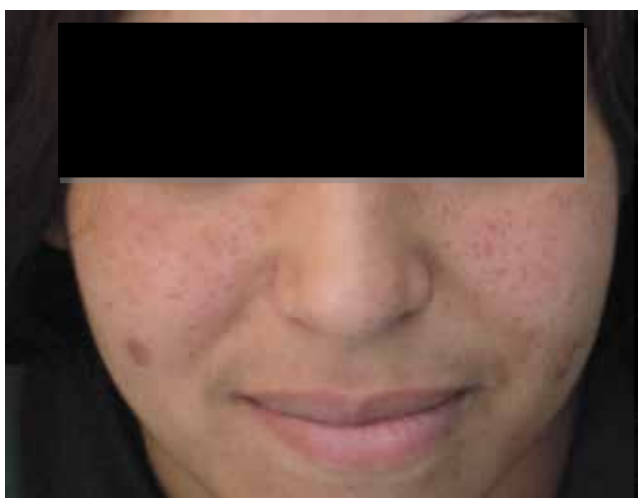

Fig. 2. Patient with the diagnosis of tuberous sclerosis with facial sebaceous adenomas.

2.8 Sturge-Weber syndrome

Sturge-Weber syndrome or encephalon angiomatosis is a rare neurocutaneous disorder characterized by a leptomeningeal angiomatosis. Main clinical features include the presence of facial port wine nevus recognized at birth usually in the distribution of branches of the trigeminal nerve. Symptoms classically start in childhood but persist through adulthood. Intractable epilepsy will be present in 75-90% of patients, 60% of them candidates for surgical treatment. Congenital glaucoma, progressive hemiparesis, learning disabilities and leptomeningeal angiomatosis are usually present (Di Rocco & Tamburrini, 2006).

The diagnosis is confirmed by brain MRI that characteristically demonstrates brain volume loss in T1 sequences, with loss of superficial vascularization and leptomeningeal enhancement after gadolinium administration. T2 sequences shows confirm these findings and may demonstrate the presence of coarse calcifications, although computed tomography scans may be the exam of choice to identify calcified lesions. Hemispheric angiomatosis predominates but some patients have a more localized lesion, with involvement of posterior regions being more frequent. The electroencephalogram usually shows nonspecific or diffuse hemispheric changes.

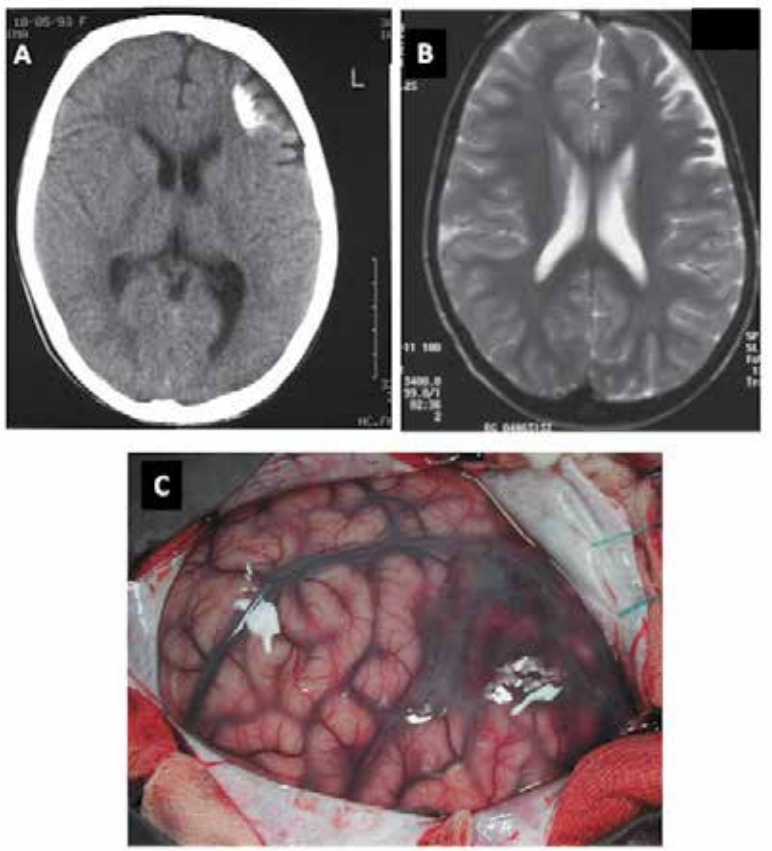

Fig. 3. Frontal lobe lesion of Sturge-Weber syndrome. A. Computerized tomography showing a coarse calcification. B. MRI with frontal focal atrophy. C: Intra-operative classical leptomeningeal angiomatosis.

Surgery may be an option in patients with refractory epilepsies and hemispherotomy is the most appropriate treatment. The installation of permanent neurological deficits needs to be discussed.

2.9 Rasmussen encephalitis

First described by Theodore Rasmussen in 1958, this rare disease probably has an immune-mediated substrate, related to both humoral and T lymphocytes, usually affecting one brain hemisphere, and leading to progressive atrophy with loss of neurological function (Mastrangelo et al, 2010; Bien et al, 2005). The age of onset is between three and seven years of life, but there are descriptions of cases that seizures initiate in adulthood. Progressive hemiparesis, mental retardation and behavioral changes can settle in evolution. Seizures is classically hemi-clonic and syndrome may have a fast devastating evolution, with the installation of motor deficits and continuous motor seizures in few months or have a more slowly evolution. Language disorders are common when disease involve the dominant hemisphere, even if seizures started in early ages.

EEG shows delta waves include polymorphic in the affected hemisphere associated with asynchronous slow waves and epileptiform discharges. MRI demonstrates in initial phases an enhancement of signal in T2 or FLAIR sequences in insula or motor strip. With disease evolution unilateral enlargement of the ventricles and other cerebrospinal fluid spaces, basal ganglia and cortical atrophy, mainly in central regions develop and may be identified in T1 or T2 sequences.

Therapy with corticosteroids or immunosuppressors can be used, but the treatment of choice that provides better results is the hemispheric surgery (Hart et al, 1998; Villemure & Mascott, 1995; Villemure & Daniel, 2006).

2.10 Brain tumors

Brain tumors are common cause of refractory epilepsy in children. The most frequently tumor types observed are gangliogliomas, dysembryoplastic neuroepithelial tumors, pilocytic astrocytomas, oligodendrogliomas and ependymomas. The hypothalamic hamartomas constitute a very especial tumor type, with characteristic symptoms. The treatment of choice is surgery, that can provide substantial benefit reducing seizure frequency and severity and allows the identification of tumor type (Tian et al, 2011).

The hypothalamic hamartoma is a congenital lesion of the tuber cinereum presenting with the classic triad of gelastic seizures (generally characterized by tearfulness or laughter), central precocious puberty and behavioral disturbance. Its clinical course is often progressive, with mental development deteriorating and the occurrence of major complex partial or tonic seizures. Recent studies have demonstrated the intrinsic epileptogenicity of hamartoma (Maixner, 2006).

EEG may be normal or show unspecific diffuse slowing. MRI is characteristic, showing a rounded lesion, with regular edges, hypointense on T1 and T2, firmly adhered to the mammillary bodies and the thalamus (Maixner, 2006). The treatment of precocious puberty is essentially clinical. Surgery is recommended as the sole indication for improvement of epilepsy, with resection or disconnection of the lesion (Machado et al, 1991; Siwanuwatn et al, 2008; Yasargil & Abdulrauf, 2008).

2.11 Non-lesional epilepsies

Recently, an increasing number of studies had been reported considering epilepsy surgery for the treatment of refractory epilepsy in non-lesional epilepsies. Long term follow up

demonstrate that patients with normal MRI submitted to surgery have a overall smaller chance of being seizure free after surgery, independent of the lobe of the resection (Téllez-Zenteno et al, 2010). A similar outcome had been reported in children and adults

3. Surgical techniques

Following the establishment of drug refractory epilepsy and completion of comprehensive preoperative evaluation, surgical treatment can be offered, according to the results of this assessment, being driven primarily by underlying disease and the region to be addressed. Patients may be submitted to resective or palliative procedures, depending on pre-operative exam conclusions with surgical techniques following the general standards established in pediatric neurosurgical practice.

The operating room should be wide to allow the presence a multidisciplinary team consisted of anesthesiologist, neurosurgeons and neurophysiologists. Surgeries in children are usually extensive. Craniotomies and subsequent durotomy should be broad, allowing intraoperative electrographic study and exposure of the anatomical landmarks of each procedure. Most commonly used incisions are:

- "Question-mark"or "inverted question mark, " initiated at the root of the zygoma and extended superiorly to the superior temporal line or above, more frequent used for temporal lobe or hemispheric surgeries.
- "Barn Door" or "barn door", which facilitates approaches involving multiple lobes, starting frontally on the previous line of insertion of the hair and then passing the following paramedian lambdoid suture.
- Bicoronal or classical, mainly for frontal lobe approach.

Intraoperative electrocorticography is currently used to localize seizure onset, guiding extension of resection. This has a particular importance in patients with brain tumors, cortical development malformations and other neocortical lesions. Although evidence that support its utility is controversial, many pediatric centers use it routinely (Gallentine & Mikati, 2009). Cortical stimulation during surgery in children is usually restricted to motor area strip localization. It's a reliable and safe technique and its use in children may need an experienced electrophysiologist, since higher amperage thresholds is frequently necessary.

Intraoperative ultrasound, neuronavigation and surgical microscopes are fundamental tools currently used in epilepsy surgery. In particular, neuronavigation represent a potential technique that permit a better identification of lesions limits contributing to complete resection (Stone & Rutka, 2008).

3.1 Resective procedures

Resective surgeries are the procedure of choice in patients with refractory epilepsies and involve part of a lobe, an entire lobe or multiple lobes, depending on the extension of the epileptogenic zone.

3.1.1 Lesionectomies

Advances in neuroimaging allowed the identification of discrete anatomical lesions that are correlated with seizure onset. In some patients, the resection of such a lesion is sufficient to achieve seizure freedom, being an efficient modality for medically intractable epilepsies

(Bourgeois et al, 2006). Focal resections may be indicated in the cases that electrographic ictal findings are strictly localized and coincident with lesions such as small tumors, cortical development malformations, cavernous angiomas, etc. (Figure 4). The extent of the resection will be determined by the nature of the lesion and intraoperative electrocorticography findings, especially in patients with cortical development malformation. Patients with persistency of seizures may need extension of the initial resection with a lobectomy.

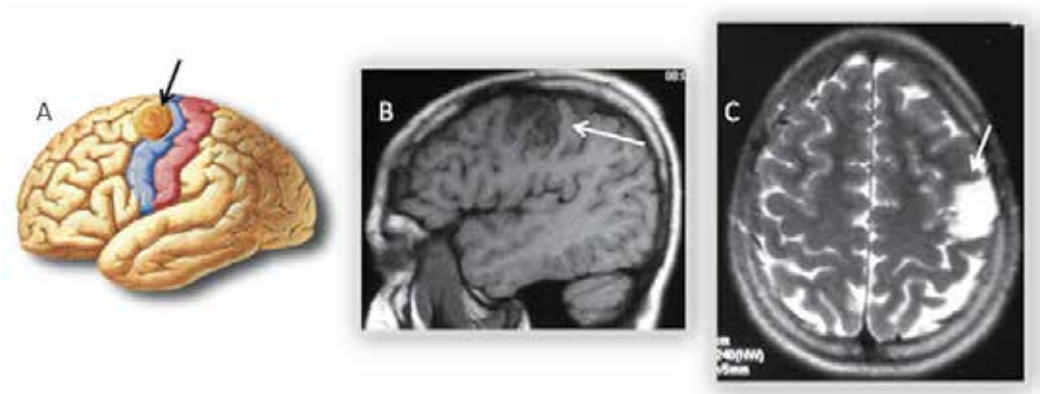

Fig. 4. Peri-rolandic epilepsy – surgical technique. A: schematic image ilustrating the localization of the brain lesion (arrow). B: sagital and C: Axial post-operative magnetic resonance image showing resection region.

3.1.2 Lobectomies

Lobectomies consist of the resection of an entire or almost entire lobe. It may be done in any lobe, but in most cases involve the temporal lobe. Frontal and parietal resections are limited to motor strip that may be identified during surgery by direct cortical stimulation and the use of neuronavigation. Occipital resections are limited by the parieto-occipital sulcus.

Extratemporal resections constitute the largest percentage of surgical procedures for epilepsy in children, and refer to isolated lobectomies (partial or full frontal - paramedially frontopolar and lateral convexity, parietal, occipital), or delimited corticectomias and multilobar resections. The most common pathology in these cases is cortical dysplasia, followed by tumors. Cortical resection in the rolandic region in children with intractable epilepsy is possible, but usually results in worsening or the development of new sensory or motor deficits. Accurate mapping of regions of functional cortex and epileptogenic zones may minimize these deficits with a satisfactory seizure outcome (Benifla et al, 2009). Some authors consider the possibility of direct cortical stimulation with awake craniotomy in children, but a careful neuropsychometric and neuropsychiatric evaluation should be carried out pre-operatively (Tobias & Jimenez, 1997). Overall outcome of extratemporal resections is usually inferior to that observed in temporal lobectomies (Harkness, 2001).

In children, temporal lobe epilepsy associated with mesial temporal sclerosis corresponds approximately for 40% of surgeries above six year old. Patients with temporal lobe epilepsy are usually divided into three groups (Adelson, 2001) to better define the therapeutic strategy: A first group refers to cases of typical mesial temporal sclerosis, which indicates

the standard resection, these patients have good prognosis after surgery (seizure control in 70% of cases (Villarejo et al, 2000). A second group includes the temporal tumors, in which we chose to perform temporal lobectomy with amygdalo-hippocampectomy. The tumor resection is the most important factor that influences the postoperative prognosis (Iannelli et al, 2000). The last group concerns the temporal cortical dysplasia, most often neocortical and should be guided by resection electrographic findings and, if possible, remove extensive cortical abnormalities that may be present. Standard temporal lobectomy involves resection of 4 to 4.5 cm (nondominant hemisphere) or 3.5 to 4 cm (dominant hemisphere) from the tip of the temporal lobe, resection of the amygdala and hippocampus after entry into the temporal horn of lateral ventricle.

3.1.3 Hemispheric surgeries

Hemispherotomy and its variations are generally performed in hemiparetic patients with severe, intractable epilepsy arising from one cerebral hemisphere. The neurosurgeon Walter E. Dandy already described hemispheric surgeries technique in the early twentieth century (Dandy, 1928), with performance of anatomical resection. Since a high long term complications rate was observed with this procedure, surgery approach was modified with the development of combined limited brain resection and disconnection. In 1983, Rasmussen described his elegant technique for hemispheric disconnection associated with small resections. Since then many techniques have been developed, such as hemidecortication, and techniques of disconnection by parasagittal (Delalande & Dormuller, 2008), trans-sylvian (Binder & Schramm, 2006) and peri-insular (Villemure & Mascott, 1995). The surgical technique to be chosen will depend on the conformation of the pathological brain, and also the familiarity and experience of the surgical team.

Hemispherotomy (Figure 5) is the surgical procedure of choice for cases of Rasmussen encephalitis, hemimegalencephaly, atrophy and porencephaly hemispheric ischemic sequelae of arterial trunks, among other diseases and in some series seizure freedom is nearly 70 to 80% (Limbrick et al, 2009). Motor and cognitive outcomes after hemispherectomy are variable and depend on many predictors including etiology and duration of seizure disorder, age at the time of surgery, premorbid status, and postsurgical seizure control and an effective rehabilitative program is essential after surgery (Samargia & Kimberley, 2009).

3.2 Palliative procedures

In patients where it is not possible to demarcate precisely the epileptogenic zone, but with incapacitating epilepsies, palliative procedures may be proposed. The goals of these procedures are based in the fact that a favorable impact with respect to quality of life may be achieved with the reduction of the morbidity and the number of seizures. This result may permit reduction of the amount of anti-epileptic drugs, with a better behavioral, cognitive and intellectual development. In general, palliative procedures are indicated in patients with high seizure frequency, patients with drop attacks with repetitive trauma or patients with more severe forms of epilepsy syndrome. Medically intractable tonic and atonic seizures may be responsive to either vagus nerve stimulation or corpus callosum section, with less morbidity with the first and greater likelihood of seizure improvement with the second (Rosenfeld & Roberts, 2009).

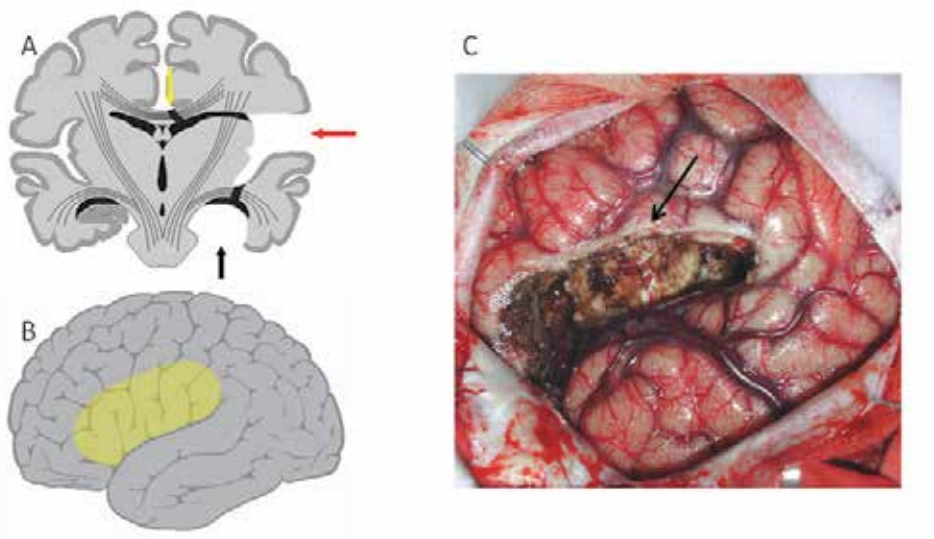

Fig. 5. Hemispherotomy consist of a resection of the insular lobe and the mesial portion of the temporal lobe, with disconnection of the temporal peduncle, basal ganglia and callosotomy (A and B). C: Intra-operative image demonstrating the insular resection.

3.2.1 Vagus nerve stimulation

Vagus nerve primary function is parasympathetic regulation of autonomic visceral activity and influences many regions of central nervous system, through its extensive connectivity. Inputs first achieve the nucleus of solitary tract and then projects to reticular formation, hypothalamus, hippocampus, amygdale, dorsal raphe nucleus, locus ceruleus, thalamus and cerebral cortex. This widespread cortical influence was first described in 1938 by Bailey & Bremer, however, the exact mechanisms by which vagus nerve stimulation reduce seizure frequency is still unknown.

The system consists of a generator positioned in the chest wall, near the clavicle and an electrode that is implanted around the vagus nerve in the neck. The generator is programmed externally with increasing current according to seizure frequency. Optimal stimulation parameters, interval between each programming and the high limits of stimulation have yet to be determined (McLachlan, 2001).

The efficacy and safety of vagus nerve stimulation has been studied in several patients, including adults and children with refractory epilepsies, with satisfactory results even in small children (Alexopoulos et al, 2006; Benifla et al, 2006; García-March et al, 2008; Elliot et al, 2009; Coykendall et al, 2010; Elliot et al, 2011). It may be indicated in patients with focal or generalized epilepsies and when associated with other methods including antiepileptic drugs, ketogenic diet and resective surgeries approximately 60% of the patients experienced at least 50% reduction in seizure frequency (Elliot et al, 2011).

Rutka et al. recently described the experience of the Hospital for Sick Children in Toronto, Canada, and reported good results, with 45% of cases (in a series of 41 children) a reduction of at least 50% of seizures (38% had a reduction greater than 90%), 12.5% had a decrease in duration and intensity of crises. Only 5% of pacemakers implanted had to be removed due to side effects (Benifla et al, 2006). Another interestingly study in a small series of patients

with tuberous sclerosis demonstrated 82% of the cases (nine of 11) with at least 67% reduction in seizure frequency (Elliot et al, 2009), suggesting this could be an option for patients which epileptogenic zone could not be determined.

3.2.2 Corpus callosotomy

Corpus callosotomy may be a partial (anterior two thirds) or complete disconnection. Because of its inherent risks, primarily related to brain retraction, and disappointing results, this procedure has been abandoned and / or replaced by the implementation of the vagus nerve stimulator. It is particularly indicated in patients with diffuse lesion (Figure 6) or normal image that a focal focus could not be identified. Better response is observed in patients with drop attacks secondary to atonic seizures, but patients with tonic and myoclonic seizures may also have some improvement. Children submitted to corpus callosotomy are usually severely handicapped but even in these patients a disconnection syndrome may occur (Lassonde & Sauerwein, 1997). Disconnection syndrome is a complex set of signs and symptoms that affects motor control, spatial orientation, vision, hearing and language (Jea et al, 2008) but its anatomical basis are not totally understood.

Some authors advocate the use of corpus callosotomy as an initial step for localization of surgically amenable seizure foci, in patients with apparent generalized or multifocal seizures (Lin et al, 2011).

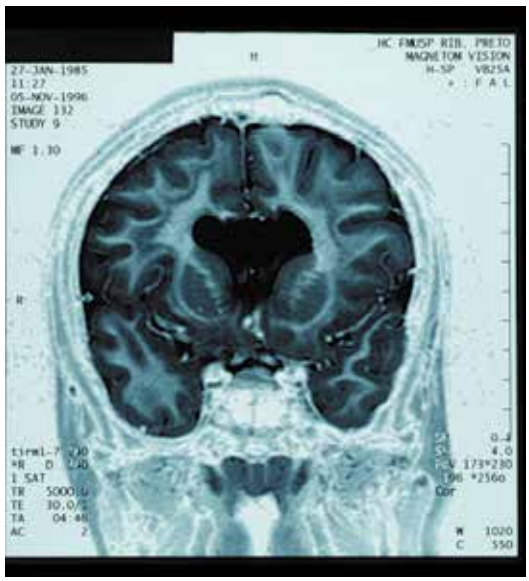

Fig. 6. Patient with a double cortex that was submitted to total callosotomy.

3.2.3 Multiple subpial transections

Described in 1989 by Morrell (Morrell et al, 1989), consist of the performance of multiple lines of section in cortical surface, with the goal of stopping the horizontal cortical connections and reduce the spread and propagation of epileptic activity. In order to preserve the function of the area transect vertical connections are maintained. Mainly used in surgery involving eloquent areas, provides satisfactory results in about 40% of cases. It is also indicated in cases of Landau-Kleffner syndrome. Although in these cases the result is

controversial, improvement in communication and behavior have been reported (Gordon, 1997).

4. Complications and prognosis

The epilepsy surgery in childhood, at first sight, leads to higher risk of complications, since children often requires major procedures with a potential risk of installation or worsening of neurological deficits. However, long term children evolution demonstrates a significant reduction on seizure morbidity and mortality after surgery. Experienced groups report a relatively low incidence of post-operative major complications. The main acute complications are bleeding, infection and hydrocephalus. Transient neurological deficits may occur in the frontal and peri-insular resections and permanent neurological deficits is usually observed in that patients that previously eloquent areas were programmed to be involved in the resection. To deal with these surgical sequelae is essential that patients be evaluated in a well-established rehabilitation program.

With respect to prognosis, this depends greatly of the pathology and extent of surgical resection. The success rate is generally high, reaching, in our series, total control (Engel I) in 64.8% of cases (Terra-Bustamante et al, 2005), and may be even greater in certain situations, such as epilepsy and temporal tumor resection. In case of maintenance of epileptic seizures, the clinical evaluation and preoperative tests described above must be repeated and reoperation may be considered.

5. Conclusions

Medically intractable epilepsy is a condition with chronic recurrence of seizures that often requires surgery to reduce or eliminate them. Surgery for epilepsy in childhood has become an effective method in treating this condition, and should be indicated as early as possible. Peculiarities of epilepsy in children should be considered to achieve optimal results. Although a reduction of seizures is the primary goal of surgery, the maintenance of cognitive and motor development milestones is essential to allow the child have a quite normal life in adulthood.

Extratemporal epilepsy in children closes more cases compared to those observed in adults, but still dominates the temporal lobe as the site of ictal onset, and surgical results are very encouraging. Surgical option should take in account several factors such as child´s age, underlying pathology and lesion extension. Neuronal plasticity can be an ally for the development of minor post-operative neurological deficits.

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10

Corpus Callosotomy in Pediatric Intractable Epilepsy: Microsurgical Technique Implication and Variation

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1. Introduction

Medically intractable epilepsy is considered for surgical intervention first for resection of localized area of brain in which cases seizure control is expected generally. Nevertheless, those with non-localizing lesions in the imaging studies as well as multifocal spikes in electroencephalography (EEG) are not candidates for the resective surgery. For palliative intervention, corpus callosotomy may be considered for these patients. Early detection of proper candidates for surgical intervention in pediatric patients with medically intractable seizures may give a better chance of recovering their developmental potential by protecting the brain from further epileptic discharges.

2. Back ground with historical development

The cerebral hemispheres are connected by six midline commissural structures: the anterior commissure, posterior commissure, corpus callosum, hippocampal commissure, the massa intermedia of the thalamus, and the fornix. Corpus callosum is the largest commissure and represents large areas of cortex in bilateral cerebral hemispheres. The concept behind the callosotomy is the hypothesis that the corpus callosum is the most important pathways for the spread of epileptic activity between the hemispheres especially in the secondarily generalized seizures. As to support the hypothesis, more than 60% of the 300 million fibers in the corpus callosum are fast conduction myelinated fibers. (Aboitiz, Scheibel et al. 1992; Tomasch 1954).

The first callosotomy was done by Dandy during a brain tumor operation in 1992, however, Van Wagenen and Herren were the first to apply the procedure to undertake the procedure for epilepsy patients in 1940. (Van Wagenen and Herren 1940) The first operations were consisted of right frontal craniotomy with the sagittal sinus and anterior falx divided. The lateral and third ventricles were entered during callosotomy and the one side of fornix or anterior commissure was disconnected. In 1960's, Bogen and colleagues developed the two types of commissurotomy, complete vs. partial. Partial commissurotomy consisted of anterior 1/3 of callosotomy, anterior commissure, and one fornix for the patients with epileptic discharges from frontal and temporal areas. (Wyler 1993) In 1970, Lussenhop first

reported their application of corpus callosotomy in children with intractable epilepsy. (Luessenhop 1970; Crowell and Ajmone Marson 1972) In 1970's, surgical microscope was first used for callosotomy by Wilson and his extraventricular approach prevented postoperative hydrocephalus. (Wilson, Reeves et al. 1978) Wyler further refined microsurgical technique in callosotomy entering the cavum septum pellucidum between the two pericallosal arteries in 1990's. (Wyler 1993) Currently, endoscopic anterior callosotomy and radiosurgical callosotomy are some new approaches attempted by some investigators. (Pendl, Eder et al. 1999; Tubbs, Smyth et al. 2004; Eder, Feichtinger et al. 2006)

Along with clinical application of callosotomy, experimental data has accumulated as well over the years. Erickson's work established the major role of corpus callosum as the seizure propagation pathway in the monkeys. (Pendl, Eder et al. 1999) Effect of the callosotomy in the seizure generalization has also been demonstrated in animal studies.(Crowell and Ajmone Marson 1972; Marcus and Watson 1966)

3. Indication

The common indication for callosotomy is those types of seizures of generalized or partial seizures with rapid secondary generalized patterns and without localizing lesions. Most effective seizures that are controlled with callosotomy are the atonic or tonic seizures characterized by sudden drop attacks that result in catastrophic events of self inflicting trauma to the patients as well as major burden to the parents. Many investigators have reported the elimination or reduction of frequency as well as the severity of the drop attacks most effectively compared to any other seizure types. (Gates, Leppik et al. 1984; Purves, Wada et al. 1988; Nordgren, Reeves et al. 1991; Spencer, Spencer et al. 1993)

Majority of patients with medically intractable seizures without localizing lesions undergoing callosotomy usually comprise of many different types of seizures. Infantile spasm, Lennox-Gastaut Syndrome, and West syndrome are the well known syndromic epilepsy with multiple seizure types that are good candidates for the callosotomy. Primary generalized seizures with tonic or tonic-clonic seizures are also found to respond well.

In our institute, the followings are the criteria for callosotomy candidates. 1) Medically intractable seizures that are treated over two years with use of all standard anticonvulsant medications in adequate serum level. 2) Types of seizures that are potentially amenable to callosotomy as mentioned above. 3) There is no identifiable single localizing lesion for resection. 4) Seizures that could be localized to one hemisphere or single foci after the callosotomy. Mental retardation is not contraindication for the surgery

4. The debate on extent of callosotomy

Debate still exists on extent of callosotomy and the indication for the completion of the callosotomy. Historically, callosotomy was tailored to the seizure types and location of seizure discharge by the extent of disconnection and completion of disconnection is done in staged fashion in order to circumvent the possible complication of callosotomy such as split-brain syndrome and posterior disconnection syndrome. Therefore, most epilepsy centers undertake 2-stage operation. (Spencer, Spencer et al. 1988; Andersen, áRogvi-Hansen et al. 1996) After 6-months from partial section, persistent generalizing seizures may benefit from completion of commissurotomy and second surgery is undertaken in most cases. Purves et al supported the anterior callosotomy alone is sufficient for some patients controlling

seizure. (Purves, Wada et al. 1988) However, the seizure outcome is far better in total callosotomy compared to partial callosotomy in many series especially in pediatric patients without concerned neuropsychological complications.(Rathore, Abraham et al. 2007) We had the same 2-stage callosotomy principle previously as well. With retrospective review of our series, patients with total callosotomy had better seizure outcome than partial callosotomy without neuropsychological deficits.(Kim, Yang et al. 2004) The results of Lassonde and Sauerwein, Lassonde et al and Maehara and Shimizu have similar outcome supporting our data.(Lassonde, Sauerwein et al. 1991; Lassonde and Sauerwein 1997; Maehara and Shimizu 2001) Therefore, in our institute, young patients before puberty with drop attacks and intractable generalized tonic clonic seizures are selected for the one stage total callosotomy with less complications related to surgeries with change in paradigm of treatment policy.(Shim, Lee et al. 2008)

5. Surgical procedure in Severance Children's Hospital Epilepsy Clinic

Presurgical evaluation is done by a multidisciplinary team of pediatric neurologists, neurosurgeons, neuroradiologists, clinical psychologists and the neuromodulation technicians. It includes detailed medical history of patients with physical and neurological examination. Continuous EEG with video monitoring is undertaken to identify the seizure types. Magnetic resonance imaging include diffusion tensor imaging is routinely done and ictal and interictal SPECT, and PET scan are done in most cases. Neuropsychological evaluation is routinely done to check the cognitive function as well as the social behavior adaptation using Korean Wechsler Intelligent Scale for children. EEG, MRI and neuropsychological testing and repeated postoperatively as well.

General anesthesia is used and intraoperative electorcorticography is used in selected cases for investigation only. Patients are positioned supine on operating table and head fixating pin is not used. Patient's head is rested on gel donut pillow and fixed to the table with plastic tapes around the donut pillow and the head. Currently, for one stage operation, we have developed no shaving with absorbable skin suture policy. Patients' hair is parted at the incision line and separated with rubber band or iodine oint for the short hair. Bicoronal skin incision is used over the coronal suture centered more to right except in cases where the dominant pathology is on the left side or other causes difficulty in entering the non dominant hemisphere. Craniotomy is made one centimeter crossing the sagittal suture with 6 centimeter total width and 4 centimeter anterior and 3 centimeter posterior to coronal suture in most cases. Special care should be taken making the craniotomy across the sagittal sinus. Dura is opened in curvilinear fashion based on the sagittal sinus and parasagittal draining veins are dissected and protected during interhemispheric dissection. Initial interhemispheric dissection is aided by self retaining retractor holding the brain on both sides. Surgical microscope is installed. Exposed cortex is protected with cottonoids. Interhemispheric dissection is aided by bipolar cautary and cottonoids used as the retractor on anterior and posterior ends of dissection. Meticulous dissection of arachnoid attachments leads to CSF leakage and brain relaxation is achieved without using mannitol or lumbar drainage of CSF preoperatively. Care should be paid to take enough time for brain relaxation before hemispheric retraction to avoid retraction injury. Adequate dissection exposes the paired pericallosal arteries on whitish background of corpus callosum. Dissection should continue until the genu and isthmus are exposed.

Callosal disconnection is done using microdissector and miscrosuction at the body level between the pericallosal arteries. Under microscope, the midline can be easily identified by the small arteries supplying the callosum itself entering perpendicularly into the midline. In addition, midline dissection will expose the midline cleft formed by the wall of lateral ventricles (Figure 1).

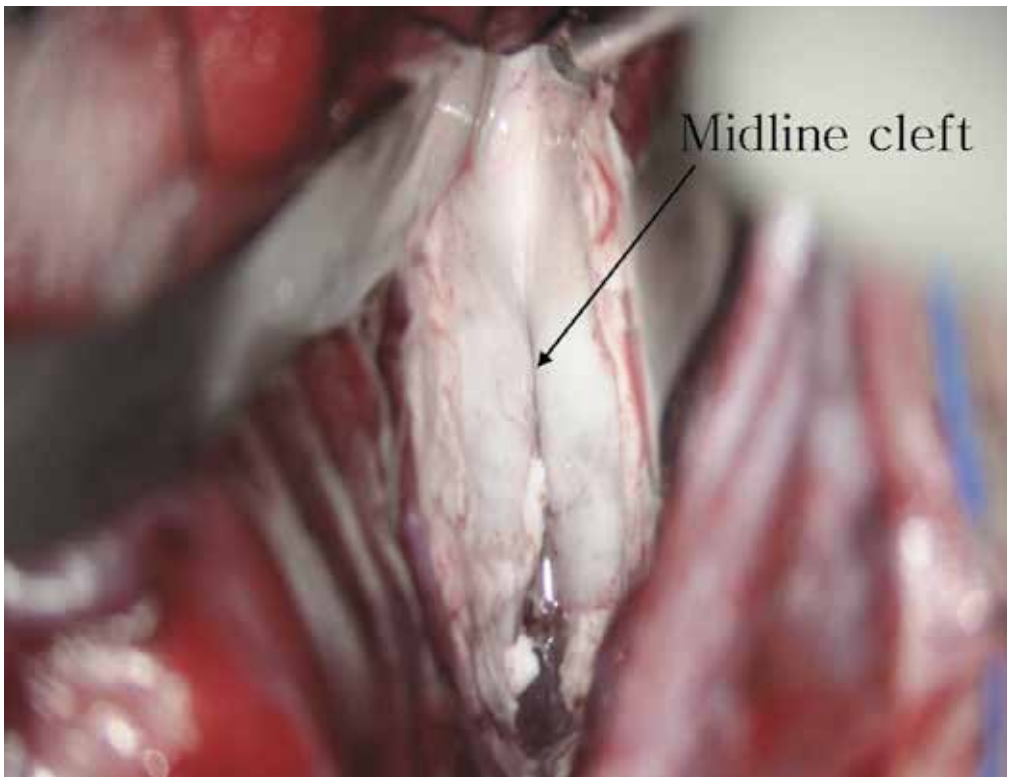

Fig. 1. Callosotomy following midline cleft

The midline cleft is followed down to the roof of third ventricle and anterior callosotomy is carried out. Anterior commisurotomy is carried out until the arachnoid membrane is exposed until the dorsum of anterior cerebral artery is exposed. For better view, head elevation may be required during anterior callosotomy. After completion of anterior callosotomy, the midline cleft is followed posteriorly with lowering the patient head position. Posterior callosotomy is completed when dissection is followed until the arachnoid membrane covering the vein of Galen and the internal cerebral vein. (Figure 2) Complete hemostasis is achieved using bipolar cautary.

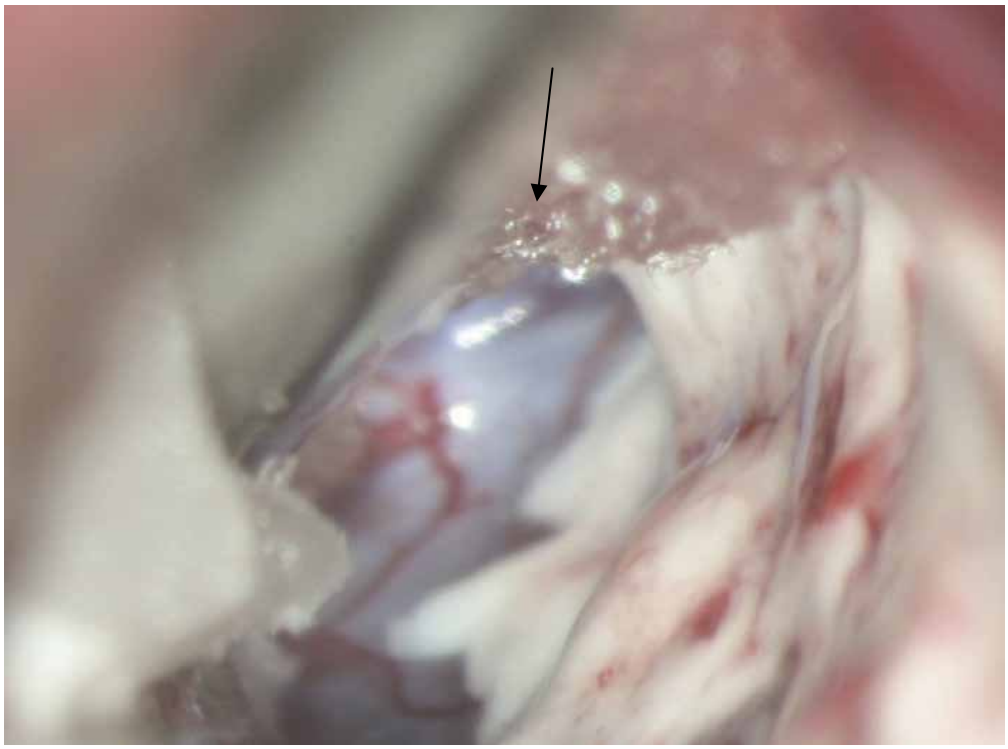

Fig. 2. Boundary of posterior callosotomy

Black arrow indicates arachnoid membrane covering the vein of Galen and internal cerebral vein is exposed indicating the completion of posterior callosotomy.

Navigation system is not an essential part of the surgery but it may assist the midline section and confirm the length or selectiveness of callosotomy in special cases where length of commisurotomy is tailored.(Jea, Vachhrajani et al. 2008) Intraoperative ECOG is not used routinely unless specific area of interest existed.

After saline irrigation confirming complete hemostasis, dura is closed with nonabsorbable monofilament sutures in water-tight fashion. Bone flap was fixated with metal craniofix buttons or absorbable buttons. Galea and subcutaneous suture is done using absorbable multifilament sutures with a subgaleal drainage tube inserted. Skin is closed with rapid vicryl 3-0. A drain is removed on postoperative day 2 and wound care is done with regular shampoo and topical antibiotic oint until the sutures are dissolved. Patients are monitoring in neurosurgical intensive care unit for overnight and transferred to the general ward the next day. Patients are usually discharge in a week after postoperative MRI taken.

Postoperative MRI is taken with DTI images to confirm the extent of callosotomy before patient's discharge. (Figure 3a, b, c) Patients are followed closely at the epilepsy outpatient clinic for seizure progression and control. Neuropsychological testing is followed after surgery at the outpatient clinic.

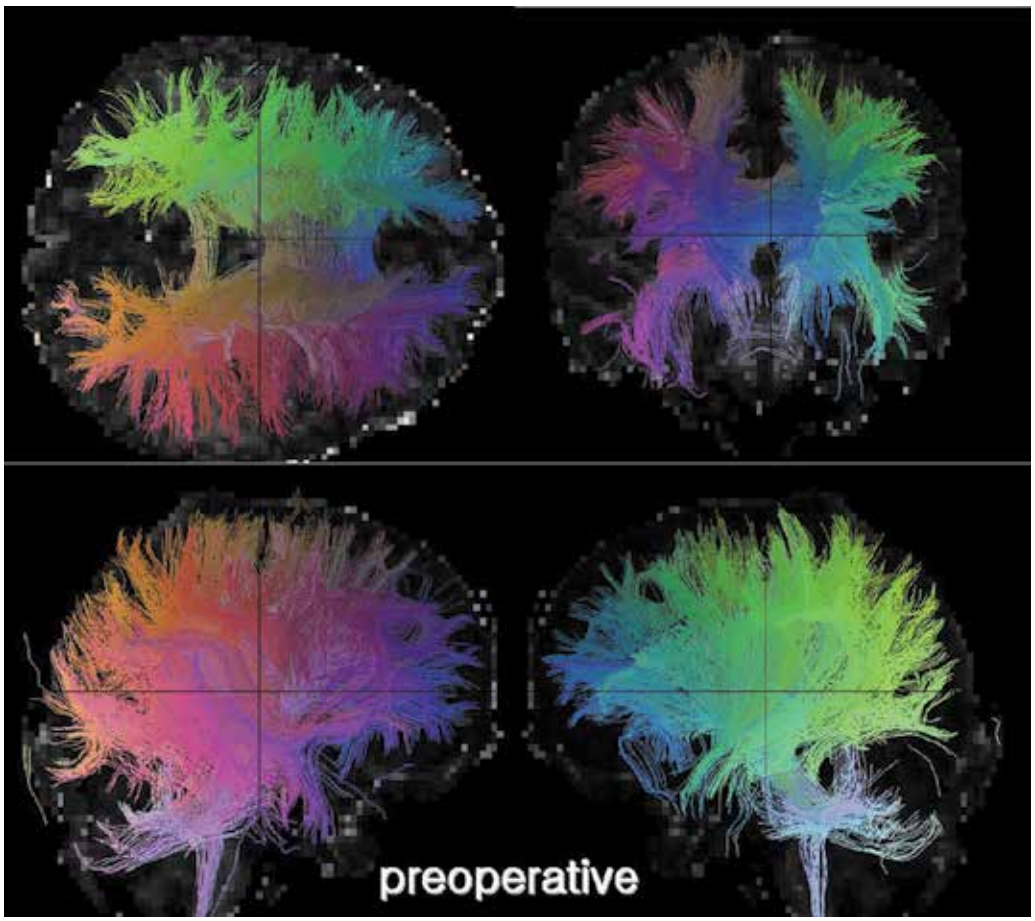

Fig. 3a. Preoperative DTI

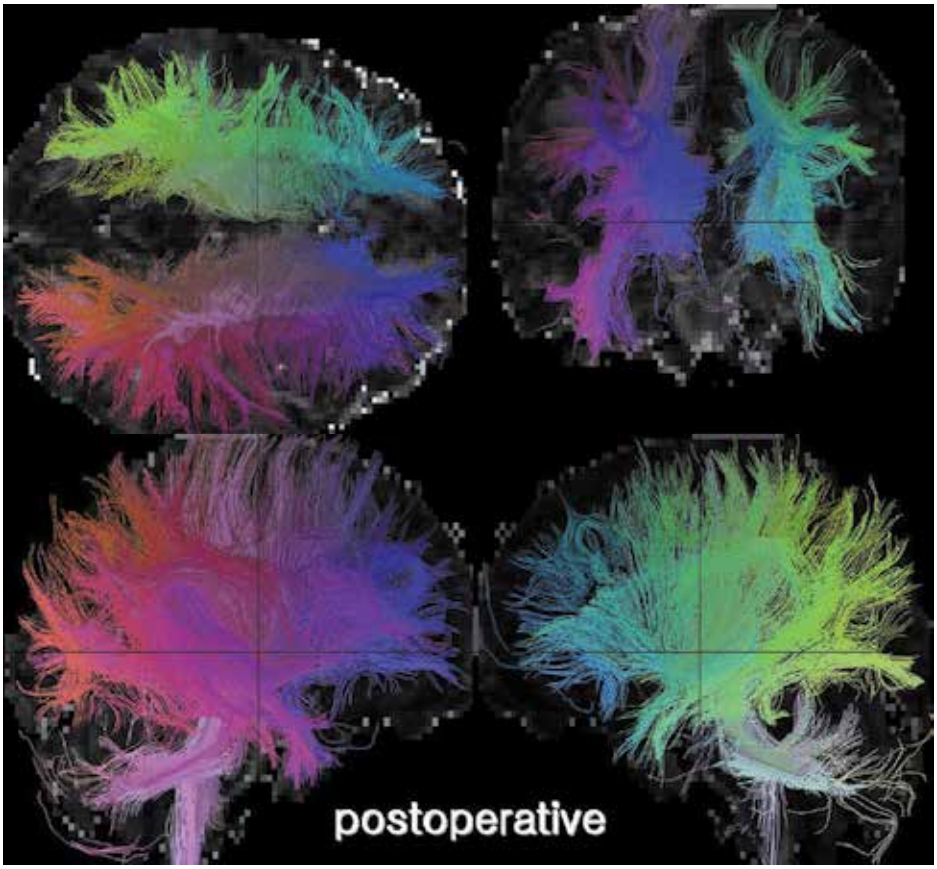

Fig. 3b. Postoperative DTI

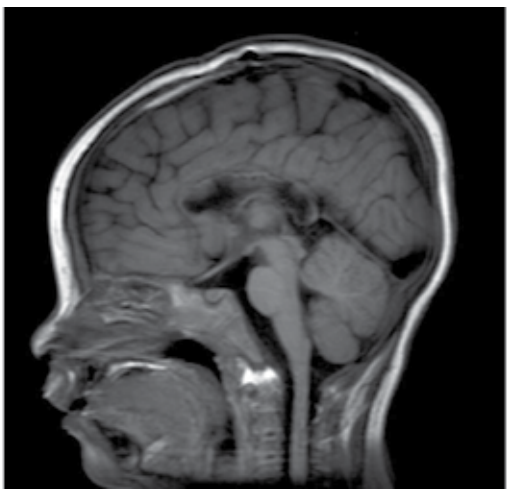

Fig. 3c Midsagittal section of MRI Postoperative DTI shows total disconnection of callosal fibers in Fig 3b and misagittal section of MRI confirming total callosotomy.

6. Outcome

Seizure outcome after callosotomy varies with investigators. In 1993, analysis of multicenter results was reported by Engel Jr. et al. Among 563 patients, 7.6% became seizure free and 60.9% improved. (Engel Jr., Van Ness et al. 1993) Recent long term follow-up results by Sunaga shows drop attack seizure free rate of 90% with total callosotomy and 54% with partial callosotomy with mean follow up of 7 years. Relapse rate of drop attack was 36% after 6 years from surgery. Total callosotomy patients had less relapse rate (7%) compared to partial callosotomy cases (31%) (Sunaga, Shimizu et al. 2009). Tanriverdi et al also reported the seizure outcome of 95 patients who was undergone callosotomy for seizure control. Generalized tonic clonic seizure types and drop attacks were the most well responding seizure types. Two third of their patients had favorable outcome with those seizure types. The seizure outcome was related to the extent of callosal section in their report. (Tanriverdi, Olivier et al. 2009) Pinard et al showed better outcome with total callosotomy in drop attacks among pediatric West syndrome cases. (Pinard, Delalande et al. 1999)

Most patients being candidates of callosotomy experience multitude of seizure types. Therefore, it is feasible to analyze the outcome by the seizure types. Favorable outcome as more than 50% reduction in seizures was noted in generalized tonic-clonic seizures (38-86%), generalized tonic seizures (43-60%), atonic seizures (60-83%) and complex partial seizures (50-51%).(Fuiks, Wyler et al. 1991; Oguni, Olivier et al. 1991; Reutens, Bye et al. 1993) Our data shows 35% seizure free rates in total. 76.4 % showed significant improvement after surgery and drop attacks was the seizure type with most effective result (91.2%). Generalized tonic-clonic seizures were also well controlled with total callosotomy (83.3%). Complex partial seizures, myoclonic seizures show less favorable outcome compared to drop attacks and GTC seizures. (Shim, Lee et al. 2008) Absence seizures are also well respond to the procedure according to Roberts and Siegel even though the procedure was not targeting the seizure type (Roberts and Siegel 2006).

Drop attacks are one of the most difficult seizures types for the patients as well as the caregivers. After the callosotomy, reduction of drop attacks is dramatic and the quality of life for the patient as well as the family has improved. Yang and his co-workers investigated the overall satisfaction and quality of life in 25 families. Mean reduction of severity of seizure activity was 64%. 76% of parents were satisfied with the surgical result and 72% described good level of satisfaction for family's quality of life. The key life domains showing improvement after surgery were level of self-care, family life and school performance. They reported significant improvement in hyperactivity, attention span, and social skills in 11 patients. (Yang, Wong et al. 1996) Similar results were produced by Gilliam and colleagues with improvements in alertness and responsiveness in children and 85% of families were satisfied with the operation. (Gilliam, Wyllie et al. 1996) Our results show 64.7% of parents reported improvement in overall daily function and 73.5% of parents show some satisfaction with the surgical result. Parents with younger patients expressed better satisfaction than parents of older children. These correlate with better functional outcome in younger patients with seizure control. These may indicate younger patients have better chance of recovering the neuropsychological and functional loss due to pervasive epileptic discharges.

Cognitive function is affected as well. Some reported improvement in cognitive function resulted from diminished seizure activity as well as the reduction of seizure medication.(Nordgren, Reeves et al. 1991) For our experience, with improved seizure

control, most patients' alertness and response to the surrounding have improved especially in the younger children. Majority of our patients had severe or profound mental retardation preoperatively and those with mental retardation showed better outcome. It may be due the fact the younger patient group has much retardation and may gain more from the surgery. Lassonde et al reported some benefit for all children regardless of their age with marked improvement in social adjustment and higher IQ associated with better outcome in patients younger than 13. (Lassonde and Sauerwein 1997) Shimizu and colleagues reported 77% improvement in overall behavior and 60% improved in expansion of vocabulary. No worsening of cognitive function was detected in this study. (Shimizu and Maehara 2000)

7. Morbidity

Hydrocephalus was common surgery related morbidity for callosotomy especially with surgical techniques entering the lateral and third ventricles in old days. With improvement in microsurgical techniques, hydrocephalus became rare complication. Aseptic meningitis, septic meningitis or ventriculitis, frontal lobe swelling and infarction and postoperative hematoma (subdural and epidural) are possible complications. Sagittal sinus tearing with bleeding and wound infection are some of the surgery related complication. In our experience, with no hair shaving and absorbable skin suture, wound complication or infection has not occurred. Aseptic meningitis occurs with continued fever for a week and subsides spontaneously or with use of short term steroids.

Neuropsychological complications well studied in the callosotomy are acute disconnection syndrome, posterior disconnection syndrome, split-brain syndrome, and deficit reinstatement. Acute disconnection syndrome includes mutism, difficulty in speech initiation, left side hemiparesis and urgency incontinence. There are debates on the effect of acute disconnection vs. surgical retraction on the parasagittal cortex on these symptoms. These phenomenons usually disappear in a week after surgery. In our series, two patients showed mutism and apraxia which recovered shortly.

Posterior callosal section is well known for disconnection syndrome characterized by interhemispheric sensory dissociation. Sensory input from the non dominant hemisphere has no connection to the language dominant hemisphere. Incomplete section is known to preserve the dominant hemispheric access to the contralateral brain. Split brain syndrome is present in patients with near total or total callosotomy. Language impairment, hemisphere competition and disordered attention-memory sequencing are the signs of the split brain syndrome. These usually resolve itself with time. Deficit reinstatement usually occurs to patients with mixed cerebral dominance or transcallosal compensation due to early hemispheric injury. The preoperative lateral deficit may exacerbated or newly appear after callosotomy.

Some patients especially younger than 10 years of age do not experience these disconnection syndromes after total callosotomy. (Lassonde, Sauerwein et al. 1991; Lassonde and Sauerwein 1997; Rougier, Claverie et al. 1997; Sauerwein and Lassonde 1997; Pinard, Delalande et al. 1999; Rathore, Abraham et al. 2007) The callosal connection and bihemispheric connection are known to be completed at the age of 10 or 11 years. Therefore, early functional absence of callosal connections may lead to development alteration and selective reinforcement of the connection that are normally reinforced in usual

circumstances. In addition, due to long term effect of intractable seizures, language and motor function may be dominant in both hemispheres.(Mamelak, Barbaro et al. 1993) These may explain the absence of disconnection syndrome in young patients with total callosotomy and better functional outcome in these patients after surgery.

8. Conclusion and future modification

Callosotomy in pediatric epilepsy is a valuable tool to control seizure early on in order to protect the developing brain from further damage and to give chance to recover neuropsychological function from damage done by seizure itself as well as seizure medication. We advocate one stage total callosotomy in young patients with medically intractable epilepsy without localizing lesions especially effective in drop attacks and secondary generalized epilepsy. With improvement in microsurgical techniques, excellent seizure outcome as well as functional outcome may be reached without previously known high rate of morbidity and mortality. Early detection of patients required for surgical intervention is very important to increase the benefit of early seizure control in recovering lost neuropsychological functions. Patient selection, tailoring of the surgery and excellent surgical skill are mandatory in order to deliver the promised results for intractable epilepsy patients as well as for their family.

Currently with development of surgical aides such as neuronavigation and intraoperative MRI, more selected callosotomy may be attempted in older patients with higher functional baselines. Using diffusion tensor imaging overlaid on the navigation system prior to surgery may be used to depict the tracts from area of interest during operation and can help tailor the extent of resection. In addition, callosotomy may be used as localizing tool for epilepsy with suspicion of localizing lesion, nevertheless cannot be delineated due to fast generalization of epileptic discharge. After disconnection of the callosal fibers, the hidden epileptogenic focus may reveal itself and the seizure may be controlled with further resective surgery. Some of rare intractable seizures such as startle epilepsy may be benefitted from callosotomy as well.

9. Acknowledgement

We acknowledge the great success of our epilepsy clinic to the well-coordinated multidisciplinary team work.

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Part 4

Social Aspects of Epilepsy

11

Childhood Age Epilepsy and Family

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1. Introduction

Epilepsy is a common neurological disorder in childhood. It is the most widely seen chronic neurological disease in the terms of childhood and affects both the child himself and the family because of its psychological and social results. Parents of children with epilepsy, like parents of children with many other chronic conditions, are faced with a constant feeling of uncertainty about their child's condition. Although the negative effect of epilepsy on patient's psychosocial well-being has been increasingly documented in the last decade, the influence of the condition on the family has attracted much less interest. Studies indicate that epilepsy may cause high levels of psychosocial difficulties for all family members, including stigmatization, stress, psychiatric morbidity, marital problems, poor self esteem and restriction of social activities. For this reason, in case any one of the family members undergoes epilepsy, it should not be focused on just patient's problems considering the other family members can affect this situation, preventive strategies that might protect all family members' psychology should be developed. In this part, reviews the present state of family research, examining the influence of childhood epilepsy on the psychological and social well-being of family members.

2. What is a chronic disease?

Chronic diseases are slowly progressing medical cases, causing permanent deficiency, caused by more than one risk factor, lasting at least three months or more, requiring a long term care and nursery and affecting the life quality of a person (Ben-Shlomo & Kuh, 2001, Kuh & Smith, 2005, Gamborg et al., 2011). Of the diseases included in chronic disease definition are heart diseases, such as chronic coroner heart diseases and cardiac insufficiency, hypertension, diabetes, chronic lung diseases and asthma, chronic kidney diseases, depression, epilepsy, cancer and osteoporosis. These diseases take the first place in death reasons in both all developed and developing countries (Wang et al., 2011). In 2005, WHO re-emphasised the importance of chronic (non-communicable) diseases as a neglected global health issue. Chronic diseases—mainly cardiovascular disease, cancer, chronic respiratory diseases, and diabetes—were estimated to cause more than 60% (35 million) of all deaths in 2005; more than 80% of these deaths occurred in low-income and middle-income countries. 50 % of the deaths are at the age 70 or under (Abegunde et al.,2007). The last reports in the USA indicate that half of the adult community (nearly 130 million) has one or more chronic diseases. 83 % of health expenses are done on chronic diseases (Highlights, National Health Expenditures 2002& 2003). Chronic diseases not only take the

first place in the list of death reasons all over the world but also they have the highest rate on health expenses. Chronic conditions such as cardiovascular diseases, cancer, diabetes, arthritis and respiratory diseases are major killers in the U.S. and a major source of illness, hospitalization, health care costs and long-term disability.60- 80 % of health expenses are done for the diagnosis and treatment of these diseases. Especially, the treatment of hypertension, diabetes and cancer is a big financial burden for a society (Projected Population of the United States, by Age and Sex: 2000 to 2050, Flegal et al., 2001)

2.1 Childhood chronic diseases

In all societies all over the world infants are valuable individuals cared and educated as adults of the future and the needs of whom are tried to be fulfilled. The preparations for the new individual in the family start with the beginning of pregnancy period. Although traditions vary in different societies, the common point is the care to the mother. The needs of child increases and differs from the moment it is born. Children can get chronic diseases by birth or later (Er, 2006). The idea that childhood is important for adult health is not new in epidemiology or public health but was the prevailing model of health in the first half of the 20th century (Kuh & Davey, 1993, Davey et al., 2001*)*. Unlike a child with a temporary sickness, the child with a chronic illness must cope with knowing that the disease is here to stay and may even get worse. Almost all these children initially refuse to believe they are ill, and later feel guilt and anger. The young child, unable to understand why the sickness has occurred, may assume it is a punishment for being "bad" (Collins, 2002). Some of the children who have a chronic disease may never be as healthy as they were before they were diagnosed with this illness. 10-15 % of children under 16 years of age affected by chronic, long-term conditions. Children with chronic physical disorders have twice the risk of psychosocial maladjustment compared with healthy children. This "second handicap" poses a significant mental health problem. Much of the research reviewed represents replication of what is already known and important areas of enquiry have been neglected. Investigators are urged to work towards the further identification of high risk characteristics and to apply these to the development and evaluation of new preventive and therapeutic approaches for these children and their families. (Pless & Nolan, 1991) Most children and adolescents with chronic diseases have symptoms that can be acute, which means they start suddenly and last a short period of time. Some youth with chronic diseases may go into remission, or not have symptoms for some time. Chronic childhood diseases are various; anomalies by birth, heart diseases by birth, epilepsy, chronic kidney insufficiency, cancer types, hemophilia, diabetes, cystic fibrosis and asthma are common infancy diseases (Newacheck, 1989). Infancy period diseases are defined as infancy period chronic health problems if they affect infants' daily activities more than 12 months, require to spend much time at home or in a hospital and if their treatment and medical expenses are much (Perrin et al.,1993). Life expectancy and life of quality have been increased with recent studies in childhood chronic diseases (Grootenhuis et al.,2007).

2.1.1 Childhood chronic disease and child

How is a child's life affected by a chronic disease?

Different chronic diseases affect children differently. Regression can be observed in some children who have infancy chronic disease. On the other hand behavior disorders can be seen in children during a chronic disease or other serious diseases, the treatments of which last so long. They get psychological, developmental and environmental problems with the

disease (Prug & Eckhardt, 2000, Erdoğan & Karaman, 2008). The level of the effects of a chronic disease to an infant depends on the time when the disease erected, whether it dates back to the birth, whether the disease is genetic and how old the infant is. It is known that chronic diseases have effects on infants' psychological developments. Chronic disease can cause different effects on different infants (Hergenrather & Rabinowitz, 1991, Sean, 2002, Wise, 2007). Chronic diseases typically affect children's lives in negative ways. If a child has a chronic disease, some problems might include: Discomfort or loss of energy, restriction of activities, disruption of his life due to medical treatment, isolation from family and friends feeling self-conscious, embarrassed, or stigmatized if his disease makes him different from other people. The children who have chronic diseases are at more risk than those who lead healthy lives in terms of having behavioral disorders (Rodenburg et al., 2006). A chronic disease is not only effective on infancy development but also has negative effects on academic development of a child. Some school children who have chronic diseases may have lack of attendance to school due to their treatment periods (Bruzzese et al.,2009). Therefore one of the most important problems for children who have chronic diseases is the difficulty in gaining their independences, caused by their parents and doctors. Parents always tend to protect their chronic diseased children and doctors may also contribute this overprotection by emphasizing restrictions.

2.1.2 Childhood chronic disease and family

Life expectancy and life quality in infancy period diseases is increased according to the studies in recent medical disciplines. Diseased child and the family are exposed to psycho-social effects caused by the disease more with the increasing life expectancy (Wise, 2007, Erdogan & Kahraman, 2008). Childhood chronic illness influences not only the child with the illness but it also the family. A chronic disease of a child is a traumatic situation for a family. Families who learn that their children have a chronic disease have similar phases. The first phase is astonishment and refusal. The child and the family who learned the diagnosis encounter with a case which they have never known before and which requires a long term struggle. The family may think the diagnosis is wrong; also they may act as if they could not understand the disease and its seriousness. The first phase is to accept and recognize the disease, and this will both affect both the treatment and process of the disease. The second phase is 'anger and indignation'. The anger seen in this phase is mostly reflected to the treatment team. This phase is followed by another one, 'feeling guilty'. It is the phase in which some questions such as 'Why us? Why is our child?' are frequently asked. Some families may perceive the disease as a punishment for them. This is clearer if the disease is genetic based. The acceptance of the disease is expected at the end of all these phases. This acceptance will affect the permanence and efficiency of the disease positively. Child and the family may remain in one of these phases or they may go back to the previous phase. The reaction given by each family to live a chronic diseased child and the intensity of this reaction may vary (Santacroce, 2003, Er, 2006). The extent to which the illness influences the child and family varies according to factors such as the age of the child, the child's adaptation level and ability, interaction between child-mother-father, family balance, seriousness of the illness, pain, medication, and limitations and length of the illness. Numerous researches have shown that child illness can negatively affect parents and siblings. There are differences in mother and father roles in the families who have a sick child (Riddle, 1989, Knafl & Zoeller, 2000). Mostly mothers undertake the job of nursery of

the sick child and fathers have an assisting role. It is more difficult for the families in which both father and mother work. Studies indicate that parents (especially mothers) who have a sick child are under more stress and have higher anxiety level than those who do not have a sick child. (Melnyk, 1994, Esdaile et al., 2003, Hasting, 2003, Macias et al.,2003). Some psychiatric problems such as somatic complaints, depression and anxiety disorder are more frequently observed on mothers who have a chronic diseased child than those who do not have a chronic diseased child (Glidden & Schoolcraft, 2003). Various factors such as economic conditions, educational level, jobs, marital adjustment and social security of parents, the type and the severity of the chronic disease, the age of the child and much requirement for medical help (for example; epileptic seizure) affect parents to accept the chronic diseased child, to perceive the disease and to cope with stress (Goldberg et al.,1990, Hanson & Hanline, 1994). To cope with decreasing life quality and increased level of anxiety, families should seek professional support and become informed about their child's illness and treatment options. There is widespread recognition that the presence of a chronic childhood illness can be a source of increased stress and distress among family members, which can lead to disruptions in intrafamilial relationships and family structure (Rausch, 2002, Cieurzo, 2002, Fritts, 2004, Herzer, 2010). Despite the detail that is provided on the potential negative outcomes of children and families who have chronic illnesses, most of these families show admirable resilience. Most children adjust to their illnesses within one year and most families achieve healthy stable functioning with accommodations for the illness. The challenge of adjusting to a chronic illness can provide an excellent opportunity for a child or adolescent to master crucial skills, such as emotion regulation and problem-solving (Le Blanc et al., 2003). Childhood researchers have consistently demonstrated that family functioning is a powerful determinant of overall quality of life and well-being in youth with chronic medical conditions (Herzer et al., 2011).

3. Childhood epilepsy

Epilepsy is one of the most common serious neurological disorders in childhood. Childhood epilepsy is among the most prevalent and important neurological conditions in the recent years (Ronen et al.,2003, Jonsson & Eeg-Olofsson, 2011). Population based studies report prevalence rates of 3.6 to 4.2 per 1000 for children in developed countries (Sidenvall et al.,1996, Beilmann et al.,1999) and approximately double these rates in developing countries (Sridharan & Murthy, 1999, Nicoletti et al.,1999, Christianson et al.,2000, Duggan, 2010, Malik et al.,2011). It is defined as more than one unprovoked seizure and is essentially a clinical diagnosis based on an eye witness account of the attacks. When a child or adolescent presents with their first seizure, a detailed history should be sought for other seizure types that may not have previously been appreciated. An electroencephalogram (EEG) provides supporting evidence for diagnosis of a specific epilepsy syndrome; if a routine EEG is normal, a sleep deprived study should be considered. In individuals with focal epilepsy not classified as idiopathic partial epilepsy, magnetic resonance imaging (MRI) should be performed (Carney, 2005).

Classification of the epilepsies

The International League Against Epilepsy (ILAE) classifies epilepsy syndromes as:

- idiopathic – epilepsy develops in an otherwise normal child, and symptomatic – epilepsy occurs in the setting of a known or suspected abnormality of the central

nervous system. For example, a child with developmental delay has symptomatic epilepsy, as does an individual with hippocampal sclerosis.

The epilepsies are further subdivided into:

- generalised – seizures arise from both hemispheres simultaneously, and partial (or focal) epilepsy – which begins in one part of the brain and may secondarily generalise (Carney, 2005).

Epilepsy can be observed at any age. However, it is frequently seen at early ages. Most epileptic patients have their first epilepsy seizure before age 20. Epilepsy affects 3-5 % of people during their developmental periods (Baum et al.,2007). Epilepsy is characterized by its episodic and chronic nature. The seizures usually produce brief periods of disruption, which include phenomena such as loss of consciousness, bodily distortion, injuries, unusual and often frightening psychological experiences as well as urinary and bowel incontinence. The unpredictability of seizure recurrence is a constant threat to the patient with epilepsy and his or her family. Apart from the episodic seizures, there are many other ever-present factors – social, psychological, behavioral, educational, cultural and so forth – which affect the lives of children with epilepsy- their families and their close social networks. These factors vary considerably from one person to the next, but have a significant impact on the daily quality of life in every affected individual (Ronen et al.,2003). Epilepsy is a complex neurological condition with many possible co-morbid features. Learning Disorders (LD) are more common in children with epilepsy than in the general population. LD are defined as disorders that interfere with academic performance or with daily activities that require reading, writing or mathematical skills in subjects with a normal intelligence quotient (IQ). The prevalence of LD in the general population has been found to be 2-10%, and reading disorders are the most frequent subtype. As a consequence, the risk of cognitive impairment in children with epilepsy is high (Pavlou & Gkampeta, 2011). Thus in addition to the need to address the etiology and treatment of seizures it has become increasingly recognized that professionals should attend to the impact of seizure disorders on the lives and well-being of children as they perceive the issues themselves. Many childhood epilepsy syndromes are readily treated and have an excellent prognosis. Accurate and early diagnosis may ameliorate the psychosocial impact of these disorders on children and their families.

3.1 Psychological effects of epilepsy on children

Psychological and social factors investigated as potential influences on the behavior of children with epilepsy are reviewed. The majority of studies have occurred since the mid 1980s, when Hermann and Whitman (1986) brought attention to the lack of research in this area and noted that a number of psychosocial variables had the potential to explain the development of psychopathology in persons with epilepsy. In pediatric epilepsy, these variables are related to aspects of the family environment, which have been found to influence the development of behavior problems in general population children (Cummings et al., 2000, Austin, 2004, Noeker et.al., 2005). Epidemiological studies over the past 30 years have shown that behavioral disturbances are up to 4.8 times higher in children with epilepsy than in general population children (Davies et al., 2003, Austin & Caplan, 2007). It is nowwell accepted that as a group children with epilepsy have high rates of behavioral disturbance (Rodenburg et al., 2005) and psychiatric diagnoses (Ott et al., 2001; Caplan et al., 2004). In general, children with epilepsy display more attention problems and internalizing problems (withdrawal, somatic complaints, anxiety, and depression symptoms) than they

do externalizing problems such as acting out and conduct problems (Ott et al., 2001; Caplan et al., 2004) A recent meta-analysis of findings from 46 studies contrasted behavior problems in children with epilepsy to control groups, siblings, and children with other chronic childhood conditions (Rodenburg et al., 2005). There is no evidence of psychiatric disorders and/or specific personality traits associated with epilepsy at childhood and adolence ages (Otero 2009). Embarrassment, inhibition, desperation, behaviors based on fear and dependence are usually observed on epileptic children. Anxiety and social regression are also seen frequently. Long term clinical observation studies indicate that epileptic children are at more risk being unemployed, failing school, isolating socially, depending their families economically and having a less marriage rate than those who are healthier (Dunn, 2003, Spangenberg & Lalkhen, 2006, Kerimoglu et al.,2010). Despite the high prevalence of LD with childhood epilepsy, a healthy family and school environment can help reduce its impact on the patient's quality of life (Pavlou & Gkampeta, 2011). Hoare et al., (2000) stated in their studies in which they compared the life quality of epileptic children and that of diabetic children that epileptic children are more negatively affected by psychosocial development and health problems than diabetic children. Results indicated that attention problems, thought problems, and social problems tended to be specific to children with epilepsy, whereas problems with withdrawal, somatic complaints, anxiety/depression, delinquency and aggression were similar to those found in either their healthy siblings or in children with other chronic physical conditions (Rodenburg et al., 2005). Family members' beliefs and feelings related to epilepsy are relevant because of the stigma commonly associated with epilepsy. On the basis of the model it would be anticipated that more negative attitudes and greater perceived stigma related to the epilepsy would be associated with greater child psychopathology (Rodenburg et al.,2006, Shore et al.,2009). Parents' level of perceived stigma related to their child's epilepsy was associated with more depressed mood and behavior problems in children with chronic epilepsy (Buelow et al.,2006). Moreover, perceptions of felt stigma had a stronger association with depression diagnoses in adolescents with epilepsy than did parent perceptions, family adaptive resources, or family stress. Just as found in adults with epilepsy, there does seem to be an association between depression and epilepsy in children and adolescents. Ettinger et al.,(1998) reported elevated scores on the Child Depression Inventory in 26% of a sample of children 7–18 years of age with epilepsy. Adequate monitoring, education targeted at reducing felt stigma, and family intervention programs are needed for early intervention (Adewuya & Ola, 2005). Depression in children and adolescents with epilepsy is a common but often unrecognized disorder. Both epilepsy and depression are characterized by a chronic course and poor long-term psychosocial outcome. Just as found in adults with epilepsy, there does seem to be an association between depression and epilepsy in children and adolescents. Ettinger et al., (1998). reported elevated scores on the Child Depression Inventory in 26% of a sample of children 7–18 years of age with epilepsy. The risk of suicide is even greater in depressed youth with epilepsy than in the general youth population. Educating parents about mood disorders may allow them to be more receptive to psychiatric treatment for their child or themselves. Epidemiological and clinical data on depression in children/adolescents with epilepsy are presented. Seizure-related and general risk factors for the development of depression in youth with epilepsy are reviewed (Plioplys ,2003). Clinicians should consider both neurological and psychosocial factors, including the family system, when treating psychopathology in children with epilepsy (Hodes, 1997, Rodenburg et al., 2005).

3.2 Childhood epilepsy and family

This last decade has seen a dramatic increase in the number of research articles which focus on psychosocial aspects of epilepsy, with areas such as patients' quality of life, social support, and psychiatric difficulties increasingly being addressed. The diagnosis of childhood epilepsy brings with it a series of consequences for the family, not least for the parents: the 'loss of a perfect child', and the 'realization that the child might always be different from the other children (Ellis et al., 2000 **,** Ronen, 2003). Diagnosed with epilepsy live in families facing great sorrow. Nownothing will not be the same for them. Many families in this situation of anger, resentment, guilt feelings and thoughts will dominate. Uncertainty of where and how e child will spend the epileptic seizure, as well as for families with children, especially tonic-clonic fit to witness an extremely worrying situation. Families of children with epilepsy suffer significantly more stress than families of children with infrequent seizures or of healthy controls (Ferrari et al., 1989, Thompson & Upton, 1992). As parents search for a cause or explanation for the epilepsy, there may be the attachment of blame in the family leading to a family spiral of blame and guilt. Furthermore, parents may introduce the concept of stigmatization to their child, as they may fear that others may hold negative stigma against their own child (Ellis et al., 2000). Family members' perceptions of epilepsy may be an important factor in adjustment of the family. Indeed, in some cases it may be more important than the severity of the epilepsy (Shore 2002, Lv, 2009).

The severity of the disease, frequent seizures, no responding to drugs, frequent hospitalization and tests increase the anxiety. Socioeconomic conditions and educational level of families, family relations and adjustments, the response given to previous stress experiences and the ways coping with it are leading factors in this challenging period. Therefore, the families who have healthy relations and methods to cope with the difficulties are more successful in treatment process. Epilepsy requires cooperating for a long time with the treatment team since it is a chronic disease. Sympathetic and supporting approaches of the treatment team are vitally important for both the patient and the family. Informing the patient and the family about the treatment of epilepsy increases the treatment adjustment. However, as in all chronic diseases, the patient and the family sometimes can have problems related to the course and the treatment of the disease and the treatment team. Reactions of the families in different socioeconomic classes may differ in such kind of cases even though they change from a society to another one. As well as the usual difficulties of the disease, changing roles and socioeconomic classes after losing social and vocational statue may result in different reactions. There are differences between the roles in socioeconomic groups. For instance, mothers in middle class are responsible for obtaining knowledge about the disease and they usually undertake the role of being a moderator between the child and the family and the child and the doctor. On the other hand, mothers in a lower socioeconomic class are under more stress and responsibility. It is argued that epileptic children's mothers have more stress than their father and this is caused by mothers' roles in the society. It is emphasized that in mother's role a mother identifies with her child and she does not perceive her child as an only individual but her extension. It is also stated that there is a quite pervious stint between the emotions of the mother and her child, and the mother perceives the child's experiences as if she had them. The risk of having seizure for an epileptic child is rather stressful for the mother. It is notified that mothers who have epileptic children have psychological problems. Shore et al., (2002) defined the correlation between infancy epilepsy and depression in mothers. The depressions of mothers who have

epileptic child are caused by many factors. Among these, expectations of epileptic children from their families, stigma and the frequency of behavioral disorders of children can be mentioned (Vona et al., 2009, Wagner et al.,2009, Bozkaya et al.,2010). Mothers of children with additional psychiatric problems are found to have higher rates of psychiatric disturbances themselves, although it is impossible to disentangle cause and effect in this subject (Hoare 1984, Terra et al., 2011). Risk for clinical depression is common among mothers of children with new-onset epilepsy. Health care professionals should consider routinely assessing maternal depression during clinic visits for pediatric epilepsy (Ferro et al., 2011). It is known that the mother is primarily responsible for the sick child in the family, but the facilitative role of father to help mother is ignored. Even though there are studies related to the mothers of epileptic children, the psychological features and the emotional process which fathers have not known exactly. Also, there have been studies related to the effects of infancy diseases on parents, but the knowledge about the healthy children who are an important part of the family is restricted. A sick child's siblings are quite sensitive to the sickness. They can have emotions such as depression, feeling guilty, anger, anxiety and social isolation. In a serious sickness period healthy siblings are unhappiest and most emotionally ignored individuals of a family. Emotional needs of healthy siblings can be ignored when all attention is paid to the sick child. In this case, a healthy sibling during this period of loneliness, sadness and feelings of parents of not viable. The parents more concerned with physical health of healthy siblings, the emotional problems of healthy siblings often are not noticed. Children with epilepsy more exhibits psychiatric symptoms than their siblings in sibling researchs. Siblings of children with epilepsy compared with children in the general population, more often developed psychiatric symptoms. Siblings of children with chronic epilepsy also have increased behavioral issues, mostly in externalizing behaviors (Mims, 1997, Baca et al.,2010). The functioning of families of children with chronic disease, the negative effects of the disease status is known. Pressure faced by parents of children with epilepsy can lead to tension in function of marriage. Especially with frequent bouts of uncontrollable epileptic children and their families may be over-protective or restrictive. Mother and father often fall disagreements and may be forced to decide. Epilepsy is the power of the child's parents work and therefore affects the family's economic status. It is an illness with multiple consequences and costs for children, families and society. There are only a few studies published on the cost of childhood epilepsy. Illness, for families work at home requires much more than usual and the family will bring an additional burden. In addition to age, the total cost associated with epilepsy also depends on other factors such as seizure frequency, the moment at which the illness cost is estimated and the local health care system. The chronic illnesses not only have an influence on the physical and psychological development of children, they also impose costs on the family and society. Childhood epilepsy has greater economic costs than those generated by more prevalent, chronic diseases (Argumosa & Herranz, 2004). Families try to cope with a variety of ways children have chronic disease. The disease, how raising children, how with leisure time and family members and relations may be affected. Parents of children with epilepsy, like parents of children with many other chronic conditions, are faced with a constant feeling of uncertainty about their child's condition (Hobdell et al.,2007). This uncertainty can lead to a decreased ability to cope as evidenced by increased stress levels, negative mood states, and impaired family functioning. Because altered coping in the parent may have a profound negative impact on the child's psychosocial adjustment to living with a chronic condition, it is important to identify ways to facilitate positive coping skills in the parent (Duffy, 2011).

4. Conclusion

Childhood epilepsy have a significant effect on the patient's own life and all the family. In other words, childhood epilepsy affects both the child himself and the family because of its psychological and social results. Childhood epilepsy might have differences on the points of symptom, cause, medical treatment, strategy, course, restriction in daily activity and long-term effect. However, in all chronic diseases the child and family have the same common effects that cause stress reaction. In the studies, the increasing economical responsibility of the families whose children undergo chronic diseases, parents taking their children to the hospital very often, examination appointments, changing family roles through the disease and the widespread parents' stressors about sentimental adaptation are distinctively described. Still, epilepsy in childhood is different from the other chronic diseases due to the fact that its sudden symptoms and early unpredictable effects are all specific for itself. Epilepsy is the most widely seen neurological disease in the terms of childhood and adolescence and affects both the child himself and the family because of its psychological and social results. When the children get the epilepsy diagnosis, they usually face with many psychological stressors along with the ones about their health. Being different from the other chronic diseases the fact that epileptic attacks might not probably be predicted earlier decreases greatly the epileptic people's perception of controlling their own lives. Studies about the issue make it clear that epileptic children have much more psychological problems than the ones who have other chronic diseases. Epilepsy in the term of childhood can have negative effects on the family. Thus many parents become scattered when their children get the epilepsy diagnosis. The main reason of it is labeling about the situation. Family has to face a lot of problems at the moment when their children get the epilepsy diagnosis. Their typical first reactions are shock, desolation, mourning and depression. The effect of epilepsy in child and the family's daily life is due to some factors. Childhood epilepsy can affect all the family due to the fact that the family demands distinctive changes in using all the sources at present. However, although the parents whose children have epilepsy experience a lot of psychological problems, this situation is mostly neglected. In many studies about epilepsy, despite the fact that the patient's quality of life and relationship with the family are examined, in few ones problems belonging to family members that result from epilepsy are pointed. Clinicians should consider both neurological and psychosocial factors, including the family system, when treating psychopathology in children with epilepsy.

5. Acknowledgment

We offer thanks to our team for suggesting that we write a book about.

6. References

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12

Health-Related Quality of Life in Children and Adolescents with Epilepsy: A Systematic Review

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1. Introduction

With the patients' preferences in the centre of contemporary medicine, it was developed the patient-reported outcome (PRO) concept that represents the patient's report of a health condition and its treatment regimen (Acquadro et al., 2003). This general term includes different sources of information coming directly from patients about their health; each providing a unique and valuable perspective like well-being, functional status, health-related quality of life (HRQOL), and others. The primary values of PROs are considered as indicators of the impact of disease, essential parts for evaluating treatment efficacy and interpreting clinical outcomes, and key elements in decision-making. Coming directly from a patient about his health, PROs are equally valuable as other reports coming from the observations of that patient, e.g. physiological or clinical data.

Nowadays, the concept of the HRQOL appears as the most significant PRO, frequently reported in prevention, treatment, and rehabilitation. This concept represents the patient's evaluation of the impact of a health condition and its treatment on daily life (Acquadro et al., 2003). HRQOL is a multidimensional, changing construct that covers physical, emotional, mental, social, and behavioral components of well-being and functioning as perceived by patients (Ravens-Sieberer et al., 2006). Although a subjective construct, HRQOL is conceptualized through objective indicators as well, and from a measurement perspective, qualitatively and quantitatively observed (Verdugo et al., 2005). The term is separated from its "parent", quality of life (QOL), which implies on an evaluation of the impact of all non-health-related aspects of life on general well-being (FDA, 2006).

Systematizing the current pediatric literature, HRQOL is defined as "functioning, feelings about functioning, health, and value assigned to duration of life" (Davis et al., 2006). The main identified components in the construct are physical and psychological well-being, energy and vitality, self-perception, cognitive functioning, social functioning and support, autonomy and independence, psychological relations to the material environment, and general health perception and life quality (Ravens-Sieberer et al., 2006). Adolescents' HRQOL is a separated construct, with maturation, intimacy, and sexuality as important components added to its assessment (Frisein, 2007). Considering the methodology of

HRQOL assessment, important issues are age, developmental characteristics, self-rating and proxy responding, generic and disease specific approaches, psychometric considerations, and cross-cultural settings (Erling, 1999; Christakis et al., 2001; Barnes & Jenney, 2002; Matza et al., 2004; De Civita et at., 2005; Ravens-Sieberer et al., 2006). First, HRQOL assessment should consider relevant age groups (mainly up to 3, 4-7, 8-12, and 13-16 year-olds), with developmental characteristics specified; physical, psychological, and social. Then, it must be determined an age-appropriate rating, whether a child can rate own HRQOL, or a proxy should be considered. Finally, based on the aims of assessment, appropriate questionnaire should be selected respectfully of type (generic or specific, profile or index, and utility measure), psychometrical characteristics (reliability, validity, responsiveness, and interpretability), and an emphasis put on the cultural settings. Therefore, the evaluation of HRQOL in a group of children or adolescents should include all relevant domains to that group and it should be performed applying appropriate methodology, taking into account sophisticated measures developed and regulations asserted (De Civita et at., 2005; Ravens-Siebere et al., 2006; Davis et al., 2006).

Pediatric epilepsy is a very complex neurological condition primarily characterized by unexpected, episodic, and chronic nature of variety of seizures, but also by different developmental, psychological, behavioral, educational, and social difficulties. As such, pediatric epilepsy has pervasive impacts on all aspects of a child's life (Ronen et al., 2003). Over the past 25 years or more, an extensive literature has examined the impacts of pediatric epilepsy and its co-morbidities on children's lives. A number of studies evaluated the impact of epilepsy on general health, emotional well-being, psychosocial functioning, family, and so on. Epilepsy impact was far more frequently evaluated considering HRQOL, which includes the perceived impact of epilepsy and its treatment on everyday living and functioning. Only with HRQOL, it has become possible to perceive how a child/adolescent with epilepsy lives from day to day, considering his/her well-being and functioning in a variety of domains (physical, cognitive, psychological, social, school, etc.).

The findings of studies from two past decades generally showed that HRQOL in pediatric epilepsy is significantly affected in many domains, primarily cognitive, psychological, and social. Nevertheless, a number of studies that evaluated HRQOL had methodological shortcomings (like not defining domains of interest, age-inappropriate assessments, inappropriate questionnaires used, cross-sectional design, etc.) and findings of different studies were often contradictory (Ronen et al., 2003; Lach et al., 2006). Considering this, it is not possible to draw general conclusions about specific domains of HRQOL affected in children and adolescents with epilepsy and to understand the nature and dynamics of epilepsy and its treatment impacts on everyday living and functioning in this population.

Therefore, this review was organized with the aims to identify in a systematic way the domains of HRQOL affected in children and adolescents, the predictors of HRQOL, and the impacts on HRQOL of specific and non-specific epilepsy treatments (antiepileptic drugs (AEDs), epilepsy surgery, vagus nerve stimulation, and others).

2. Methods

2.1 Search strategy

Three independent computerized searches of the literature for the period 1st January 1996 to 31st January 2011 were performed in Pubmed, Scopus, and Web of Science. Besides, a detailed search of main relevant journals was performed: epilepsy (Epilepsia, Epilepsy & Behavior, Epilepsy Research, Seizure, Epileptic Disorders, Epilepsy Abstracts, Epilepsy

Currents, and Epilepsies), child neurology (Developmental Medicine and Child Neurology, Journal of Child Neurology, and Pediatric Neurology), and patient outcome assessment (Value in Health, Health and Quality of Life Outcomes, and Quality of Life Research). The term "epilepsy" was combined with other key terms: children, adolescents, quality of life, QOL, health-related quality of life, and HRQOL. The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the searches.

2.2 Selection criteria

The following selection criteria were set: (1) the study population was children and/or adolescents up to 18 years of age; (2) HRQOL was the primary or secondary endpoint of the study; (3) HRQOL was assessed with an epilepsy specific and/or generic questionnaire/s previously validated; (4) the data for overall and/or domains of the questionnaire/s used were reported; and (5) the study was published in a peer-review journal. Based on the previous analyses of epilepsy specific questionnaires for HRQOL assessments in children and adolescents, eleven questionnaires were available (Ronen et al., 2003a; Waters et al., 2009) - Impact of Childhood Neurologic Disability Scale – ICND (Camfield et al., 2003), Quality of Life in Epilepsy for Adolescents questionnaire – QOLIE-AD 48 (Carmer et al., 1999), HRQOL in Pediatric Epilepsy Scale (Arunkumar et al., 2000), Quality of Life in Childhood Epilepsy Questionnaire – QOLCE (Sabez et al., 2000), HRQOL Instrument for Children with Epilepsy – CHEQOL-25 (Ronen et al. 2003), Epilepsy and Learning Disabilities Quality of Life Scale – ELDQOL (Buck et al., 2007), DISABKIDS Chronic Generic Measure, with Epilepsy Specific Module (Simeoni et al., 2007), Glasgow epilepsy outcome scale for young persons – GEOS –YP (Townshend et al., 2008), Epilepsy and children questionnaire – ECQ (Coda et al., 2001), Escala de calidad de vida del niño con epilepsia – CAVE (Herranz & Casas, 1996), and HRQOL for Brazilians – QVCE-50 (Maia Filho et al., 2007). Lists of different generic HRQOL questionnaires were provided in (Davis et al., 2006; Solans et al., 2008).

The described inclusion criteria were applied to the initial 1208 hits. Based on titles and abstracts of articles, 155 articles were potentially applicable from all three searches. When PDF files were obtained for these 155 articles, the selection criteria were applied again to the full articles' text and 44 remained to be included in this review.

2.3 Quality assessment

Two investigators (Stevanovic and Tadic) assessed the methodological quality of all 44 selected studies using a 17-item standardized checklist of predefined criteria (Table 1). The checklist was a modified version of an established criteria list for systematic reviews (Kuijpers et al., 2004; Mols et al., 2005; Den Oudsten et al., 2007). Each item of a selected study that met the criterion was assigned one point. If an item did not meet a particular criterion or was described insufficiently or not at all, no point was assigned. The highest possible score was 17. Studies scoring 70% or more of the maximum attainable score (i.e. ≥12 points) were rated to be of "high quality", studies scoring between 50% and 70% (i.e. 8-11 points) were rated as "moderate quality", and studies scoring lower than 50% (i.e. ≤ 7 points) were rated as "low quality" studies.

Positive if:
QOL assessment
A. A psychometrically sound questionnaire used
B. A reason given for choosing a certain questionnaire
Study population
C. Children and/or adolescents and parents/caregivers included
D. Inclusion and/or exclusion criteria considered (at least age, duration of symptoms, and relevant comorbidity)
E. Participation rates for patient groups described and these rates exceeded 75%
F. A description of the sample included socio-demographic (at least age, gender, and educational status) and epilepsy variables (at least type, age at onset, duration, and treatment)
G. Information is given about the ratio non-responders versus responders or no selective response
H. The setting of requirement given (i.e. general practice, hospital, occupational setting, etc)
I. The process of data collection described (e.g., interview or self-assessment, etc.)
Study design
J. The data prospectively gathered
K. The follow-up period of at least 6 months
L. Drop-out/loss to follow-up < 20%
HRQOL Results
M. The sample size (the number of cases equaled at least ten times the number of variables in the multivariate analysis)
N. The results reported overall and specific HRQOL domains (at least mean and standard deviations)
O. The results compared between two or more groups (e.g., health population, groups with different severity of epilepsy or age) and/or compared with at least two time points (e.g., longitudinally or pre- versus post-treatment)
P. The data for children and adolescents presented separately
Q. Predictors described using regression analyses or structural equation modeling

Table 1. List of criteria for assessing the methodological quality of HRQOL studies

2.4 Data extraction and synthesis

Data were extracted of the selected studies regarding a study population, design, HRQOL questionnaire/s used, HRQOL domains and predictors studied, and treatment reported. All measures used for HRQOL assessments in the selected, besides holding the title of quality of life of HRQOL, are very different from each other on several aspects despite having adequate psychometric properties, especially in epilepsy (Ronen et al., 2003). Therefore, in order to facilitate interpretation and comparison of the results of the studies that used different questionnaires, the following HRQOL domains were considered: general health, physical, cognitive, psychological, general behavior, social, family, school, and epilepsy specific domain. Where appropriate, to the domains were added specific subdomains evaluated by the questionnaires used (i.e. psychological domain (emotional well-being,

anxiety, etc.) or cognitive domain (attention, memory, etc)). HRQOL predictors were considered as demographic, social, psychological, and epilepsy specific. For epilepsy treatment, AEDs, epilepsy surgery, vagus nerve stimulation, and others interventions/drugs were considered relevant.

The domains of HRQOL affected in children and adolescents were identified from the synthesis of consistent findings from the studies that compared HRQOL between children and adolescents and controls or from the synthesis of consistent findings from the studies using the same questionnaire. Next, HRQOL predictors were identified from the synthesis of consistent findings from the studies that used regression models to evaluate predators of HRQOL. Finally, the impacts on HRQOL of specific and/or non-specific treatments were identified from the synthesis of consistent findings from the studies that consider some treatment.

Findings were considered consistent if ≥ 75% of the studies that investigated a domain/predictor showed the same direction of the association. Five levels of evidence were defined as modified according to the study of Mols and colleagues (Mols et al., 2005) (Table 2).

Strong	Consistent findings (≥75%) in at least two high-quality studies or one high-quality study and at least two moderate studies
Moderate	Consistent findings (≥75%) in one high-quality study and one moderate- or low-quality study or at least three moderate studies
Weak	Findings of one high-quality study or consistent findings of two moderate studies or at least three low-quality studies
Inconclusive	Inconsistent findings or less than three low-quality study

Table 2. Level of evidence

3. Results

3.1 Study characteristics and methodological quality

Forty-four analyzed studies were published after 1999 and mostly in the USA, Canada, and Australia (Table 3). Thirty-one studies were cross-sectional, 12 follow-up, and one randomized clinical trial (RCT). In 15 studies, HRQOL was compared between children and adolescents and controls (general population or chronic illnesses), while a specific and/or non-specific treatment was considered in 15. Nine studies evaluated HRQOL in adolescents and nine evaluated HRQOL as self- (child/adolescent) and parent-rated. The study samples included between 9 and 474 participants.

There was disagreement between the two reviewers when scoring the articles, mainly due to differences in applying the criteria B, E, G, and M. These disagreements were solved through discussion in a consensus meeting. The quality scores ranged from 7 (low) to 14 points (high), with the mean score of 10. Methodological shortcomings mainly concerned the reason given for choosing a certain questionnaire (B), the rater, children and/or adolescents and parents (C), the participation rates (E), the follow-up period (K), the sample size (M), the data presentation, children and adolescents (P), and the predictors (Q).

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Children and adolescents with epilepsy				
Ronen et al., 2010, Canada	12 (E, K, M, P, O)	CHEQOL-25, children, adolescents, parents,	Design: cross-sectional Number (m/f): 131 (NA) Age (years): 7.8-16 Epilepsy type: different types	• Predictors : duration of epilepsy, age at epilepsy onset, number of AEDs, side effects of AEDs, attention and conduct problems, anxiety, intelligence, autonomy, social support, family structure, social skills, parent mood, and victimization
Yam et al., 2008, China	12 (B, E, K, P, Q)	CHEQOL-25 children, adolescents, parents,	Design: cross-sectional Number (m/f): 266 (NA) Age (years): 8-18 Epilepsy type: different types Control group: 381 CAWE from Canada	• CAWE from Hong Kong had lower levels of HRQOL in the interpersonal, secrecy, and worries domain compared to CAWE from Canada • There was acceptable agreement between children and parents, but parents tended to underestimate the HRQOL of their children
Verhey et al., 2009, Canada	11 (B, G, K, P, Q)	CHEQOL-25, children, adolescents, parents,	Design: cross-sectional Number (m/f): 391 (189/202) Age (years): 8-17 Epilepsy type: different types	• Lower levels of parent–child agreement on the more abstract domains of HRQOL in CAWE (secrecy and concerns) • Parent perspectives alone are insufficient to measure their child's HRQOL
Mathiak et al., 2010, Poland	11 (B, C, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 31 (19/12) Age (years): 6-15 Epilepsy type: different types	• CAWE with right-hemispheric foci had lower levels in emotional (including anxiety) and social (including stigma) domains
Clary et at., 2010, USA	10 (B, C, E, K, M, O, P)	QOLCE, parents	Design: cross-sectional Number (m/f): 132 (69/63) Age (years): 6-17 Epilepsy type: different types	• Predictors: age at onset (emotional well-being), intelligence (cognitive functioning), depression, withdrawal, attention problems, atypicality, and aggression (cognitive function, emotional well-being, and behavior)
Ferro et al., 2011, Canada	10 (B, C, G, K, P, O, N)	QOLCE, parents	Design: 24-month-follow-up Number (m/f): 339 (177/162) Age (years): 4-12 Epilepsy type: newly diagnosed, different types	• Maternal depressive symptoms had significant negative impacts on HRQOL in CAWE. This relationship was moderated by family resources and partially mediated by family functioning and demands
Yong et al., 2006, China	8 (A, B, C, D, E, K, N, O, P)	QOLCE, parents	Design: cross-sectional Number (m/f): 418 (241/177) Age (years): 4-18	• Predictors: child's educational degree, mental development, age at onset and diagnosis, seizure frequency, number of

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Epilepsy type: different types	AEDs, economic status, parental health (depression and anxiety)
Li et al., 2008, China	7 (A, B, C, D, E, K, N, O, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 340 (203/137) Age (years): 4-18 Epilepsy type: different types	• Parental anxiety is inversely correlated to HRQOL in CAWE
Wirrell et at., 2005, Canada	7 (A, B, C, G, K, M, N, O, P, Q)	QOLCE, modified version, parents	Design: cross-sectional Number (m/f): 57 (27/28) Age (years): 4-16 Epilepsy type: different types Control group: 55 healthy and controls with chronic conditions	• Sleep problems correlated with lower levels of overall HRQOL and in physical, social, and cognitive functioning and behavior domain
Haneef et al., 2010, USA	11 (D, E, G, K, P, Q)	PedsQL, children, adolescents, parents	Design: cross-sectional Number (m/f): 100 (59/41) Age (years): 2-18 Epilepsy type: different types Control group: literature data	• CAWE had lower physical, emotional, social, and school functioning compared to the normative data • CAWE had significantly lower physical and school functioning compared to other chronic illnesses as self-rated, and lower physical, emotional, and social functioning as parent-rated • Children with well-controlled epilepsy and a neuropsychiatric comorbidity had lower HRQOL in all domains than those without a neuropsychiatric comorbidity • Lower levels of HRQOL were observed in refractory than in well-controlled epilepsy
Ingerski et al., 2010, USA	9 (B, D, E, F, G, K, P, Q)	PedsQL, children, adolescents, parents,	Design: cross-sectional Number (m/f): 105 (71/34) Age (years): 2-18 Epilepsy type: NS Control group: different chronic conditions (7)	• Children and adolescents with epilepsy had similar or better levels of HRQOL than others with chronic conditions
Modi et al., 2010, USA	7 (B, C, D, E, G, J, K, M, P, Q)	PedsQL, parents	Design: cross-sectional Number (m/f): 53 (27/26) cases with a single seizure and 56 (35/21) cases with a newly diagnosed epilepsy Age (years): 2.1-17.9 Epilepsy type: different types Control group: normative data	• Children with a single seizure and newly diagnosed epilepsy had lower physical, emotional, social, and school functioning compared to the normative data • No significant differences were found between children with a single seizure and children with newly diagnosed epilepsy

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Lagunju et al., 2009, Nigeria	7 (A, B, C, D, E, F, K, O, P, N)	PedsQL, children, adolescents, parents,	Design: cross-sectional Number (m/f): 66 (33/33) Age (years): 5-15 Epilepsy type: different types	• Predictors : seizure severity and family disruption
Baca et al., 2010, USA	12 (B, G, K, P, Q)	CHQ-CF87, CHQ-PF50, children, adolescents, parents	Design: cross-sectional Number (m/f): 279 (149/130) Age (years): NS (mean 13 (2.6)) Epilepsy type: different types Control group: 143 healthy siblings	• CAWE had lower levels of physical function and physical role limitations as self-rated than their siblings • Patents of CAWE reported lower levels of physical and psychosocial functioning than for their siblings and as compared to the normative data • There is significant differences in child self-report versus parent report of HRQOL for CAWE compared with sibling controls
Miller et al., 2003, USA	10 (B, C, D, E, K, M, P)	CHQ-PF 50, parents	Design: cross-sectional Number (m/f): 41 (23/18) Age (years): 4-19 Epilepsy type: different types Control group: 41 age- and sex-matched healthy controls	• CAWE had lower levels of global health, physical functioning, roles (physical, emotional, and behavioral), mental health, self-esteem, parent impact, and family activities compared to healthy controls • Predictors : comorbid neurological impairments and number of AEDs
Tse et al., 2007, Canada	11 (B, C, K, O, P, Q)	ICND, parents	Design: cross-sectional Number (m/f): 101 (52/49) Age (years): 3-17 Epilepsy type: different types Control group: 101 siblings	• CAWE with better social skills had better HRQOL (in overall and impact of epilepsy on behavior, cognition, and physical/neurological disability domain)
Montanaro et al., 2005, Italy	9 (B, C, D, E, F, K, P, Q)	ECQ, children, adolescents	Design: cross-sectional Number (m/f): 140 (70/70) Age (years): 7-16 Epilepsy type: different types Control group: healthy controls	• CAWE had lower levels of psychological and social functioning than healthy controls, but similar levels of school functioning
• ***Adolescents with epilepsy***				
Devinsky et al., 1999, USA	13 (C, E, K, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 197 (96/101) Age (years): 11-17 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : age, epilepsy severity, side effects of AEDs (neurotoxicity), and socioeconomic status

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Stevanovic, 2007, Serbia	12 (C, E, G, K, M)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 71 (39/32) Age (years): 11.5-18 Epilepsy type: different types	• Males and females had similar levels of HRQOL, except that female perceived grater epilepsy impacts • Attitudes toward epilepsy and social support domain with the lowest scores • Predictors : number of AEDs, epilepsy concern, and female gender
Adewuya, 2006, Nigeria	10 (A, B, C, K, M, N, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 86 (50/36) Age (years): 12-18 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : number of AEDs, duration of illness, side effects of AEDs, general psychopathology, and parent mood (depression)
Benavente-Aguilar, et al., 2004, Spain	10 (B, C, E, K, M, O, P)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 66 (36) Age (years): 10-19 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : epilepsy severity and side effects of AEDs
Turky et al., 2008, UK	10 (C, E, G, K, M, N, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 56 (25/31) Age (years): 11-17 Epilepsy type: different types	• Predictors : seizure frequency and the presence of special educational needs
Wu et al., 2010, China	12 (B, C, E, K, M)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 47 (26/21) Age (years): 11-17 Epilepsy type: different types Control group: 47 age- and sex-matched healthy controls	• No differences between males and females • Social support domain with the lowest score • AWE had more impaired aspects of memory, concentration, physical functioning and social support compared to normal controls • Predictors : seizure worry, age at epilepsy onset, and fear of injury
• ***Specific epilepsy types or specific populations with epilepsy***				
Connoly et al., 2006, Australia	13 (C, K, M, P)	CHQ-PF 50, QOLCE, parents	Design: cross-sectional Number (m/f): 30 (22/8) Age (years): 7-12 Epilepsy type: benign rolandic epilepsy (BRE)	• Children with BRE had lower levels of self-esteem, anxiety, depression, and impact of the illness on the family compared to normative data, but similar levels of physical functioning • Predictors : general intellectual ability and parental emotional impact

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Northcott et al. , 2007, Australia	10 (B, C, G, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 40 (16) Age (years): 6-12 Epilepsy type: BRE Control group: 40 age- and sex- matched healthy controls	• Children with BRE had lower levels of cognition, attention, memory, anxiety, self-esteem, and general health compared to healthy controls
Sabaz et al., 2001, Australia	12 (B, C, K, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 94 (46/48) Age (years): 4-18 Epilepsy type: different types with and without intellectual disability	• Intellectually normal CAWE had higher levels on physical restrictions, attention, language, control/helplessness, social interactions, social activities, and behavior than CAWE and intellectual disability (IQ < 70)
Sabaz et al., 2003, Australia	12 (C, G, K, P, Q)	CHQ-PF 50, QOLCE, parents	Design: cross-sectional Number (m/f): 119 (63/56) Age (years): 4-18 Epilepsy type: epilepsy syndromes	• Symptomatic epilepsy syndromes had lower levels of physical function, social limitations due to behavioral difficulties and physical health, self-esteem and emotional impact compared to idiopathic epilepsy syndromes
Wanigasinghe et al., 2010, Australia	7 (B, C, E, I, K, M, N, O, P, Q)	PedsQL, parents	Design: cross-sectional Number (m/f): 63 (41/22) Age (years): 4-20 Epilepsy type: epilepsy in hemiplegic cerebral palsy (CP) Control group: hemiplegic CP without epilepsy	• Emotional, school, and social functioning were significantly lower in children with CP and epilepsy than in those without epilepsy
Wake et al., 2003, Australia	7 (B, C, D, E, F, G, K, M, P, Q)	CHQ-PF 50, parents	Design: cross-sectional Number (m/f): 80 (45/35) Age (years): 5-18 Epilepsy type: different types in CP Control group: children with CP, but without epilepsy	• Children with CP and epilepsy had lower levels of self-esteem and difficulty getting along in the family
• ***Antiepileptic drugs (AEDs)***				
Jakovljevic et al., 2008, Serbia	10 (B, C, D, E, K, M, N)	QOLIE-AD-48, adolescents	Design: 3-months-follow-up Number (m/f): 21 (NA) Age (years): 8-20 Epilepsy type different types Frequency of assessments: two Drug: valproate	• Memory/concentration and physical functioning domain inversely correlated with the serum concentrations of valproate

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Gupta et al., 2004, India	10 (A, B, C, K, M, P, Q)	QOLCE, parents	Design: randomized, double-blind, placebo-controlled trail Number (m/f): 31 (18/12) Age (years): 3-12 Epilepsy type: different types Frequency of assessments: two Drug: melatonin and valproate	• Significant improvement on attention, memory, language, other cognitive processes, anxiety, and behavior after adding melatonin to valproate
Jung et al., 2010, Korea	9 (B, C, E, G, P, Q, H, I)	K-QOLCE, parents	Design: 6-month-follow up Number (m/f): 474 (276/198) Age (years): 4-17 Epilepsy type: different types Frequency of assessments: two Drug: topiramate	• Significant improvement after 6 months was observed in energy/fatigue, anxiety, self-esteem, concentration, memory, language, social activities, and behavior domain • CAWS receiving only topiramate showed a greater improvement with regard to the cognition and behavior domain than those taking polytherapy
Vovk et al., 2010, Serbia	7 (B, C, D, E, F, K, M, N, O, P)	QOLIE-AD-48, adolescents	Design: 3-month-follow-up Number (m/f): 26 (11/15) Age (years): 8-54 Epilepsy type: different types Frequency of assessments: two Intervention or drug: topiramate	• Topiramate plasma concentration did not correlate with HRQOL
Ficker et al., 2005, USA	10 (B, C, G, H, K, N, Q)	QOLIE-AD-48, adolescents	Design: 3-month-follow-up Number (m/f): 39 (NA) Age (years): 12-17 Epilepsy type: partial epilepsy Frequency of assessments: two Intervention or drug: carbamazepine	• There were significant improvements in epilepsy impact and health perception domain in CAWE taking carbamazepine
• ***Epilepsy surgery***				
Van Empelen et al., 2005, The Netherlands	14 (D, M, Q)	HAY, children, adolescents, parents	Design: 24-month-follow-up Number (m/f): 21 (4/17) Age (years): 6.2-16.8 Epilepsy type: symptomatic	• Improvement in physical, cognitive, and social activities after 6 months • CAWE felt less bothered at 24 months about the seizures; cognitive and social activities, as

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Control group: reference data for healthy children Frequency of assessments: four Intervention: epilepsy surgery	well as feelings about seizures and epilepsy treatment improved, while the frequency of concerns and feelings of inferiority because of having a chronic illness decreased • No significant differences were found between children (6–12 years) and adolescents (older than 12 years) • Before surgery, children felt less bothered with respect to physical, cognitive, and social activities than their parents did. Two years after surgery, they still felt less bothered than their parents did about cognitive activities. Additionally, their feelings with respect to general physical complaints and to seizures were more positive than those of the parents
Zupanic et al., 2009, USA	12 (B, J, K, P, Q)	QOLCE, QOLIE-AD-48 parents/care givers, adolescents	Design: cross-sectional Number (m/f): 83 (35/48) Age (years): 0-21 Epilepsy type: symptomatic Frequency of assessments: once Intervention: epilepsy surgery	• Physical activity, cognition, social activity, and general health were significantly better in children with seizure-free outcomes than in children who were not seizure-free (parents rates) • There was no difference in levels of HRQOL (QOLIE-AD 48 domains) between adolescents who were seizure free and adolescents who were not after surgery
Sabaz et al., 2006, Australia	12 (B, C, D, M, P)	QOLCE, parents	Design: 18-month-follow up Number (m/f): 35 (NA) Age (years): 6-18 Epilepsy type: symptomatic Frequency of assessments: three Intervention: epilepsy surgery	• CAWE who were seizure free postoperatively showed improvements in social interactions, social activities, anxiety, control-helplessness, physical restrictions, and general health • Predictors : seizure outcome (seizure freedom) and baseline levels of HRQOL
Mikati et al., 2010, Lebanon	8 (A, B, C, D, H, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 19 (11/8) Age (years): 2-14 Epilepsy type: symptomatic	CAWE who underwent surgery had higher levels of behavior than non-operated CAWE, but similar levels of physical activates, emotional, cognitive and social

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Control groups: 19 non-surgery partial epilepsy matched controls; 19 matched healthy controls Intervention: epilepsy surgery	functioning CAWE who underwent surgery had lower levels of physical functioning and general health than healthy controls
Mikati et al., 2008, Lebanon	8 (A, B, C, D, H, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 17 (10/7) Age (years): 4-16 Epilepsy type: symptomatic Control group: 12 non-surgery epilepsy matched controls Frequency of assessments: once Intervention: epilepsy surgery	CAWE who underwent surgery had higher levels of physical activities, emotional well-being, and general health than non-operated CAWE Type of surgery (temporal vs. extratemporal) was not associated with HRQOL
Vagus nerve stimulation (VNS)				
Sherman et al., 2008, Canada	11 (B, C, M, N, P, Q)	ICND, parents	Design: 1-year-follow-up Number (m/f): 34 (10/14) Age (years): 3-18 Epilepsy type: different types Control group: 19 children with chronic epilepsy Frequency of assessments: two Intervention: VNS	Pre-implantation, VNS children as a group had significantly poorer HRQOL compared with the chronic epilepsy group in terms of epilepsy-specific and global domains During the follow-up, the children in both groups showed no changes in epilepsy-specific quality of life A greater number of children in the VNS group had meaningful increases in HRQOL compared with the chronic epilepsy group, but this difference did not reach statistical significance
You et al., 2007, Korea	9 (B, C, D, E, M, N, P, Q)	QOLCE parents	Design: 6-year-follow-up Number (m/f): 28 (16/12) Age (years): 2y5m – 17y10m Epilepsy type: different types Frequency of assessments and timing: four Intervention: VNS	VNS improved memory, mood, behavior, alertness, achievement, and verbal skills as HRQOL domains
Mikati et al., 2009. Lebanon	8 (A, B, C, D, K, M, N, P, Q)	QOLCE, parents,	Design: 0.4-3.9-year follow-up Number (m/f): 11 (NA) Age (years): 5-18 Epilepsy type: different	CAWE with VNS had improvement in social domain only

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			types Frequency of assessments: two Intervention: VNS	
Epilepsy - nonspecific pharmacological treatments or interventions				
Yoo et al., 2009, Korea	9 (B, C, D, E, G, K, M, P)	QOLCE, parents	Design: 2-month-follow-up Number (m/f): 25 (17/8) Age (years): 6-17 Epilepsy type: different types Frequency of assessments: two Drug: osmotic-controlled release oral delivery system (OROS) methylphenidate	After two months of OROS methylphenidate treatment, levels of physical restriction, self-esteem, memory, language, other cognition, social interaction, behavior, and general health domain improved
Conant et al., 2008, USA	8 (B, C, D, E, G, K, M, P, Q)	QOLCE, parents	Design: 10-week-follow up Number (m/f): 9 (NA) Age (years): 8-16 Epilepsy type: different types Frequency of assessments: two Intervention: karate program	Significant improvement on memory after passing the karate program

CAWE – children and adolescents with epilepsy, CHEQOL-25 – HRQOL Instrument for Children with Epilepsy, QOLCE – Quality of Life in Childhood Epilepsy Questionnaire, QOLIE-AD 48 – Quality of Life in Epilepsy for Adolescents questionnaire, PedsQL – Pediatric quality of life inventory (Varni et al., 2001), CHQ-CF87 and CHQ-PF50 – Child Health Questionnaire (Landgraf, 1996), ICND – Impact of Childhood Neurologic Disability Scale, ECQ – Epilepsy and children questionnaire, HAY – How Are You (Bruil, 1999), NA – not available, AEDs – antiepileptic drugs

Table 3. Overview of the studies included in the analyzes

3.2 Health-related quality of life

Children and adolescents with epilepsy had significantly lower levels of functioning and well-being in physical, psychological (including emotional, general mental health, and self-esteem), social, school, and family domain compared to healthy controls, siblings, and/or the normative data (Miller et al., 2003; Montanaro et al., 2004; Modi et al., 2009; Haneef et al., 2010; Baca et al., 2010). One study reported that children and adolescents had significantly lower physical and school functioning compared to other chronic illnesses as self-rated, and lower physical, emotional, and social functioning as parent-rated (Haneef et al., 2010). Nevertheless, one study showed that children and adolescents had similar or better levels of HRQOL as others with chronic conditions (Ingerski et al., 2010). Finally, children and adolescents with refractory epilepsy or neuropsychiatric co-morbidities had low levels of physical, emotional, social, and school functioning (Haneef et al., 2010).

Six cross-sectional studies evaluated HRQOL in adolescents with epilepsy using the QOLIE-AD 48 (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007; Turky et al., 2008; Wu et al., 2010). In these studies, the attitudes towards epilepsy and social domain were with the lowest scores, when the scores of all eight QOLIE-AD 48 domains were compared in-between. Only one study reported that AWE had more impaired aspects of memory/concentration, physical and social functioning compared to normal controls (Wu et al., 2010). There were no differences between males and females in the social, health perception, memory/concentration, physical functioning, stigma, attitudes toward epilepsy, and school behavior domain evaluated by the QOLIE-AD 48 (Stevanovic, 2007; Wu et al., 2010).

Several studies evaluated HRQOL in specific epilepsy groups. In two studies, HRQOL was evaluated in children with benign rolandic epilepsy and psychological domain (including anxiety, depression, and self-esteem) was more affected than others were (Connolly et al., 2006; Northcott et al., 2007). Further, one study reported that intellectually normal CWE had higher levels on physical, cognitive (attention, language), psychological (control/helplessness), social and general behavior than CWE and intellectual disability (IQ < 70) (Sabaz, 2001). One study reported that symptomatic epilepsy syndromes had lower levels of physical, psychological, and social compared to idiopathic epilepsy syndromes (Sabaz, 2003). Finally, two studies analyzed HRQOL in epilepsy in cerebral palsy and reported decreased levels of functioning and wellbeing in different domains (Wake et al., 2003; Wanigasinghe et al. 2010).

Finally, four studies reported that there was acceptable agreement between children/adolescents and parents, but parents tended to underestimate the HRQOL of their children (Miller et al., 2003; Van Empelen et al. 2005; Yam et al., 2008; Verhey et al., 2009). The level of agreement between child self-report's and parent proxy was lower on the more abstract domains of HRQOL (feeling, secrecy, concerns, etc.) (Van Empelen et al. 2005; Yam et al., 2008).

3.3 Predictors

Different demographic, social, psychological, and epilepsy specific variables were investigated as predictors of HRQOL in children and adolescents and all were summarized in Table 4 according to the levels of evidence found.

3.3.1 Impacts of AEDs on HRQOL

Two studies evaluated the impact of topiramate (Jung et al., 2010) and carbamazepine (Ficker et al., 2005) on HRQOL in children and adolescents. Topiramate treatment led to significant improvements after 6 months in psychological (including energy/fatigue, anxiety, and self-esteem), cognitive (including memory and language), social, and general behavior domain. Adolescents with partial epilepsy treated with carbamazepine had significant improvements in epilepsy impact and health perception domain.

In one RCT, the impact of adding melatonin to valproate on HRQOL was evaluated (Gupta et al., 2004). The findings suggest that significant improvements were found on cognitive (including attention, memory, language, and other cognitive processes) and general behavior after adding melatonin to valproate.

Two studies evaluated the relationship between the serum concentrations of valproate and topiramate and HRQOL (Jakovljevic et al., 2008; Vovk et al., 2010). For valproate, it was

reported that memory/concentration and physical domain were inversely correlated with the serum concentrations, while for topiramate, the correlation between the serum concentrations and HRQOL was not observed.

Strong	Moderate	Weak	Inconclusive
Children and adolescents			
Age at epilepsy onset, number of AEDs, parental depression (Miller et al., 2003; Yong et al., 2006; Ronen et al, 2010; Clary et al., 2010; Ferro et al., 2010)	Attention problems, intelligence, family including, structure, parental anxiety, etc. (Yong et al., 2006; Li et al., 2008; Lagunju et al., 2009; Ronen et al, 2010; Clary et al., 2010)	Social skills, duration of epilepsy, side effects of AEDS, conduct problems, autonomy, social support, victimization (Ronen et al, 2010; Tse et al., 2007)	Seizure frequency, seizure severity, comorbid neurological impairments, psychological problems (conduct, anxiety, depression, withdrawal, atypicality, aggression), child's educational degree, mental development, economic status (Miller et al., 2003; Yong et al., 2006; Lagunju et al., 2009; Clary et al., 2010)
Adolescents			
Seizure worry/concern, side effects of AEDs (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007; Wu et al., 2010)	Epilepsy severity, number of AEDs (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007)	Age, socioeconomic status, fear of injury, age at epilepsy onset, female gender (Devinsky et al., 1999; Stevanovic, 2007; Wu et al., 2010)	Duration of epilepsy, seizure frequency, general psychopathology, special education needs, parent mood (depression) (Benavente-Aguilar et al., 2004; Adewuya, 2006; Turky et al., 2008)

Table 4. Predictors of HRQOL in children and adolescents with epilepsy

3.3.2 Impacts of epilepsy surgery on HRQOL

Five studies, two follow-ups, evaluated HRQOL in children and adolescents with symptomatic epilepsy who underwent epilepsy surgery (Van Empelen et al., 2005; Sabaz et al., 2006; Mikati et al., 2008; Mikati et al., 2010; Zupanc et al., 2010). All studies reported that epilepsy surgery improved different HRQOL domains in children and adolescents compared to non-operated children and adolescents or healthy controls. However, there were no differences in HRQOL between adolescents who were and who were not seizure free after surgery (Zupanc et al., 2010). No differences were found between children and adolescents (Van Empelen et al., 2005), while seizure outcome (seizure freedom) and baseline levels of functioning strongly predicts HRQOL in this population (Sabaz et al., 2006).

3.3.3 Impacts of vagus nerve stimulation on HRQOL

Three follow-up studies evaluated HRQOL in children and adolescents with implemented vagus nerve stimulation (VNS) (You et al., 2007; Sherman et al., 2008; Mikati et al., 2009). In general, VNS improved different HRQOL domains in children and adolescents, mainly cognitive, psychological, and social (You et al., 2007; Sherman et al., 2008). However, there was no statistical difference between those children with and without VNS (You et al., 2007).

3.3.4 Miscellaneous

One follow-up study reported that after two months of OROS-methylphenidate treatment added to AEDs improved physical, psychological (including self-esteem), cognitive (including memory and language), social interaction, general behavior, and general health domain (Yoo et al., 2009). One follow-up study reported that a 10-week karate program for children and adolescents significantly improved memory in cognitive HRQOL domain (Conant et al, 2008).

4. Discussion

This is the first systematic review synthesizing different studies that evaluated HRQOL in children and adolescents with epilepsy over 12 past years. The affected domains, predictors, and impacts on HRQOL of specific and non-specific treatments were reviewed. Previous reviews evaluated methodological issues in HRQOL assessment, components of theoretical model, and determinants of HRQOL in pediatric epilepsy (Ronen et al., 2003a; Cowan & Baker, 2004; Maia Filho et al., 2004; Lach et al., 2006; Waters et al., 2009).

4.1 Summary of evidence

Combining the selected studies, the following evidence was found for different aspects of HRQOL in children and adolescents with epilepsy.

First, strong evidence was found that children and adolescents have more affected HRQOL in physical, psychological, and social domain than healthy children and adolescents, while the findings were inconclusive for the findings for other HRQOL domains or when children and adolescents were compared to other chronic conditions. When only adolescents with epilepsy were considered, strong evidence was found that specific HRQOL domains affected were attitudes toward epilepsy (negative epilepsy perceptions) and social domain, while there were no differences between males and females. Additionally, weak evidence exists that adolescents with epilepsy had more impaired aspects of memory, concentration, physical functioning and social compared to normal controls. The above findings were based on comparisons between children and adolescents and healthy children and adolescents, including siblings, and/or the normative data for the questionnaires, and only a few studies included other chronic conditions as controls. Therefore, the affected domains, physical, psychological, and social, could be also affected in other chronic conditions to different degrees and it does not mean that these domains are specifically affected in epilepsy. It would be necessary to include different chronic conditions to study domains specifically affected in this population.

Second, strong evidence was found that parent perspectives alone are insufficient to measure their child's HRQOL. In pediatric epilepsy, parents tended to underestimate the HRQOL of their children and perceived differently domains that are more abstract. Although the child and parent perspectives may be different, resulting in different scores,

both are potentially valid and need to be considered in HRQOL assessments (Eiser & Morse, 2001a; Eiser & Morse, 2001b).
Third, in specific groups of children and adolescents with epilepsy, only moderate evidence was found that in benign rolandic epilepsy psychological domain (including anxiety, depression, and self-esteem) was more affected than others were. For others, the findings are inconclusive and no evidence could be found.
Forth, considering HRQOL predictors, strong evidence was found for age at epilepsy onset (younger age), a number of AEDs (more AEDs), and parental depression as the predictors when children and adolescents were considered together. Moderate evidence was found for attention problems, overall intelligence (lower) and family (including its structure, parental anxiety, etc.). Specific to adolescents only, seizure worry/concerns and side effects of AEDs were found as strong predictors and epilepsy severity, while a number of AEDs as moderate. The predictors of HRQOL were not studied in children only. Other predictors were with weak to moderate evidence or the findings are inconclusive. The previous narrative review showed that different aspects of epilepsy and its co-morbidity affect HRQOL (Lach et al., 2006). The results of this review showed that epilepsy variables affect HRQOL to different degrees, as well as psychological and sociodemographic variables. Nevertheless, strong predictor is parental depression, especially maternal. One study demonstrated that maternal depressive symptoms had significant negative impacts on HRQOL and this relationship was moderated by family resources and partially mediated by family functioning and demands (Ferro et al., 2010).
Finally, considering the impact of antiepileptic drugs or vagus nerve stimulation on HRQOL domains, the findings are inconclusive and no evidence could be found. Strong evidence was found that significant postoperative improvement was observed in physical, cognitive, social, and general health domain. However, this might not be the real picture about impacts of antiepileptic treatments on HRQOL, because there are no data from clinical trials that use HRQOL and other PRO as clinical endpoints. Therefore, this finding need to be taken with some reserve.

4.2 Strengths and limitations

There are several obvious methodological shortcomings in the set of the studies available for this review.
First, in most of the studies, there was small sample size and none of the studies calculated the number of subjects needed. Considering that HRQOL is a highly variable characteristic, there is a need for much more subjects in order to analyze differences between different groups or different times of assessment (Cramer, 2002; Fayers & Machin, 2007). Second, in most of the studies, HRQOL was evaluated for both, children and adolescents, and only one study separately reported the findings. However, it was demonstrated that HRQOL has specific characteristics and dynamics in childhood and adolescents and it has to be evaluated separately (Ravens-Siebere et al., 2006; Davis et al., 2006). Third, nine studies evaluated HRQOL as self- (child/adolescent) and parent-rated thus, comparing their results could be a source for type II error. Forth, most of the studies failed to state why particular HRQOL questionnaire was used. Stating that the reason for selecting a measure was its sound psychometric characteristics is of smaller value, because one of the basic principal in HRQOL assessment is using a psychometrically sound measure. A questionnaire should be selected considering the underlying theoretical model of assessment, objectives of assessment, population of interest, and so on (Ronen, 2003; Lach et al., 2006; Waters et al.,

2009). Fifth, HRQOL was analyzed mostly determining statistical significance between the groups or assessments. Any parameter for detecting a clinical significance or clinically meaningful change was not included, except by Sabaz and his colleagues who applied multivariable statistics for detecting subtle changes in HRQOL after epilepsy surgery (Sabaz et al., 2003).

The review itself has some limitations. First, the review included enough studies to extract the findings considering the specific HRQOL domains affected in children and adolescents when healthy controls were included. However, small number of studies compares children and adolescents and children with other chronic conditions. Additionally, small number of studies evaluated HRQOL in specific antiepileptic treatment, so the findings from the analyzed studies might prevent from drawing valid evidence. Second, as mentioned above combining the results of different studies that used parent or child reports for HRQOL could be a source for type II error. Third, there could be language bias, whereas only studies in English were included, besides that language was not exclusion criteria for selecting studies.

5. Conclusion

Based on the findings and evidence found, it could be concluded that children and adolescents have more affected HRQOL in physical, psychological, and social domain than healthy children and adolescents. In adolescence, attitudes toward epilepsy and social domain are the most affected. Age at epilepsy onset, a number of AEDs, and parental depression are important HRQOL predictors, but specific to adolescents only, seizure worry/concerns and side effects of AEDs were found as strong predictors. Further, the parent perspectives alone are insufficient to measure their child's HRQOL. Finally, epilepsy surgery improves HRQOL in physical, cognitive, social, and general health domain. For the other epilepsy treatments, no valid evidence was found.

Undoubtedly, the results indicate that more research on HRQOL in this population is needed. General recommendations for future research should include the following. First, more studies are needed that compare HRQOL in epilepsy and other chronic conditions. Second, more data should be available from clinical trials that used HRQOL. Third, HRQOL predictors need to be evaluated with structure equation models in order to demonstrate the role of possible risk, moderators, and mediating factors. Finally, the methodological shortcomings of the available studies stated in the limitations of the review have to be avoided following epilepsy specific and general recommendations for patient-outcome assessments (Leidy et al., 1998; Scientific Advisory Committee of the Medical Outcomes Trust, 2002; Terwee et al., 2007; Fayers & Machin, 2007).

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13

Frontal Lobe Epilepsies: Neuropsychological and Behavioral Consequences in Children

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1. Introduction

The frontal lobes of the brain constitute more than a third of the human cerebral cortex and are characterized by a complex functional organization supporting higher level integration circuits. Based on its cell architecture, the frontal lobe can be divided into two parts, the posterior and anterior, each with important functional characteristics. The posterior part controls motor activity and can be further divided into a premotor area that controls preparation for movement, and a motor area that governs the actual performance of movements. The anterior part, or prefrontal cortex, is fundamental to the processing of higher cognitive functions, such as planning, inhibitory control and capacity for judgment, and in mood control (Grossi & Trojano, 2007). Behind the complex functioning of the frontal lobe lie ample networks that involve cortical and subcortical structures. Diffusion tensor imaging studies have confirmed the presence of these multiple connections with age-related and gender-related changes (Pal et al., 2011).

The complexity of the frontal lobe, in terms of its neuroanatomy and connections, determines a marked variability in the epileptic manifestations with fast and inter- and intra-hemispheric propagation.

Generally speaking, focal epilepsies are often associated with neuropsychological, behavioral and emotional problems that can also affect a patient's adaptive functioning (Cornaggia et al., 2006). A frontal localization of the epileptic focus correlates with executive dysfunctions. The executive functions refer to higher-order, self-regulatory, cognitive processes that aid in the monitoring and control of thought and action. Numerous processes are associated with executive functions, the most important being anticipation, goal selection, planning, initiation of activity, self-regulation, mental flexibility, attentional control, metacognitve abilities such as error correction and detection, and the use of feedback. Executive skills are also implicated in motor planning, controlling impulses and regulating behavior (Lezak et al., 2004), as well as in emotional responses, behavioral and social actions. They consist of those capacities that enable a person to engage successfully in independent, purposeful, self-serving behavior (Gioia, et al. 2001).

Executive functions have been conceptualized as multiple process-related systems, that are inter-related, inter-dependent and function together as an integrated supervisory or control system (Lezak et al., 2004). Anderson (2002) proposed a model of executive functions

comprising four discrete but inter-related executive domains that work together to enable 'executive control'. These domains are: a) attentional control, which includes the capacity to selectively attend to specific stimuli and inhibit arrogant responses, the ability to focus attention for a prolonged period, the regulation and monitoring of actions; b) information processing, in terms of fluency, efficiency and speed of output; c) cognitive flexibility, i.e. the ability to shift between response sets, learn from mistakes and devise alternative strategies, divided attention and working memory; and d) goal setting domains, which include the ability to develop new initiatives and concepts, plan actions in advance and approach tasks in an efficient, strategic manner.

Executive skills emerge in the first year of life and develop rapidly throughout childhood: they begin to mature between 4 and 7 years of age, while the greatest changes occur between 8 and 12 years old, but the efficiency of an individual's executive abilities continues to increase between 12 and 15 years old and even in adulthood. The different functions in the executive domains develop at different rates. For example, attentional control appears to emerge in infancy and develops rapidly in early childhood. In contrast, cognitive flexibility, goal setting and information processing have a sensitive period between 7 and 9 years of age, and are relatively mature by the time a child is 12. A transitional period is thought to coincide with the start of adolescence, and executive control would emerge soon afterwards (Hughes et al., 2010). The frontal lobes mature progressively at neuroanatomical level too, the result of a combination of myelogenesis (Klingberg et al., 1999) and synaptogenesis (Huttenlocher & Dabholkar, 1997) interacting with the environment.

This chapter concentrates on nonlesional epilepsies involving the frontal lobe: first, we briefly describe the characteristic EEG discharges; then we concentrate on the neuropsychological and behavioral consequences, in the light of the complexity of frontal regions; finally, we pay attention to the interactions between EEG features, demographic variables and neuropsychological outcome.

2. Frontal lobe epilepsy

2.1 Characteristics of EEG discharges

Frontal lobe epilepsy (FLE) is the second most common type of focal epilepsy, accounting for 20-30% of cases. It is also the second most frequent reason for the surgical treatment of epilepsy, affecting approximately 20% of patients with refractory focal epilepsy (Lee et al., 2008). The EEG trace shows partial frontal anomalies frequently with a secondary generalization and a rapid and diffuse propagation of the epileptic activity to the contralateral hemisphere. The seizures deriving from this type of anomaly are usually brief, rich in motor signs, and often occur at night, though their precise features depend on the lateralization and specific site of the epileptic focus (Patrikelis et al., 2009). Usually, a focus in the primary motor cortex prompts focal motor seizures, while foci in the supplementary motor area give rise to tonic seizures, and involvement of the orbital, medial and dorsolateral regions induces complex partial seizures.

2.2 Neuropsychological functioning

The number of works on adult subjects has increased in recent years. Adults with FLE generally have an intelligence within the normal range and deficits in response inhibition and impulse control, attention, motor programming and speed (for a review see Patrikelis et al., 2009). Fewer studies have been performed on patients of developmental age. FLE

children share many of the features of frontal lobe dysfunctions in adult patients, but the differences in the neuropsychological tests used and, more importantly, the late development of the frontal lobe and the functions it serves mean that findings in adults cannot be extended to patients of developmental age.

Most studies on children with FLE reported cognitive capacities in the normal range (Culhane-Shelburne et al., 2002; Hernandez et al., 2002, 2003; Luton et al., 2010; Riva et al., 2002, 2005), whatever the features of their seizures. Prevost et al. (2006), on the other hand, conducted a retrospective study on 21 children with FLE with a mean age of 6 years (though the age range was very wide, from less than 1 to more than 13 years of age), and found that only 52% had a normal IQ, as measured with the Wechsler scales (WPPSI-R and WISC-III); more detailed results are not provided, however.

In actual fact, the majority of the studies on FLE children investigate the efficiency of their executive functions comparing them to children with temporal lobe epilepsy (TLE) and generalized epilepsy with absences (GEA) besides to children tipically development.

Hernandez et al. (2002) compared 16 children who had frontal lobe epilepsy with 8 cases of TLE and 8 of GEA, all between 8 and 16 years old; they used a broad neuropsychological test battery to determine whether children with FLE had deficits in only some or all of the components of executive skills. The FLE children showed deficits in planning ability, as assessed by the Tower of London (TOL) test, in which children are asked to copy a modeled pattern of three colored beads in a prescribed number of trials, planning and anticipating their actions. The FLE children's initial planning times were shorter, but their total performance times were longer: they both made their first move immediately after the model was placed before them, and they ignored the instruction to move one bead at a time, but they took longer to complete the models than the children with TLE or GEA, and the healthy control group. No significant differences were seen between the groups for the number of models completed in the first trial or the total number of trials needed to correctly reproduce the model proposed by the examiner (variables that reflect the subject's planning ability). These findings globally indicate that these children's poor planning ability is due mainly to a tendency to act impulsively: they tended to start working on the task promptly but inaccurately, subsequently slowing down and taking a long time to complete the process. The authors also reported deficits in the Verbal Fluency Test, in which children are asked to a produce as many different words as possible according to a given letter (phonemic condition) or category (semantic condition) within one minute. The majority of FLE children has considerable difficulty generating words in the phonemic condition. There may also be a reduced output in the semantic condition, however, as recently confirmed by Luton et al. (2010) in 20 children with FLE aged between 8 and 19 years. In quality terms, there are reports of an initially very long latency (with children taking 20 seconds or more to produce their first word) and continuous hesitations throughout the test. Riva et al. (2005) also found a limited efficiency in terms of verbal fluency, with significantly lower results for phonemic fluency, while semantic fluency was within normal range in 17 FLE children 6-14 years of age. A limited output was recorded in a design fluency task too, with a significantly higher number of perseverative than non-perseverative errors (Riva et al., 2002, 2005). The test involved the child first having to draw as many different abstract shapes as possible (free form); then, in the second part of the test, a set number of lines was specified for each shape (fixed form). Perseverations (i.e. repetitions of designs) are considered a problem typical of patients with frontal lesions, and especially those involving the prefrontal cortex.

The difficulties in verbal and design fluency tasks would seem to that FLE children have greater difficulty both in mobilizing their resources to initiate a verbal and non-verbal search, and in being flexible in their search strategy in compliance with certain rules.
In a later work, Hernandez et al. (2003) looked at sustained attention and inhibition control using visual and auditory tasks. FLE children had a significantly lower Perceptual Speed Index in the WISC-III, scoring lower in both the Symbol Search and the Coding subtests (although the difference was only statistically significant for the former) by comparison with GEA children, but not with TLE children. It is important to emphasize that the results for FLE children fell in the borderline range vis-à-vis normative scores, while the other clinical groups had scores within the average range. Qualitative analyses showed that FLE children were not only slower, but they also made more mistakes than the other groups. In addition to these two tests with visual stimuli, an auditory version of the Continuous Performance Test (CPT) was administered, in which children had to respond only to the letter A, to assess sustained attention and inhibitory control. FLE children were impaired more than TLE children, but not more than GEA children. All three groups omitted some targets, but FLE children produced significantly more false-positive responses. Here again, this finding suggests an impulsive response mode and a weaker capacity to inhibit irrelevant, but highly activated response patterns. Children with FLE fared poorly also in a second conditions of the CPT, in which a target letter changes following an alphabetical sequence posing considerable demands on working memory. They obtained fewer correct responses than the other two groups because they lost the sequence much earlier in the course of the task: the majority of children with FLE (63%) did not produce more than four correct responses before losing track of the sequence.
Culhane-Shelburne et al. (2002) also studied attention abilities, inhibitory control and flexibility of response, comparing 12 FLE children with 15 TLE children between 8 and 18 years of age. In spite of there was a marked variability within both groups, the results confirm the FLE children's difficulties in the sphere of attention and control over highly activated responses, but not the specificity of this deficit respect to TLE children. In the Test of Variables of Attention (TOVA), a computerized fixed visual continuous performance task, the mean scores for both inattention (errors of omission) and impulsivity (errors of commission) fell below 2 standard deviations from the norm, with no significant differences emerging between FLE and TLE children while in the Stroop Color Word Test onley the FLE children made more mistakes.
Auclair et al. (2005) compared the performance of a sustained attention task in 18 FLE children, 10 children with TLE and 9 controls, aged 8 - 16 years. The task they used was developed starting from LaBerge's theory of attention (1997), which distinguishes between three aspects of attention, i.e. selection, preparation and maintenance. The children had to respond to a target presented in the center of a display and ignore a distracter appearing to the right or left of the target. The distracter was presented before the target and the relative frequency of presentation of the distracter and target varied within a set of trials (0%, 33%, 67%). This task requires a high level of attention control, and should therefore strongly involve executive control, which requires planning, decision-making and self-regulation related to attention control. The authors reported a deficit in preparatory attention in FLE children by comparison with both controls and cases of TLE. Preparatory attention is prolonged and focuses on a particular forthcoming target, often in the presence of distracting stimuli (LaBerge, 1997). This aspect of attention is largely influenced by the expectation that a given event will occur and enables a faster and more efficient response to

competing stimuli. FLE children reacted more slowly to a target stimulus as a function of how often the distractors appeared during the test, i.e. the higher the likelihood of a distractor appearing, the longer the time it took them to react to the target stimulus. This indicates that FLE children have an impaired sensitivity to the chances of a distractor appearing and are consequently less able to resist this interference, suggesting that impairments involving frontal regions reduce the individual's ability to prepare to focus their attention on the upcoming target.

Deficits in attention skills are consistent with clinical observations in children with frontal lobe injuries of different aetiology, such as tumour, stoke, cerebral marfomations, trauma (Jacobs et al., 2007), and also with imaging studies showing a reduced activation in the frontal cortex in patients with attention deficit disorder (Helpern et al., 2011).

Another important function of the executive domain is cognitive flexibility. In FLE children, there are clinical descriptions of rigid, inflexible behavior, difficulty changing activity or procedure, failure to adapt to new or unusual demands. Neuropsychological laboratory measures are not sensitive enough to identify mental flexibility problems, however. To the best of our knowledge, only Igarashi et al. (2002) found deficient results in the Wisconsin Card Sorting Test (WCST) in 15 FLE children 8-20 years of age. The mean results indicated a lower number of matching criteria and a higher number of perseverative errors by comparison with 19 children with TLE, with and without structural lesions, and 30 controls. Riva et al (2002) reported an impaired performance with more perseverative responses and numerous non-perseverative errors, but these results were not confirmed in a subsequent study on a larger sample (Riva et al., 2005). Hernandez et al. (2002) found no differences in performance using the WCST when FLE and TLE children were compared with cases of GEA, although the FLE children tended to perform qualitatively more impulsively (e.g. placing the card quickly without paying attention to the feedback), or they had greater difficulties in following instructions (e.g. taking any card from the pile in spite of being repeatedly told to always take the first card). When the results were compared with normative scores, all the children with epilepsy completed an adequate number of categories, but the FLE children seemed to produce more perseverative responses and perseverative errors. A possible explanation for this lies in that the WCST is a multifactorial task that involves functions that are not all mediated by the frontal lobe (Sanchez-Carpintero & Neville, 2003) as confirmed by lesional studies that found no differences between patients with and without frontal lesions (Nyhus & Barcelò, 2009).

Working memory and strategic memory skills are also affected in patients with frontal epilepsy. Several studies have used the California Verbal Learning Test, which involves learning a list of semantically correlated words and then investigating its recall after presenting an interfering list (immediate recall), and again after a 20 minute interval (delayed recall). FLE children have a normal capacity for immediate and delayed recall (Culhane-Shelburne et al., 2002; Hernandez et al., 2003; Riva et al., 2002) but learning slope showed that the FLE children tended to decline in the last of the five trials, while children with temporal or generalized epilepsy showed a marked increase in the number of items they recalled. This difference was not statistically significant, but suggests a limited capacity of FLE children to sustain adequate attentional levels over time. No significant differences emerged concerning the number of perseverations or semantic clusters during the five learning trials, or in the immediate and delayed recall of the first list (Hernandez et al., 2003; Riva et al., 2005), whereas there was evidence of a significantly higher number of intrusions

and a weaker capacity to resist retroactive and proactive interferences (Hernandez et al., 2003).

Tasks that entailed copying and recalling visual material confirmed that FLE children have a poor visuo-perceptive organization and a greater impulsiveness in completing the copy, which led to a lower accuracy when it came to recalling the stimulus. In the Rey Complex Figure Test, FLE children scored lower than TLE and GEA children for copying the figure and also for immediate recall (Hernandez et al., 2003). The role of the frontal lobes in the memory process can be defined as strategic, i.e. the frontal lobes exercise control over memory by coordinating, elaborating and interpreting the associations taking place in the medial temporal lobe (Stuss & Levine, 2002). Neuroimaging studies with fMRI (Prince et al., 2005; Wagner et al., 2001) provide evidence of the activation of frontal brain areas associated with the organization of material during encoding. The frontal lobe also has a role in compiling retrieved material into an episodic representation, and monitoring the relevance of retrieved information according to a task-related goal (Cabeza et al., 2003; Fletcher et al., 1996).

Few studies have investigated language skills: Cohen and Le Normand (1998) conducted yearly evaluations of receptive and expressive language skills in a sample of 6 children with left frontal seizures, comparing the results with a control group. Analyses of individual language trajectories revealed a clear dissociation in linguistic performance between comprehension and production. Linguistic comprehension gradually improved, reaching normal performance levels by the age of 7, while production remained rather poor even later on. Vannasse et al. (2005) found that school-aged children with FLE had significant deficits in phonological processing tasks when compared with children with TLE and GEA; more specifically, FLE subjects fared poorly on more elaborate or cognitively demanding metaphonological tasks. These findings suggest that an epileptic dysfunction originating from the frontal lobes hinders the more elaborate acquisitions involved in phonological development. These results are consistent with previous findings from neuroimaging studies on dyslexic individuals, which revealed activation anomalies in the frontal lobes (Pugh et al., 1996).

Finally, taking a look at fine unimanual and bimanual coordination and the planning and execution of sequences of single motor actions, there are reports of FLE children being slow and having a reduced manual dexterity, with sluggish and stiff or, conversely, over-hasty movements (Hernandez et al., 2002; Riva et al., 2002, 2005). They appear to find it difficult to maintain a fluid sequence of movements and tend to use spatial or verbal strategies to orient their movements, particularly during the performance of Luria's Motor Sequences task, which involves mutual and asymmetrical gestures with both hands, in which FLE children make far more mistakes in the motor sequence, rarely getting the sequences completely right, with a greater impairment in the intermanual tests and when using the non-dominant hand - a finding interpreted as relating to this hand being less well trained and consequently less able to perform new motor tasks. This would seem to indicate that frontal lobe epilepsy interferes with the more complex aspects of motor activity, which involve both the hemispheres (Hernandez et al., 2002).

2.3 Behavioral features

Frontal anomalies not only affect the higher cognitive functions, they also cause emotional and behavioral problems (Prevost et al. 2006); in this setting, data come both from direct clinical observation and from questionnaires completed by parents, who generally report

irritability, hyperactivity, impulsiveness, hyperkinesia and mood changes (Parisi et al., 2010).

Using the Child Behavior Checklist (CBCL), FLE patients have returned higher scores than TLE children on the Attention problem scale, and than GEA children on the Thought problem scale. Attention problems reported by the parents of children with FLE include absentmindedness, confusion, daydreaming, nervousness, anxiety, impulsiveness, difficulty in maintaining their concentration and in remaining seated. Irritability and concentration difficulties are frequently reported by parents of TLE children too, while absentmindedness and social immaturity are more often reported for cases of GEA. It is only for FLE children, however, that attentional problems fall within the clinical range. The thought problems frequently described in FLE children were recurring ideas and repetitive behavior. Also in the Competence scales of the CBCL parents report FLE children tending to be less socially active than other children with epilepsy: they rarely join groups or associations, the quality and quantity of their friendly relations are inferior, and their school performance is worse, although no significant differences emerge. These findings could be due to the questionnaire being designed mainly to investigate the children's emotional-behavioral functioning, while the Competence Scale is less sensitive. Parents have also reported having lower expectations concerning their epileptic children's academic performance (whatever the type of epilepsy involved), and their chances of becoming independent and being successful in life, by comparison with their other non-epileptic sonsA retrospective study reported cognitive and behavioral difficulties in a small sample of school-aged FLE children: the majority had an attention deficit disorder with hyperactivity or impulsiveness (14 of 21 children) and other behavioral problems (8 of 21); 60% (6 of 10) had learning difficulties requiring special support teaching. Almost all children whose seizures had begun before 6 years of age developed a learning disability. Their poor school performance seems to have numerous causes, involving behavioral more than cognitive problems (Prevost et al., 2006). It may be that children react to the constant negative feedback from the environment and such lower expectations may prevent children from reaching their full potential, accentuating their difficulties (Hernandez et al., 2003).

A review of qualitative data suggests that behavioral and academic problems are common in children with epileptic anomalies, but the Behavior Rating Profile-Second Edition (BRP-2) has not proved sensitive enough to detect the particular problems shown in FLE children (Culhane-Shelburne et al., 2002). Luton et al. (2010) used the Behavior Rating Inventory of Executive Function and confirmed that FLE children have a limited capacity for self-regulation and independent organization, they are easily distracted, and they have difficulty in completing a task assigned to them and in assessing their own progress as they go along.

The cognitive and behavioral problems of children with focal epilepsies often also interfere with the development of adaptive and social skills (Cornaggia, 2006). This was confirmed by Culhane-Shelburne et al. (2002), who reported a poor adaptive functioning, as assessed using the Vineland Adaptive Behavior Scales (VABS), in which FLE children obtain slightly lower than normal scores in all three subdomains: Communication, Daily abilities and Socialization. A two-step regression procedure showed that some of the measures of executive functioning have a strong bivariate relationship with the total score on the VABS. This would seem to confirm that executive functions are a crucial component not only of cognitive development, but also of adaptation to life in developmental age.

2.4 Relationship between neuropsychological data and clinical features

In dealing with the relationship between neuropsychological data and clinical variables, it is important first of all to consider that the majority of studies contain speculations on the qualitative analysis of the data without using statistical analyses. It is generally agreed that the impairment of a patient's neuropsychological function is greater, the earlier the age of onset of their epileptic seizures, particularly as concerns the executive functions, which have a lengthy developmental trend and functional improvements can occur into adult age (Hernandez et al., 2002, 2003; Prevost et al., 2006, Riva et al., 2002, 2005; Upton & Thompson, 1997). Cognitive evaluation and clinical follow-up should therefore be particularly accurate in patients with early-onset epilepsy.

Some works compared younger children (8-12 years) with older children (13-16 years), finding that the children under 12 had a worse outcome for verbal search, working memory, sustained attention, verbal and visual memory and behavioral problems. Comparisons between younger and older children with FLE also showed that the younger children did less well in uni- and bimanual tasks for the non-preferred hand, in the alternate tapping task for the preferred hand (Hernandez et al., 2002), in the working memory condition of the CPT, and in the copy and immediate recall on the Rey Complex Figure Test (Hernandez et al., 2003).

There are few and controversial data relating to the correlation between the frequency of seizures and neuropsychological findings: one study by Riva et al. (2002) reported a significant correlation with the Picture Completion Test of the WISC-R, which was not confirmed in the subsequent study (Riva et al., 2005).

No studies have found different types of cognitive function based on the side of the epileptic focus and its uni- or bilaterality. The often troublesome differentiation between left and right frontal dysfunctions in FLE may be attributable to the widespread, bilateral, rapid propagation of frontal seizures, which may make lateralized differences in cognitive measures difficult to distinguish. Unfortunately it is impossible to divide patients according to the exact location of their epileptic focus on the basis of EEG findings obtained with surface recordings and clinical ictal features. This problem can be addressed by means of thorough neuropsychological tests on different frontal functions in patients with FLE undergoing presurgical invasive deep-electrode EEG recordings, correlating their cognitive profiles with the seizure lateralization identified (Patrikelis et al., 2009).

3. Benign epilepsy of childhood with centrotemporal spikes

3.1 Characteristics of EEG discharges

Benign epilepsy with centrotemporal spikes (BECTS) or rolandic epilepsy is the most frequent form of epilepsy in school-aged children, accounting for 15%-25% of all childhood epilepsy. Seizures commonly occur during sleep, often in the early morning hours, with focal paresthesias and tonic or clonic arm or facial contractions, and may subsequently become generalized. Daytime seizures may occasionally occur, however. The conditions develops between 3 and 13 years old, with a male predominance. In most patients, rolandic discharges are detected over the centrotemporal brain regions, but other regions can also be involved. The location of the interictal epileptic activity may vary, but prominently involves the temporal or rolandic regions; moreover, spikes are often multifocal with a bilateral and asynchronous presentation, and they can even show an ipsilateral location with respect to the side of the body affected by the ictal phenomena. It is important to perform a wake-sleep

EEG recording because the spike-wave discharges are activated as the patient enters the sleep phase (Shields & Snead, 2009). BECTS carries a good prognosis irrespective of any intake of antiepileptic medication, with a normalization of the EEG trace and spontaneous remission of the seizures before puberty (Stephani & Carlsonn, 2006). In a meta-analysis of studies conducted on BECTS, Bouma et al. (1997) found that 50% of patients have a normalization of the EEG by the time they are six years old, 92% by 12 years old, and there is a near 100% remission by 18 years of age. Early studies suggested an autosomal dominant inheritance, based on EEG findings in siblings (Degen & Degen, 1990; Heijbel et al., 1975), while later studies suggested a multifactorial inheritance (Doose et al., 1997; Neubauer et al., 2000). More recently, Vadlamudi (2006) conducted a multicentre study on 18 pairs of twins, and claimed that the genetic factor is less important than was initially assumed, since the study demonstrated no concordant twin pairs with classic BECTS.

3.2 Neuropsychological and behavioral profile

Numerous studies have now been performed on the neuropsychological outcome in children with BECTS. A recent literature review reported that children with BECTS are at risk of mild cognitive impairment, though the prognosis for seizure outcome is excellent (Nicolai et al., 2006). The majority of the studies report normal intellectual abilities (Northcott et al., 2005; Riva et al., 2007; Volkl-Kernstock et al, 2006). Weglage et al. (1997) and Northcott et al. (2007) recorded lower results for IQs measured with the Wechsler Scales than in controls, but the scores were within the average range for the BECTS children too. As for neuropsychological function, the recent literature reports a wide spectrum of deficits, but no uniform definition of a specific neurocognitive profile has been established as yet. The subtle dysfunctions described were only apparent on intensive neuropsychological testing at a single time in the course of epilepsy and they caused no difficulties in real life (Massa et al., 2001).

Numerous studies found deficits in speech-related abilities. Staden et al. (1998) prospectively studied 20 children, selected irrespective of any history of learning or language problems. Thirteen children (65%) showed language difficulties in 2 or more of 12 language tests, and 8 children (40%) had specific language impairments. Other works reported worse results in tasks involving expressive (Baglietto et al, 2001; Volkl-Kernstock et al, 2009) and receptive vocabulary (Danielsson and Petermann, 2009; Volkl-Kernstock et al, 2009), and in phonological awareness (Northcott et al, 2005). We studied cognitive functions and language abilities in the group of 24 children with BECTS who were compared with a group of 16 age-matched controls. In BECTS we found preserved naming skills but lower results phonemic fluency, verbal re-elaboration of semantic knowledge, and lexical comprehension (Riva et al., 2007). The review of Overliet et al. (2010) concluded that language is often affected in children with centrotemporal anomalies, although the type of impairment reported varies in different studies. More recently the same authors (Overliet et al., 2011) reported a substantial percentage of their clinical sample of 48 children with BECTS (17-21%) receiving speech therapy before the onset of epilepsy. It remains to be seen whether the language impairment develops gradually after the onset of the epileptic anomalies, or whether rolandic epilepsy and language impairment are both symptoms of an underlying syndrome, or both develop during the process of epileptogenesis, as observed in some children whose language impairment developed before the onset of epilepsy.

Another interesting area of research concerns the effects of rolandic spikes on functional lateralization of language. Already in 1988, Piccirilli et al. investigated language

organization in 22 right-handed BECTS children, 14 of them with a left-sided and 8 with a right-sided electroencephalographic focus. The children were asked to perform two tasks simultaneously, i.e. a verbal task (they were asked to repeat the names of four animals) combined with right- or left-hand finger tapping. The verbal task interfered more with right-hand than with left-hand tapping rates in children with a right-sided electroencephalographic focus and in healthy controls, while in children with a left-sided electroencephalographic focus, the verbal task equally affected left-hand and right-hand performance. The authors concluded that epileptiform activity in BECTS may modify language lateralization, suggesting a bihemispheric representation. Hommet et al. (2001) obtained similar results in 23 adolescents and young adults in complete remission of BECTS, suggesting the persistence of a long-term hemispheric language representation disorder. Although the results were not statistically significant, qualitative analysis of the dual-task procedure in a sub-group of right-handed BECTS patients showed that those in remission after an initial right seizure demonstrated the same pattern as controls, whereas BECTS patients with an initial left focus showed an inverse pattern, with a right percentage change (i.e. the functional reduction affecting the right hand due to the interference of the verbal task) lower than the left percentage change in 5 of the 6 subjects. When the same group was assessed using the Dichotic Listening task (DL), the authors found no significant differences by comparison with the control group, but they attributed this result to a likely ceiling effect and consequently lower sensitivity of the test. Lundberg et al. (2005) found that 13 children with BECTS, whose side of focus was not specified, showed a right ear advantage but a significantly worse production of correct consonant-vowel syllables for left, right or both ears compared to controls. The authors interpreted this finding as an auditory discrimination deficit due to the proximity of the rolandic areas to the primary auditory receptive area. In 24 children with BECTS compared with 16 control subjects, our group found an atypical performance on DL with a loss of the usual advantage of the right ear/left hemisphere, associated with a functional right ear/left hemisphere advantage characteristic of controls in the same age range. This is not a case of a complete rightward shift, but of the loss of the advantage of one hemisphere over the other, suggesting that left hemispheric processing superiority for phonological stimuli is functionally disturbed by the interictal spikes, leading to a bi-hemispheric representation of the phonological processing of auditory, verbal stimuli (Bulgheroni et al., 2008).

More recently, fMRI was used to assess language lateralization in 20 children and 20 healthy controls. The fMRI analyses revealed that language-related activation was less lateralized to the left hemisphere in anterior brain regions in the BECTS children than in controls. This finding is consistent with the worse results in patients on the neuropsychological measures most dependent on the integrity of anterior aspects of language skills, such as naming and sentence production. So this study demonstrated that BECTS influences a language network that involves the more anterior, and therefore frontal cerebral regions (Lillywhite et al., 2009).

Difficulties have also been reported in academic perfomances (Nicolai et al., 2007) and learning, with deficits in reading (Ay et al., 2009; Fonseca et al., 2009; Papavasiliou et al, 2005; Piccirilli et al., 2008; Staden et al, 1998) and spelling (Monjauze et al, 2005; Papavasiliou et al, 2005; Staden et al, 1998).

Memory also seems to be negatively influenced by spikes in the centrotemporal area: there are reports of difficulties in short-term verbal memory (Danielsson & Petermann, 2009; Northcott et al, 2005; Weglage et al, 1997), visuo-spatial memory (Baglietto et al 2001;

Danielsson & Petermann, 2009; Volkl-Kernstock et al, 2009) and long-term verbal memory (Northcott et al, 2005) as well as in the learning of verbal information (Croona et al, 1999; Staden et al, 1998). We also investigated verbal learning and retrieval, and the use of learning strategies with the CVLT-C. The under 10-year-old patient showed significantly worse supraspan skills and were less efficient in using a semantic clustering strategy than their age-matched controls, while no such difference emerged for the over 10-year-olds. This suggests that the capacity for a spontaneous use of a more efficient strategy matures later in BECTS children (Vago et al., 2008).

All the above-mentioned works investigated functioning in school-aged BECTS children. Danielsson & Petermann (2009) found verbal and non-verbal difficulties relating to articulation, auditory and visual memory, language comprehension and visual-constructive performance, also in 25 BECTS children aged 4 – 7 years when compared with 25 healthy controls.

Finally, studies on executive functions in children with BECTS identified mild deficits in information processing (Baglietto et al, 2001; D'Alessandro et al, 1990), in inhibitory processes (Deltour et al., 2007, 2008), in problem solving (Croona et al, 1999), in cognitive flexibility (Croona et al, 1999; Deltour et al., 2007; Gunduz et al, 1999), and auditory attention (Ay et al., 2009). Recently Cerminara et al. (2010) used a computerized test battery to assess attention ability in 21 children with BECTS compared with 21 controls. They found an impairment in selectivity (impulsiveness, focused attention, selective attention, aspects of divided attention) and in one measure of intensity (arousal) of attention in children with rolandic epilepsy. Vigilance was not impaired in the clinical subjects.

An increased distractibility, impulsiveness and hyperactivity were often reported (Giordani et al, 2006; Massa et al, 2001; Metz-Lutz et al, 1999; Volkl-Kernstock et al., 2009). Holtmann et al. (2006) administered a neuropsychological battery focusing on attentional processing, cognitive efficiency, response inhibition, visuo-spatial and verbal short-term memory and language functions in 16 children with ADHD and BECTS, 16 with ADHD but no EEG discharges, and 16 healthy controls. The first clinical group performed worse than the other two in a variety of CPT and Stroop test measures. In particular, they made significantly more commission errors, reflecting impaired inhibition of an ongoing response. They also had pronounced difficulties in the color word condition of the Stroop test and exhibited lower interference scores, indicating poor interference control. The authors concluded that the presence of rolandic discharges aggravates the course of ADHD and predisposes to a greater impulsiveness, which is usually defined as a lack of response inhibition (Nigg, 2000). In short, children with rolandic spikes show an impairment in complex executive functions, such as verbal search, use of strategy to improve verbal learning, response inhibition, and behavioral characteristics that give the impression of a dysfunction of the frontal regions. It can therefore be suggested that, despite the epileptic focus typical of BECTS being concentrated mainly in the central region, variations in its propagation may interfere with the activity of other cortical areas, such as the frontal lobe, giving rise to malfunctions that are apparently not strictly related to the primary site of the typical BECTS focus.

To confirm the behavioral findings, studies on brain volumetry confirmed anomalies in frontal lobe growth and functioning in BECTS children. Kanemura et al. (2011) examined 11 control subjects aged 4-13 years and 9 children with BECTS, two of the latter with neuropsychological impairment or behavioral problems, who were followed up for more than three years. The two children's frontal and prefrontal lobe volumes revealed a growth

impairment by comparison with the BECTS cases without deficits or the controls. The prefrontal-to-frontal lobe volume ratio also increased serially in the BECTS cases with a normal cognitive/behavioral functioning, as in controls, while it was stagnant or decreased in the BECTS cases with neuropsychological problems. Prefrontal growth also recovered more rapidly in the BECTS patient with shorter active seizure periods. So frequent spike-waves coupled with the occurrence of frequent seizures and longer active seizure periods may be associated with prefrontal lobe growth retardation, which relates to neuropsychological outcome.

3.3 Relationship between neuropsychological data and clinical features

Numerous studies investigating neuropsychological functioning in BECTS children have recently attempted to shed light on which characteristics of the EEG and which clinical variables are relevant markers of a worse cognitive outcome.

For rolandic epilepsy too, an early age of onset of the epileptic seizures correlates with a poor cognitive outcome. Piccirilli et al. (2008) suggested that seizure onset before the age of 8 years and epileptiform discharges (more than 50% of the sleep EEG recording) in several traces over more than a year are relevant markers of patients at risk of developing academic difficulties. Deltour et al. (2007) found that children with an earlier onset of seizures made more omission errors and had slower reaction times in the Continuous Performance Test.

Most authors have described improvements in neuropsychological functioning on longitudinal testing, related to a normalization of the EEG over time (Callenbach et al., 2010; Baglietto et al., 2001; D'Alessandro et al., 1990; Deonna et al., 2000; Hommet et al., 2001; Lindgren et al., 2004; Metz-Lutz et al., 1999; Northcott et al., 2007; Volkl-Kernstock et al., 2009), but there have also been reports of persistent impairments after remission of the EEG discharges (Monjauze et al., 2005).

Although some studies found that the nature of the impairments revealed by neuropsychological testing in BECTS correlated with the side of the epileptic focus (Massa et al., 2001; Piccirilli et al., 1994; Wolff et al., 2005), other studies found no relationship with the BECTS children's performance (Deltour et al., 2007; Vago et al., 2008). Studies investigating language functions using standard tests also failed to confirm any major impairment for children with a left focus (Metz-Lutz et al., 1999; Northcott et al., 2005; Staden et al., 1998; Weglage et al., 1997). Riva et al. (2007) found that children with a left-sided spike focus scored significantly worse than controls on phonemic fluency, while children with a right-sided spike focus scored significantly worse than controls in the Vocabulary subtest of the WISC-R and in the lexical comprehension test. Bulgheroni et al. (2008) found no specific influence of the side of the interictal spikes on DL performance.

Correlating the topography of the focus (in terms of the hemispheric localization and the side) with neuropsychological impairments is particularly difficult in BECTS, because spike location varies as the disorder evolves (Pinton et al., 2006) and there are reports of bilateral oscillations for the lateralized time-domain spike, suggesting a synchronized activity in a network of bilateral rolandic neurons (Lin et al., 2006). Varying spike locations on one or both hemispheres may in fact mean that BECTS should be considered as resulting from a widespread age-related hyper-excitability of the sensorimotor and latero-temporal cortices, changing its prominent location over time and leading to a functional modification that gives rise to a mild but protracted dysfunction of fine cortical processing (Kellaway, 2000). According to Metz-Lutz et al. (1999), the epilepsy appeared to disrupt response organization

rather than lateralized cognitive functions, also interfering with the development of cortical areas remote from the rolandic focus.

Some studies have correlated neuropsychological findings with the unifocal/multifocal spike location, finding that multifocal locations seem to more severely impair the cognitive efficiency of BECTS children. Multifocal anomalies seem to interfere with performance both in lexical comprehension tests and in phonemic fluency tasks, by comparison with controls (Riva et al., 2007) and had a particularly significant impact on the laterality index, with the complete loss of the right-ear advantage in favor of a symmetrical performance (Bulgheroni et al., 2008). In the work conducted by Vago et al. (2008) the majority of the under 10-year-olds (who had worse results in the CVLT) had multifocal anomalies, suggesting that the difficulties encountered might be caused by the presence of additional foci. Wolff et al. (2005) also found lower scores in cognitive tests in children with multifocal spikes. These results may mean that a widespread hyperexcitability is capable of causing more severe disruption.

The published data are not unequivocal, however, not even as concerns the correlation between spike frequency and neuropsychological functioning. Deficits in IQs correlated significantly with the frequency of spikes in the EEG (Riva et al., 2007; Weglage et al. 1997). Staden et al. (1998) reported a trend towards worse language dysfunction rates with more frequent epileptic discharges. Conversely, Massa et al. (2001) found no direct cause-and-effect relationship between the number of interictal paroxysms and cognitive symptoms, although the mean number of interictal paroxysms differed in statistical terms between their typical and complicated groups. Northcott et al. (2005) found no correlation between spike burden and difficulties in memory or phonological awareness, while Weglage et al. (1997) quantified spike frequency but did not correlate this with specific neuropsychological and language functions. Using a semiquantitative measure of spikes in EEGs recorded while awake, Staden et al. (1998) found a trend towards higher language dysfunction rates with more frequent epileptogenic discharges, whereas Bulgheroni et al. (2008) found no significant link between DL performance and interictal discharge rate, suggesting that cortical dysfunctional states depend on protracted periods of hyper-excitability leading to centrotemporal spikes, rather than on the time course (and quantity) of the spikes at the time of the DL test. It might be argued that the lack of any correlation between spike rate and neuropsychological data is due to the interval between the EEG recording on which the interictal spike rate was calculated and the neuropsychological assessment being too long to enable a detailed correlation analysis between the electrophysiological and cognitive measures, but Wolff et al. (2005) conducted a combined EEG/MEG examination chronologically very close to the neuropsychological assessment and still found no correlation between the number of spikes and the cognitive results.

4. Continuous spike and wave during slow sleep syndrome

4.1 Characteristics of EEG discharges

In electrical status epilepticus in sleep (ESES), the EEG shows a dramatic activation of epileptiform discharges during sleep, with near-continuous spike-wave discharges. It was originally believed that for a diagnosis of ESES diffuse and generalized anomalies with continuous spike-wave complexes in sleep had to occupy at least 85% of the total slow sleeping time and persist on three or more records over a period of at least 1 month (De Negri, 1997; Patry et al., 1971). The recent literature considers this definition too restrictive

and ESES-related syndromes are thought to derive from a combination of electrographic features and clinical symptoms, such as gradual cognitive and behavioral deterioration (Scheltens-de Boer, 2009). The two main representative syndromes associated with ESES are: the Landau-Kleffner syndrome, in which the EEG shows focal or multifocal spikes or spike-waves mainly in the temporal or parieto-occipital regions, which are activated in sleep; and the continuous spike and wave during slow sleep syndrome (CSWS), in which the EEG pattern is typically described as diffuse and bilateral, more rarely with a markedly asymmetrical slow wave activity over both hemispheres (Paquier et al., 2009; Rossi et al., 1999). In wakefulness, the electrographic pattern frequently shows anomalies that are focal, multifocal or diffuse, often with frontal or temporal focus (Nickels and Wirrell, 2008; Tassinari et al., 2000); some authors have reported that the frontal lobe are more involved (Nickels and Wirrel, 2008; Smith & Polkey, 2008). Eighty percent of CSWS patients have seizures, which are typically nocturnal, partial motor or generalized convulsive seizures. A characteristic of this syndrome is the presence of seizures with falls, occurring in 44% of patients (Tassinari et al., 1992). Other epileptic or paroxysmal signs include facial contractions followed by loss of consciousness, myoclonic absences (Tassinari et al., 1992), infantile spasms (Veggiotti et al., 1998) and generalized nonconvulsive seizures (Gaggero et al. in Beaumanoir et al., 1995).

CSWS syndrome is believed to be rare, with an incidence of less than 1% of all cases of childhood epilepsy (Nickels and Wirrel, 2008). The age of onset of CSWS is variable, beginning between at 1 to 14 years old, and peaking between 4 and 8 years of age (Tassinari e Rubboli, 2006). It can last from months to years, improving gradually over time, with an initial reduction in the frequency and spread of the discharges in sleep, followed by a normalization of the recordings in wakefulness, and finally by a normalization of the sleep recordings too in adolescence (Nickels & Wirrell, 2008). The evaluation of seizures is usually considered benign (Tassinari et al., 2000); in one-third of patients epilepsy persists after puberty, despite the disappearance of ESES (Scholtes et al., 2005).

4.2 Neuropsychological and behavioral profile

In CSWS it is difficult to establish the exact incidence of neuropsychological impairments because most reports describe single cases or numerically limited series and the data analyses are often not very accurate (Galonopoulou et al., 2000). For example Scholtes et al. (2005) describes the neurological and neuropsychological long-term follow-up of 10 children with global or specific cognitive deterioration and ESES-type EEG findings without specifying the case they use or providing the results in detail. Moreover, children with CSWS often have such severe behavioral disturbances in the active stage of the condition that a neuropsychological assessment becomes impossible (Veggiotti et al., 2001).

Although most patients are reported to have normal neuropsychological and motor development prior the onset of symptoms (Morikawa et al., 1995; Tassinari et al., 1992), in approximately one third of patients pre-existing neurological abnormalities are reported, such as neonatal and febrile convulsions, congenital hemiparesis, psychomotor retardation, shunts for hydrocephalus, family history for epilepsy (Galonopoulou et al., 2000). Regardless of the prior cognitive and neurological status and development, the appearance of CSWS is associated with the emergence of a new and progressive regression of global competences, with a marked impairment of IQ and behavioral abnormalities (Tassinari et al., 2000). Few papers in the past have reported on cases of CSWS without concomitant cognitive impairments (Aicardi & Chevrie, 1982; Gokyigit et al., 1986).

Attention problems and hyperactivity are prominent in CSWS patients, with deficit described in approximately two thirds of the reported case (Galonopoulou et al., 2000). There are descriptions of reduced attention span, aggressiveness, lack of inhibition (Scholtes et al., 2005; Tassinari et al., 1992; Veggiotti et al., 1998). There are also reports of bizarre behavior (Kyllerman et al., 1996; Morikawa et al., 1995), emotional lability, anxiety and phobia (Morikawa et al., 1995), and of autistic-like behavior (Bulteau et al., 1995; Kyllerman et al., 1996), although a case of CSWS with autistic regression is a rare occurrence: McVicar et al. (2005) conducted a retrospective review of children with language regression studied at their Institute for more than 12 years, finding that only 10 children had ESES, only one of whom had a history of autism and language regression.

Some works report a deterioration of language with a tendency toward expressive aphasia with lexical and syntactic difficulties, and a generally preserved comprehension (Debiais et al., 2007; MacAllister & Schaffer, 2007), learning difficulties at school, poor reasoning and short-term memory deficits (De Negri et al., 1997; Tassinari et al., 1992; 2000), and also motor impairments, such as ataxia, dystonia and dyspraxia (Maquet et al., 1995; Tassinari et al., 2000).

Roulet-Perez et al. (1993) reported clinical manifestations suggestive of a poor functioning in skills correlated to executive functions. The 4 patients showed the association of neuropsychological disorders (difficulties in verbal and non-verbal reasoning, altered temporal sequences, perseverations, reduced verbal fluency, echolalia) with behavioral disorders (lack of attention hyperactivity, impulsiveness, loss of the sense of danger, absence of inhibition, aggressiveness). Praline et al. (2003) studied the neurocognitive outcome in 7 young adults, 5 with CSWS and 2 with Landau-Kleffner syndrome, all with normal premorbid conditions. In the CSWS group only one patient still had active, treated epilepsy at the time of assessment. The neuropsychological findings in the 5 subjects led the authors to distinguish between two different groups: the first comprised two intellectually normal patients who were socially and professionally integrated; the second consisted of 3 patients who were poorly integrated because of the neurological and psychological consequences of their CSWS syndrome. They had intellectual disability, with IQs on WAIS-R indicative of a mild-moderate retardation. One of them had homogeneous mental deficiency, while the other 2 had a significantly lower non-verbal than verbal level of functioning. As for to spoken language, naming scores were normal; verbal fluency scores were pathological in 2 of the 5 patients; 3 had difficulty in sentence comprehension and 4 were deficient in reading and writing. These findings are difficult to interpret, however, because the intellectual level of these patients was low and they were behind at school. In the two subjects with a normal IQ, the author failed to identify significant frontal deficits, i.e. absence of interference in the Stroop Color Test and normal performance on Part B of the Trail Making Test. The reasons for these cognitive profiles colud be related to the topography of the interictal foci: the 5 CSWS patients studied by Praline et al. (2003) showed an epileptic focus prevalently localized in the posterior area of the brain, while the patients with dysexecutive disorder and CSWS had a frontal interictal focus during the active phase of the disorder (Roulet-Perez et al., 1993).

Kanemura et al. (2009) measured frontal and prefrontal lobe volumes using 3-dimensional MRI-based volumetry in an 11-year-old girl. Her premorbid psychomotor development was reportedly normal. After the onset of ESES, a progressive behavioral deterioration was observed, with hyperactivity, aggressiveness and disinhibition. The CSWS lasted for 5

months, the seizures first developing at the age of 5 years. The EEG abnormality recorded during ESES and in the wakeful state mainly affected the frontal region. Serial measurements (when the EEG pattern first appeared, and 6 months then 1, 2, 3 and 4 years thereafter) showed a disturbed growth in prefrontal lobe volume, and particularly in the prefrontal-to-frontal lobe volume ratio, after the appearance of the EEG pattern by comparison with FLE children with no neuropsychological disorders and 13 control subjects. The prefrontal-to-frontal lobe volume ratio increased serially in the controls and FLE children, whereas its increase declined in the patient. The ratio returned to the one seen in controls, however, after the clinical manifestations of CSWS improved. These findings provide further support for the involvement of the prefrontal cortex in CSWS, but this single case study is not enough to allow for any general conclusion to be drawn. Further studies are needed to confirm and complete these anatomical observations and extend the study of cognitive and behavioral functioning to a larger clinical sample.

4.3 Relationship between neuropsychological data and clinical features

In epileptic encephalopathies such as CSWS, the hypothesis is that the seizures or prolonged interictal epileptiform activity are responsible for the cognitive, neuropsychological and behavioral deterioration (Nabbout & Dulac, 2003). Early onset is associated with a greater functional impairment, in fact Scholtes et al. (2005) reported a better prognosis if the age of onset was 9 years or more.

The severity of ESES can vary over time between and within patients, and a direct correlation between clinical status and the spike-wave index has not been proved (Scholtes et al., 2005; VahHirtum-Das et al., 2006). As regards the localization of interictal foci, this seems to play a major part in influencing the degree and type of cognitive dysfunction in CSWS patients (Tassinari & Rubboli, 2006). CSWS patients with prominent cognitive and behavioral dysfunctions tended to have a frontal focus, while those with mainly language-related dysfunctions had a temporal focus. There is a considerable overlap between groups, however, which makes it difficult to draw clear distinctions between them (Rousselle and Revol, 1995).

With spontaneous or drug-induced improvements in the EEG findings, there is reportedly a significant but still only partial improvement on the cognitive and behavioral plane (Paquier et al., 2009; Tassinari & Rubboli, 2006). Scholtes et al. (2005) describe a good cognitive recovery after the disappearance of ESES in only 1 of 7 children, while 4 had a partial recovery. In Tassinari's study (2000), almost half (47%) of the patients with a long-term follow-up were leading a normal life, e.g. attending regular school or working; the remainder were either institutionalized or were unable to adapt properly to their working environment. It is generally assumed that the prognosis is better in patients with a shorter-lived CSWS, i.e. ESES persisting for more than two years tends to be associated with greater impact on cognitive and behavioral functioning (De Negri, 1994; Rousselle and Revol, 1995). The neuroimaging study by Kanemura et al. (2009) confirms that the duration of CSWS is a significant prognostic factor. In the work by Praline et al. (2003), this correlation was not confirmed, but the small size of their sample involved to prevent any general conclusions from being drawn. As a whole, these data are similar to those reported in the review of Galanopoulou et al. (2000) that reported a poor prognosis in half of the cases.

Treatment for CSWS aims to reverse the ESES pattern of the EEG. The goal of treatment of ESES is not only to control seizures, however, but also to improve neuropsychological function, which requires significant improvements in the encephalographic abnormalities.

5. Conclusions

Epileptic EEG paroxysms can interfere with cognitive processes. The specific nature and severity of neuropsychological problems vary according to the particular localization, diffusion and severity of EEG discharges.

The children and adolescents with epileptic anomalies involving the frontal lobe show a significant impairment of the executive abilities (abilities primarily processed by the frontal lobe), but a uniform neuropsychological and behavioral profile has yet to be established. Part of the variability could stem from the difference in the localization of epileptogenic foci within the frontal lobe, and from the tendency to spread rapidly, also to the contralateral hemisphere.

The dysfunction most frequently described is a reduced capacity for inhibitory control of previously-learned, highly-activated responses, irrespective of the type of material proposed. The majority of the neuropsychological tests used in the studies mentioned here have in common the requirement that the patient select an appropriate response and start responding, while inhibiting other, irrelevant responses. This applies to tasks that explicitly investigate these skills, but also to motor and working memory tasks.

The selective impairment of some executive skills, and the sparing of others, is further evidence of the fact that dysexecutive syndrome is not a single disorder, and executive functions depend on multiple, separate networks (Lezak et al., 2004; Stuss & Alexander, 2000), as confirmed by imaging studies (Christensen et al., 2011; Roberts & Hall, 2008).

Existing studies describing neuropsychological functioning in children with frontal epilepsies provide important information but have methodological limitations that should be addressed in future research. Such methodological implications include the size of clinical samples, clinical and epidemiological heterogeneity, psychiatric comorbidities, and the extent of neuropsychological batteries, as well as the omission of important variables related to a patient's cognitive profile (seizure severity, type of medication, lack of ecological-subjective measures indicating how patients and their families perceive their everyday functioning), which are very important and require consideration in future. Future research on larger and better-selected patient subgroups may show whether different patterns of cognitive impairment relate to different epileptogenic foci within the frontal lobe. Considering the clinical variables, we might conclude that the extent of neuropsychological impairment correlates with both the severity and the age of onset of the epileptic anomalies, that is a diffuse epileptic activity and an early age of onset have a more severe fallout on performance in neuropsychological tests. Since the onset of epilepsy can interfere with the growth of the frontal lobe and the development of the skills that it processes, future neuropsychological studies should focus on younger subjects, investigating children in preschool age, to assess their functioning profile also with a view to providing rehabilitation therapy significantly to support these skills and monitor their progress in school age.

Not having an unequivocal neuropsychological reference profile makes it necessary to conduct in-depth neuropsychological assessments to investigate each individual's functioning profile, and such assessments must also consider daily life functioning. In neuropsychological tests, a child is asked to complete a single task, within a limited time and according to more or less clear instructions concerning the start and end of the test. These conditions are very different from those of real life, where a scarcely structured setting demands decision-making and strategic processes of far greater complexity.

Adapting to daily life is even more complex, because it offers many possible solutions (also related to an individual's personal and social context), and dealing with them requires simultaneous executive processes, such as identifying relevant information and generating strategies, but also social and emotional skills, and the capacity to understand other people's points of view and signals from the environment.
The current approach is to develop so-called ecological tests using tasks similar to everyday ones to circumvent the lack of sensitivity in traditional tests (Nyhus & Barcelò, 2009).
It is also important to pay attention to qualitatively analysis of the child's performance and mistakes, which enables an assessment of the nature and efficiency of their mental processes. It is essential to observe how the proposed tasks are completed, watching how the children approach the task, what strategies they adopt, how they plan and organize their actions in order to achieve the required result, and whether or not they verify what they have done.

6. References

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14

Physiotherapy for Children with Cerebral Palsy

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1. Introduction

Pediatric rehabilitation is defined to attain the independence level of children as functionally and psychologically, in the physiological, anatomic and environmental restrictions and to increase the quality of life of the children and their family (Olney et al., 2000). The rehabilitation process requires a multidisciplinary approach. In this process, inter and intra disciplinary communications are a necessity and the role of every discipline should be actualized according to the needs of the children and the family concurrently (Johnson et al., 2001, Kwolek, et al., 2001). Physiotherapists play a key role in the team of healthcare professionals dealing with children with disability. As the 'movement expert' on the team, their main aim is to help the children achieve their potential for physical independence and fitness levels, working closely with the person - and, in the case of children and young people - their parents or caretakers. As a child grows older, the physiotherapist will advise them and their parents or caretakers on independent skills and lifestyle, enabling the young person to take on increasing responsibility in meeting challenges in education, at leisure and at home. When a young person is transferred to adult services, the physiotherapist will continue to work with him/her to solve problems (Mohay, 1996, Kerem Gunel, 2009).

2. Cerebral palsy

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Bax et al., 2005). The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, with epilepsy, and with secondary musculoskeletal problems (Rosenbaum, 2007). The estimated prevalence in the general population is 2/1000 (Odding et al., 2006).). The limitations in activity require individual rehabilitation throughout life (Shepherd, 1995). The impaired control and coordination of voluntary muscles is accompanied by mental retardation or learning disabilities in 50 to 75% of children and by disorders of speech (25%), auditory impairments (25%), seizure disorders (25-35%), or abnormalities of vision (40-50%) (Schanzenbacher, 1989).
Damage, which the central nervous system (CNS) of the children with CP cause, are disorders in neuromuscular, musculoskeletal and sensorial systems (Butler, 1999). These disorders bring posture and movement deficiencies. Functional independence levels of these children are affected negatively due to secondary disorders such as various musculoskeletal

deformations and third disorders due to different compensation mechanisms during the time. Although the damage is not progressive, results of deficiency and disability may be progressive (Butler, 2001).

The main problem in all types of CP is *motor disorders* accompanying with sensorial and cognitive problems (Tirosh & Rabino, 1989). The causes of motor disorders are; developmental retardation, abnormal muscle tone, muscle weakness, postural control deficiencies, sensorial problems, behavioural problems, orthopaedic problems, abnormal movement patterns and reflex activity, asymmetry and deformities (Styer-Acevedo , 1999). The functions that a child with CP should gain by following motor developmental milestones are delayed related to the severity of lesion. Presence of primitive reflexes which should be inhibited in the normal developmental process avoids correction and equilibrium reactions to develop (Papavasiliou, 2009).

The lesion, which is formed in CNS of a child with CP affects the proper functioning of the normal postural control mechanism. The alterations of tonus (spasticity, rigidity, dystonia) instead of normal postural tonus occurs in the form of reciprocal innervation deficiency, abnormal posture and abnormal coordination patterns, insufficient normal fixation and abnormal fixation during motion (Deon & Gaebler-Spira, 2010). Alterations in motion and posture control depend on the harmonious relation between the gravity centre of the body and the support surface. An orderly and sufficient amount of contraction should be present in muscles so as to ensure coordinated movement during a function and ensure balance. Such tonus adaptations in the muscles are automatically formed as continuous and dynamic patterns (Harris & Roxborough, 2005). Muscular tonus needs to create sufficient muscular power for resisting the gravity of the muscular tonus so that the proper posture and postural control can be achieved in children, thus desired motion can be ensured in a controlled way (de Graaf-Peters et al., 2007).

One of the main reasons in decreasing functional skill in CP is the abnormalities in muscular tonus. Such abnormalities may take place in the form of hypertonus, hypotonus or muscular fluctuation. The most frequently encountered tonus disorder is spasticity. Spasticity is a clinical table that is characterized with a speed-dependent increase in increased tendon reflex and straining reflex as a component of upper motor neuron lesion. Hypotonia is generally early infantry-specific. Mostly, it develops into spasticity, rigidity or muscular fluctuation in later periods (Krägeloh-Mann & Cans, 2009). Particularly the children already hypotonic at the onset need to be considered in this respect. Hypotonia, which results from deficiency within the facilitator control or cerebellum, may be more permanent in ataxic type. Tonus alteration may be observed over time in a child with CP, as well as various tonus disorders in various body parts in children with CP. Hypotonia may be formed in the body when there is hypotonia in extremities. Muscular tonus disorders may vary according to the general condition of the child, environmental stimuli, the force and speed of the strain imposed in the muscle (Damiano & Moreau, 2008). Hypertonia and deficiency of reciprocal innervation in children with CP, which is confronted by the increase in co-contractions explains the decrease in the motions. However, in ataxic and athetoid children, there is a decrease in co-contraction and reciprocal inhibition. Fixation skill has been decreased and an apparent deficiency has occurred in postural control due to co-contraction combined with over-mobility. Therefore, deficiency of control, balance and coordination is observed in dyskinetic children (Stanley& Blair, 2000).

Muscular weakness is a secondary development to abnormal tonus problems. Bertha and Karel Bobath have emphasized the importance of considering this situation among children with neurological disorder and have noted that muscular weakness may cause a problem when hypertonus is decreased. Also mobility inability or hypo-mobility among children with CP may cause atrophy and muscular weakness. On the other hand, muscle fails to show the existing force potential due to the deficiency in selective muscular contraction and deteriorated co-contraction mechanism. A loss may occur in the control over motor neuron pools of the spinal cord of the upper motor centres due to CNS lesion, as well, and muscular activation deficiency may occur during motion due to neurophysiologic mechanism (Bobath & Bobath, 1984).

Therefore, it is very important to increase muscular force in physiotherapy practices both for improving the function and controlling spasticity. On the other hand, it has been recently emphasized that spastic muscles were not strong, contrary to what is known, and the force of such muscles should also be assessed for the development of the functional mobility skill (Damiano et al., 2006).

While motor development retardation is considered to be the most important problem, it should also be considered that the sense integrity could also be affected. However, the motor development and sensory response after a CNS lesion are generally both affected and this effect causes developmental problems in children with CP. The long-term existence of primitive reflexes that occur during development, hypotonia, hypertonia or dystonia in muscles and muscle weaknesses that frequently accompanies may negatively affect sensory motor development negatively (O'Shea 2008). Limitation of motor capabilities and movement in children with CP negatively affects the development of the perception ability and reflects negatively on cognitive development. Children learn movements by using their senses and use the movements which they are experienced in. Children with CP, however, gain experience in abnormal movements with repetition and usage and when they want to increase their movement ability they develop new abnormal actions. This also causes asymmetric posture and inability in controlling actions in children with CP. Usage of normal sensory functions during abnormal movements is insufficient because the sensory-motor experience prevalent in children with CP. Regular sensory patterns are formed during the first years of normal children and while this enables them to do more complicated and difficult activities in the future, this balance cannot be created in children with CP. The abnormal motor patterns, undeveloped posture and abnormal tonus also negatively affect the child's physical development (Mayston, 2001, Hadders-Algra, 2001).

Sensory problems that can cause hypo-mobility, posture problems and hypo-function need to be well assessed. Proprioception, vestibular, tactile, visual and hearing senses are senses that create significant input in creating voluntary movements. While the role of voluntary control is on the foreground it is shaped by responses given to warnings of surroundings. Thus, sensory problems that accompany in children with CP negatively affect the development of movement and function (Gunel, 2006).

Various factors in children with CP constitute a foundation, on which for deformities to form, in time. Dynamic deformities, that comprise soft tissue at first, lead to structural defects in the articulars and bones with time and cause the deformity to become static (Akbayrak et al., 2005). It is important to know what factors lead to preventing and decreasing the formation of deformity and applying physiotherapy approaches in this context is important. Factors that cause formation of deformity can, in general, be listed as immobility, hypertonus, hypotonus, co-contractions and synergy patterns, muscle weaknesses, abnormal reflex movements, asymmetry, involuntary and repetitive movement

patterns, physical growth and biomechanical factors. Various sensory disorders accompanying in this table besides muscle weakness, tonus and posture defects, abnormal reflex and movement patterns create a platform for on which immobility, and as a result various contracture and deformities, to occur in children with CP. In children with widespread hypotonia, various deformities can occur generally due to muscle weaknesses and disorders in the postural control mechanism. Deformities such as scoliosis, increased lordosis and kyphosis, flexion in the thigh, valgus and hyperextension in the knees and valgus in the feet can occur frequently in these children. Hypotonus limits the movement of the articulars and also puts weakness in the antagonist muscles in the table by terms of abnormal positions of the articulars while resting and abnormal movement patterns during voluntary movements, thus being one of the most important reasons that cause deformity. With this aspect, spasticity initiates an irreversible chain of events in the muscles, ligaments, articulars and bones (Novacheck & Gage, 2007).

While the spastic muscles cause functional inability at first, it causes deformation with time. Deformities, in children with CP, caused in connection with muscle contracture should be examined under two different headings; dynamic and static. Dynamic deformity means that the contracture is affiliated with spasticity and that it does not cause any difference in the articular. The muscle tendon unit enables the articulars to passively move in agonist and antagonist directions. In the case of static deformity, however, the passive movement of the affected segment of the extremity is not possible or it is seriously limited. It is very important to support the child's functional development in order to prevent and minimize the formation of deformity. To this end, the main targets are to ensure mobility, prevent asymmetric posture and give a proper stand posture, develop normal postural mechanisms and balance reactions, ensure biomechanical normality, control involuntary movements and decrease hypertonus (Gaebler-Spira & Revivo, 2007).

Various problems of the musculoskeletal system causes various walking disorders in children with CP. Gage listed the factors that cause walking disorders in children with CP as loss in selective muscle control, existence of primitive reflex patterns, abnormal muscle tonus, imbalance between agonist and antagonist muscles and inability of balance reactions. Independent walking, which is generally delayed in children with CP, also brings about various walking disorders. Different walking disorders may occur in context with the severity of influence, dispersion and clinical characteristics. These disorders have some characteristics typical to the clinical type of children (Novacheck et al., 2010).

3. Assessment

In an assessment of a child, whose physiotherapy and rehabilitation needs were determined and then was sent to a physiotherapist, answers of questions such as "Why is physiotherapy required?", "What are the active neurophysiologic and biomechanical mechanisms?", "How do the accompanying problems effect the situation?" should be searched. The clinical type, severity of the disease, chronologic age, age of initiating physiotherapy, existence and severity of abnormal reflexes, cognitive problems appearing together, hearing disorders, visual impairment, sensory-perception problems, general state of health and the socio-cultural and economic status of the family should be considered while deciding on suitable physiotherapy methods (Stanger & Oresic, 2003). The actual question that needs to be answered within scope of the information obtained, as a result of the assessment, is what is important in the child's life. What needs to be provided is not only motor development abilities such as sitting, crawling, walking, muscle tonus regulation, balance and

coordination training. The acquisitions shall be ensured to be able to be used in daily life (Bower & McLellan, 1992).

While clinical observation is one of the most important parts of the assessment, it completes standardized tests and contributes information which carries at least the same significance. By assessing the child, according to the parameters listed below, the physiotherapist shall present a general table of the child. The child must be calm and trust the physiotherapist during the observations conducted in terms of motor, sensory, cognitive, emotional and social/family. The mother, father or the guardian undertaking the care of the child shall be with the physiotherapist during the observation. The child must not be hungry, nor should be observed right after eating. The room where the observation will be done should be quiet, at an agreeable temperature and not contain unnecessary toys and equipment; if possible it should be a room covered with material that is appropriate for the child to move on the ground, with walls painted in warm colours and should not be too small. Firstly, what the child can do on his/her own should be observed while examining the functional movements, fine and gross motor skills during the observation (Mayston, 2008).

Within the scope of the assessment to be performed in terms of motor, besides the changes in the muscle tonus, co-contraction capacities of the muscles, involuntary extremity and body movements, stabilisation of the extremities, correction, balance and protective reactions, sitting balance, upper extremity and hand functions and sensory-perception problems; orthosis, need of mobilisation tools and other aid tools, cooperation of the family and their knowledge on the disease also needs to be assessed. The assessment of the motor function should be based on the normal process of a normal motor function development but it should also be sensitive towards special problems. For motor development reflex development, proper posture, sufficient extremity movements, appropriate muscle tonus, sensory development and cognitive functions within an integral neurologic and musculoskeletal system is required. Full completion of the motor development is required for the functional independence and social and emotional development of the child. Therefore it is required to know the normal development of a child. By knowing the normal development, the developmental problems that may occur in the child due to any reason can be better understood (Tsorlakis, 2004).

The methods used for assessing spasticity take place within a wide range that extends from clinical scales to more complex systems based on Electromyographic Analysis (EMG). Collecting comprehensive history and observations are very important in assessing the effect of spasticity on functions. The muscle groups, in which the spasticity exists, and their interaction with postural reactions' effect on functions should be researched. Although assessing functional activities and daily-life activities does not directly determine the severity of spasticity, it could present an idea on the reflection of the changes of the spasticity on the functional condition. One method of assessing spasticity in the clinic is to determine the amount of resistance that the spastic muscle presents during a passive movement of the relevant extremity. Ashworth has, accordingly, defined a 5–point scale. This scale evaluates the resistance that occurs during the passive movements of the extremities with points between 0-4. Although the Modified Ashworth Scale (MAS) is a subjective method in our day, it is widely used as an easily applied method that does not require any tool in assessing spasticity. The Tardieu Scale is another scale that assesses spasticity with passive movements, as does the AS and MAS. This scale presents spasticity's nature that depends on speed. Passive straining is performed at the speed of the extremity segments falling with gravity and slower and faster than this speed. The Modified Tardieu

Scale (MTS) has added the assessment positions and spasticity angles of the extremities to the original scale. The MAS, Pendulum test and MTS for measuring the spasticity of children with CP was compared and MTS was determined to be most appropriate measurement method (Mutlu et al., 2007).
Spastic muscles limit articular movements in antagonist directions. Therefore, in addition to assessing the movement of the articular with a goniometre can also be used as an objective method although it presents conflicting results in terms of reliability. Assessments, which are not widely used in the clinic and are used more in assessments researches, are methods such as the dynamic flexometre, pendulum test, electrophysiologically assessing the H reflex and M response and the biomechanical analysis of response of the spastic muscle to angular and speed differences, etc. (Mutlu et al., 2008).
The Barry Albright dystonia scale is a highly reliable rating scale developed in order to asses the dystonia in patients with CP and traumatic brain injuries. The scoring is "none"; 0, "slight"; 1, "mild"; 2, "moderate"; 3, and "severe";4. Each region has specific descriptors for a scoring. Generally if dystonia is present less than 10% of the time it is "slight", if it does not interfere with function or care it is "mild", if it makes functional movements harder it is "moderate", and if it prevents function it is "severe" (Albright, 1996).
The changes in the muscle tonus must include the contraction capacity of the muscles, involuntary extremity and trunk movements, the stability of the trunk and extremities, correction and balance reactions, sitting balance, upper extremity and hand functions, sensory-perception problems, speech and tongue functions and dietary status. Orthosis, mobilisation and other adaption devices, the general health condition of the child and the family's socio-cultural and economical conditions should also be assessed. Various tests and batteries should be used in order to assess different parameters such as the motor and reflex development level, muscle strength, normal articular movement, functional skills, and independence level and self-care activities (Anttila, 2008).
The most widely-used test battery that measures the functional motor level in order to determine the motor development level of children with CP is the Gross Motor Function Measurement (GMFM). With GMFM, physiotherapists can define the motor function level of the child; obtain aid in specifying the targets of the treatment, follow-up the post-treatment development and present objective information regarding the child to relevant colleagues, other inter-discipliner professionals and families. It was developed in 1989 by Russell et al. by considering the motor function level of a 5-year old child with normal motor development. The GMFM measures how much of the action is achieved rather than measure the quality of the motor performance. The purpose is to determine the capacity and change. It is comprised of sections of supine-facedown positions and turning, sitting, crawling and standing on knees, standing on feet, walking and running and jumping (Russell, 1989). The Gross Motor Function Classification System (GMFCS) is a classification system developed for children with CP. The GMFCS has been developed by Palasino et al. based on the actions the child can perform from sitting to walking. It is a practical system that can be used in clinics for the rehabilitation team to classify a child with CP, observe the efficiency of the applications and follow-up on the patient in inter-intra discipliner applications. Initially, children with CP aged below 12 were divided into five levels by considering their independency in gross motor functions such as sitting, walking, mobilisation and transfer activities and the tools-equipment, tools that assist in walking that they use. As motor functions of children differ according to age, functions have been defined as under 2-years old, between 2-4 years old, between 4-6 years old and between 6-12

years old for each level. This system was extended in order to include the age ranges of between 12-15 and 15-18 years old in 2007. The Manual Ability Classification System (MACS) is a system developed in 2003 by Ellioson et al. in order to classify the ability to hold objects with hands during daily activities of children with CP between the ages of 4-18. MACS aims to specify which level represents best the child's normal activities at school, home and in society. The MACS classification should be specified based on the real performance of the child in daily life. This should not be done by performing a special assessment, but by asking a person who knows the child and how he/she generally achieves these. While specifying the MACS level, it should be kept in mind that the child's ability of holding objects is related to age. The MACS assesses the participation of both hands in an activity and cannot separately asses the hand functions. The aim of the MACS is to provide a systematic method regarding classifying how children with CP use their hands while holding objects during daily activities. MACS, focuses on manual abilities that are initiated by the person itself and especially on holding the objects surrounding them. The MACS has defined 5 levels. The differences between each level also help to specify the level which has the closest similarity to the child's manual abilities (Palisano et al., 1997, Eliasson et al., 2007, Gunel , 2009).

The Functional Independence Measure for Children= WeeFIM has been developed by using the Functional Independence Measure (FIM) developed for adults by "Uniform Data System" in 2003. It is a useful, short, comprehensive measurement method that determines the development, educational and social functional limitations of children that have CP and other development disorders. WeeFIM contains a total of 18 articles in 6 fields; self-care, sphincter control, transfers, locomotion, communication, and social and cognitive. Whether or not the child is aided, performs on time or if they required an aiding device while performing the function in each article of these fields is scored from 1 to 7. 1 point is given if they perform the mission with aid, 2 for independently performing, and 7 if they perform on the right time and safely. Accordingly, the child can score 18 the least (fully dependant) and 126 the most (fully independent) (Ottenbacher et al., 1999).

The Pediatric Evaluation Disability Inventory (PEDI), is a comprehensive clinical assessment tool that assesses the functional ability and performance of disabled children. It has been developed especially to asses the function of small children and is a distinguishing measurement method that can be used for children below 7,5 years old and also older children. PEDI, is comprised of three main sub-sections; functional abilities, help of caretakers and modifications. Each of these sections assesses self-care, mobility and social function areas. The functional abilities part comprises of 197 articles and measures the functional abilities of the child. In this section the "self-care" sub-section comprises of 73, the "mobility" sub-section comprises of 59 and the "social functions" sub-section comprises of 65 articles. The section regarding help of the caretakers comprises of 20 articles and measures the disability condition of the child according to the amount of aid required in order to perform the functional activity. The modifications section also comprises of 20 articles and shows the environmental modifications and tools that the child uses during his/her daily life. Each sub-section of PEDI can be used independently (Vos-Vromans et al., 2005).

Health-related quality of life (HRQL) is defined by the World Health Organisation Quality of Life Group as "an individual's perception of their position of life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns". The International Classification System (ICF) notes that the HQRL

should be taken into consideration in the assessments. Health-related quality of life should be considered in children with CP by terms of the child and the family. HRQL assessment in children with CP, should mostly contain physical symptoms, activity limitations, emotional stress, communication problems between the child-family, limitation of school life and difficulties experienced in the treatment of the disease. Due to the CP chart of children with CP, pain, general health, physical functions, actions with family are HRQL parameters. In comparison to normal children, as a result of CP, decrease of independency at a functional level, difficulty in daily life activities, and cognitive and sensory problems that may accompany negatively affect the HRQL in children with CP. Cognitive levels and speech functions are significant while determining the HRQL of children under 18. Therefore, surveys that measure the family's influence from the child with CP are widely used while determining the child's HRQL. It is required to develop quality of life questionnaires that comprise of questions that children that do not have cognitive problems can answer on their own. When literature is examined, we see that while assessing the HRQL of children with CP, Paediatric Outcomes Data Collection Instrument (PODCI) and Child Health Questionnaire (CHQ) are used the most. The Child Health Questionnaire-Parent Form (CHQ-PF50); is an assessment method developed to assess the HQRL of children aged between 5 and 18 (Erdoganoglu & Gunel, 2008).

Besides motor function problems being the main problem, when sensory, cognitive and mental problems accompany, the families' and caretakers', who have to take care of the children with CP, whose daily life functions and independencies are affected, all day for many years, are also affected in physical and psycho-social terms. In terms of physical and psychosocial health, the child with CP's general health, the parent's own psychological structure, social support and distribution of roles within the family are influential in the family's HRQL. General health profiles and tests that measure HRQL are mostly used for measuring the influence on families with children with CP (Erdoganoglu & Gunel, 2008).

4. Classification

CP is classified in various ways. These classifications can be grouped under various titles according to the body parts that are affected (topographic), the clinical type according to the prioritised motor findings, severity of influence and the causing pathology. In our day, the classification performed according to clinical characteristics is used the most. Classifications performed according to extremity distribution and severity take second place (Bax, 2005, Berger, 1998).

Classification according to clinical findings; is grouped under four headings: spastic, dyskinetic, ataxic and hypotonic. Most of the children with CP are of the spastic type; the ratio is approximately 70%. It is stated that the dyskinetic type occurs at ratios of 20% and the ataxic type at 10%. Some of these clinical types, especially spastic and diskinetic charts, can occur together and this is named as a mix type. Spasticity is observed in pyramidal system lesions, and extra pyramidal system involvements cause athetosis, chorea athetosis, dystonia, tremor and rigidity. Disorders in the cerebellum and the related systems, however, is clinically characterised by an ataxia (Aicardi & Bax, 1998).

The spastic type, characterised by the increase of muscle tonus, constitutes the most frequently occurring clinical chart. The muscles that are most affected by spasticity are on the upper extremity; the shoulder extensor, retractor, adductor and internal rotators, elbow flexors, forearm pronators, wrists and finger flexors. On the lower extremity; hip flexor,

adductor and internal rotators, knee flexors, ankle plantar flexors, and are sometimes evertors and sometimes invertors. Secondary weakness, various contracture and deformities and posture disorders frequently occur in the antagonists of these muscles. The periventricular leukomalacia that hold the medial fibrils of the corticospinal tract, more often cause a spastic diplegia table, while selective neuron necrosis in the cerebral cortex, parasagittal cerebral injury and intraventricular haemorrhage cause spastic hemiparesis and spastic quadriparesis tables. Besides spasticity, the suprasegmental reflexes controlled on brain stem level increases, thus, the tonic neck and labyrinth reflexes that are usually repressed are activated. While the lesion in the immature brain prevents the primitive reflexes from disappearing, the protective extensor reaction, corrective and balance reactions, which is required for motor development, postural control and ambulation and to continue during all of one's life, is delayed or obstructed. Apart from severe spastic events, it is difficult to understand spasticity in the first 4-6 months. After these months, the legs being in an extension, the shoulder being in a retraction and elbows being in a flexion position while supine, defines the table. In a facedown position, however, the tonic labyrinth reflex is dominant and the extremities are in a flexion position (Graham, 2001).

Dyskinesia caused by lesion affecting basal ganglions, is a clinical table in which involuntary and uncontrollable movements are in the foreground and can occur with various indications.

Chorea: Sudden, quick, aimless, dancing movements of the head, neck and extremities.

Athetosis: Involuntary, slow and snake-like movements. The plane, direction and timing of movements of the proximal articulars have mostly been defected. Chorea and athetosis sometimes occur at once, this is called choreoathetosis.

Ballismus: Involuntary thrusts like explosions. It is rare.

Tremor: Involuntary, rhythmic reciprocal, acute movements that occur due to the contraction of agonists and antagonists. These movements are generally more prominent in small articulars and extremity distal. It is rarely seen alone and is frequently accompanied by athetosis or ataxia.

Rigidity: Increase of tonus that includes both gravity and antigravity muscles (lead pipe and cogwheel indication).

Dystonia: Movements that are mostly characterised by constant muscle contractions in the trunk, neck and extremity proximal, causes contortions, repetitive movements or abnormal posture.

Diskinetic movements may occur in different ways. As it can occur as *intermittent spasms* characterised by increase in the flexor or extensor tonus due to tonic labyrinth and reflexes that affect the neck, it can also occur as *mobile spasms* that include the alternative flexion of extremities, extension, pronation and supination. Exaggerated movements, called *momentary localized contractions*, may occur with the muscle or muscle groups of anywhere in the body also being affected. Facial grimacing, exaggerated and asymmetric activation of the mimic muscles, rotating, bending movements of the hand and fingers, etc. *Ataxic type*; the ataxic table, developed as a result of selective neuron necrosis in the cerebellum, is characterised by disorder of teh kinaesthetic sense and balance and in-coordination. Before the child starts to walk, the first indication is hypotonia. Muscle weakness, rebound phenomenon, dynamic tremor, explosive speech, nystagmus, mental inability and astereognosis accompany in the table after the child starts to walk. Loss of balance is the distinctive characteristic of ataxia. The ataxia becomes more distinct when the child starts to walk. These children generally start walking late and their walking surface is wide while they sway while walking.

Important problems encountered in children with ataxic CP can be listed as hypotonia, occasionally increased muscle tonus, weak co-contraction, inability in postural stabilisation, dysmetria and coordination disorder in movements

Hypotonic Type

There is no normal, sufficient contraction and relaxation of the muscle. No involuntary movement occurs. It is mostly a transition stage in the development of athetosis or spasticity. It presents itself with decreased muscle tonus while at rest, decreased stretching reflex and decrease in primitive reflex patterns. In hypotonic children, decrease against passive movements, difficulty in lifting head while in facedown position, excessive flexibility in articulars especially in the ankle and wrist, weakness of the Moro and suction reflex are distinctive findings during the early phase.

Mixed Type

It is the combination of neuromuscular disorders and can occur with spasticity, dystonia and athetoid. Another classification is done according to the extremities that are affected.

Diparesis: It is a spastic CP in which mostly the lower extremities and some of the upper extremities are stiffened. It is clinically characterised distinct spasticity in the pelvis and lower extremities and moderate spasticity in the upper extremities and in-coordination.

Quadriparesis: Also named tetraparesis. It is the stiffening of the four extremities. The frequently dominant table is spasticity. In mix types, athetoid movements can be distinctive in the upper extremities while spasticity is distinctive in the lower. The severity between the right and left half of the body is differs.

Hemiparesis: Having affected the upper and lower extremity of the same side. The severity of the upper extremity is usually more. Prolonged birth, prematurity and birth asphyxia may play a role in newborns. Infections and traumas such as convulsions, meningitis, encephalitis during the early infancy and childhood may cause hemiparesis. Children which are hemiparetic before 3 years of age are generally assessed within CP.

Diparesis, hemiparesis and quadriparesis occur the most at a ratio of 75% according to the extremity stiffening in CP (Miller 2004, Matthews & Wilson 1999, Styer-Acevedo, 1999).

Recently, the clinical type of CP of children with CP is classified based on the most frequent neurologic indications. SCPE's (Surveillance CP Europe) classification system is progressing on creating an international language. According to the record system that SCPE suggests, CP;

Spastic type CP is characterised by at least two:

- Abnormal posture and/or movement.
- Increased tonus (not required to be constant).
- Pathological reflexes (increase in reflexes: hyperreflexia and/or pyramidal indications, i.e. Babinski response).

Spastic CP can be bilateral or unilateral.

Spastic Bilateral CP is diagnosed if it includes extremities on both sides of the body.

Spastic Unilateral CP is diagnosed if it includes extremities on one side of the body.

Ataxic type CP is characterised both of the below:

- Abnormal posture and/or movement.
- Loss of muscle control so that movements are performed with abnormal force, rhythm and accuracy

Both of the below are dominant in dyskinetic type of CP:

- Abnormal posture and/or movement.
- Involuntary, incontrollable, repetitive and sometimes stereotype movements.

Dyskinetic CP however, can by dystonic or choreo-athetoic:
Dystonic CP is active in both situations:
- Hypokinesis (decrease in activity, i.e. difficult movement).
- Hypertonia (tonus generally increased).
Choreo-athetodic CP is active in both situations:
- Hypokinesis (decrease in activity, i.e. severe movements).
- Hypertonia (tonus generally increased) (Krägeloh-Mann 2009, Garne et al. 2008).
International classification of functioning, disability and health (ICF), is a classification system that the World Health Organisation, which provides a standard language and conceptual frame to define health and health related situations, encourages using. The significant classification in recent years has been put forward by the International Classification of Functioning, Disability and Health (ICF) (Rosenbaum & Stewart, 2007). The complex relationship between disability, participation and environment represents an area of specific importance for children in the rehabilitation professions. The revised version of the ICF, disability and health incorporate biological and social perspectives on disablement, so as to represent fully the impact of health on a person's life, including participation in the community (Gunel & Mutlu, 2007). Sufficient and appropriate assessment tools are required in order to reveal the activity and participation limitations in paediatric rehabilitation. The ICF model functionality presents an appropriate solution method for those who want to increase the activity and participation of children at the risk level and prevent secondary disorders. Models regarding functionality and health condition constitute the foundation of training and research in clinical practices. The World Health Organisation (WHO) developed the "International Classification of Function, Disability and Health", known as the ICF, in order to record and organise comprehensive information on health and health related issues. Besides health, the ICF was aimed to be used in many fields such as creating policies regarding education, insurance, social security, human rights, work safety, health and liberty and obtaining statistics and used to determine the needs under clinical conditions, for the selection of the treatment in specific health conditions, rehabilitation and assessing rehabilitation results. The general purpose of the ICF classification is to create a common, standard language and frame for defining health and health related issues and define health components and certain components (such as education and workforce) regarding wellness. Therefore, the fields that are within the scope of ICF can be considered as *health issues and health related issues* (Mutlu et al., 2010).
As a result of an assessment conducted by selecting the required of all these assessments, it shall be possible to define the child's need for physiotherapy and rehabilitation, what could be done and the functional contributions of what has been done.

5. Physiotherapy and rehabilitation

Rehabilitation approaches of a children with CP are comprehensive, in addition to the medical and surgical applications; physiotherapy, occupational therapy, speech therapy, orthosis and other adaptive equipment, recreational activities, school and education adaptation and psychosocial support, etc. are included in rehabilitation approaches (Helders, 2003). The aim of rehabilitation in children with CP are; to minimize the effect of physical impairments, to gain independence in the community and to improve the quality of life of the handicapped children and their families who have major roles to play in the process (Cusick, 2006, Schalick, 2001). Rehabilitation in children with CP can differ due to clinical type and severity of table, additional disabilities, physiological age of children,

socioeconomic factors. In addition visual, auditory, cognitive disorders, seizures, learning disabilities and emotional problems may influence intervention outcomes (Anttila et al., 2008).

Physiotherapy plays a central role in managing the condition; it focuses on function, movement, and optimal use of the child's potential. Physiotherapy uses physical approaches to promote, maintain and restore physical, psychological and social well-being (Damiano, 2008). Children with CP's interventions have lifelong effects, and can be efficient and cost effective (Damiano, 2006). Rehabilitation team members provide services that will help them reach their full potential in their homes and communities. The rehabilitation influence is not restricted to the medical centre and treatment gymnasium, but frequently includes the child's functioning settings within the home, school, recreation, and community environments (Verschuren, 2008).

The physiotherapist focuses on gross motor skills and functional mobility in the management for the motor deficits in CP. Positioning, sitting, transition from sitting to standing, walking with or without assistive devices and orthoses, wheelchair use and transfers, are areas that the physiotherapist works on. In most settings the physiotherapist performs therapy, plans the home program, provides the interphase with the school and recommends equipment (Butler & Darrah 2001, Yigit et al., 2002).

Physiotherapists emphasize the need for the practice to be evidence-based whenever possible (Kunz 2006). Recently, reviews have addressed the effectiveness of physiotherapy interventions for children with CP focusing on neuro-developmental therapy (NDT) (Msall & Park 2008), strength training (Dagenais, 2009), conductive education (Bourke-Taylor 2007), various physiotherapy interventions (Tsorlakis et al. 2004), and orthotic management (Morris, 2002). Methods such as biofeedback and electrical stimulation, behavioural and educational approaches such as conductive education, were not included as physiotherapies but were accepted as an adjunct therapy (Colborne et al., 1994, Kerr et al., 2004).

Today, the Bobath approach, initially, aims to observe the existing performance of the child with CP, analyse it, interpret it and then enable the child to reach the maximum level of independency within the limitations of the child's potential assessment and result (DeGangi & Royeen, 1994). NGT was developed by Bertha Bobath, physiotherapist, Karel Bobath, neuropsychiatrist. At the beginning of the 1940's, Bertha Bobath combined clinical observation, neural maturation theory, hierarchic foundation and reflex development. Bobath's approach was shaped in order to involve scientific theories that were and empirical experiments that were developed and has a structure that is open to development and is dynamic. Thus, it has been developed until our day since its first application and has undergone some changes. According to the Bobath's, the motor problem is one of the most important problems and delay or disorder of normal motor development or not being able to establish postural control against gravity due to function problems in the central nervous system is the most significant factor that causes motor problems (Bly, 1991, Tsorlakis, 2004). In the 1970's, normal motor development started to be experienced, the use of key point was brought to the agenda, and approach of passive and static treatment among physiotherapists was decreased and the concept of simulation became prominent. It was seen during these years that one-on-one communication, normal postural reactions and automatic movement reactions were facilitated, more developed and functional steps of normal motor development were introduced and accurate ambulation was ensured during every phase of motor development. In the 1980's, organisation of daily life activities, positioning during the day, using assisting tools and equipment, using support points,

enabling correct sitting, carrying, transfer positions, developing sense integration, increasing function of upper extremities and hand and ensuring hand-eye coordination principles came into prominence. From the 1990's to our day, however, active dynamic treatment, training in activities to ensure functionality, developing coordination of the movement and balance, training on telescoped different activities within an action flow have gained significance. Today we see that the expression of tonus coordination is used instead of tonus inhibition and Tonus coordinating patterns (TIP) are used instead of RIP. Positioning that are tonus coordinating and aimed at revealing active movement and simulators that increase sensory-motor activity are used. One other significant development is the key point concept. It has been indicated that use of distal (such as hands, feet) and small body parts, while using key points in order to facilitate the movements, may increase the tonus and that it is better to use larger parts of the body (such as arm, forearm, legs) for facilitation of the movements. The general target is to ensure normal motor development and function and prevent contracture and deformities. The NDT method, which regards all problems occurring in the child as a result of the injury in the central nervous system, has focused on working on memory, perception, sense, postural control and abnormal patterns, reflexes and sensory motor components in the muscle tonus. It is used to facilitate special gripping techniques movement patterns, balance responses and normal muscle tonus and also to decrease abnormal movement patterns, reflexes and spasticity. During the years when the NDT was first developed, the child was more passive in this approach; however, as it has received the name of "living concept" it is observed that the child is more active now (Livanelioglu & Kerem Gunel 2009, Kerem Gunel, 2009).

The effect of the family is very important and the family must act like a part of the rehabilitation team within the scope of NDT (Butler & Darrah, 2001). There have been debates on whether NDT principles affect motor development in terms of reflex and hierarchic model of motor control is focused on only neural explanation. For instance, in the motor control model, the central nervous system is regarded as one of the systems that affect only motor behaviour. Motor control is also affected by cognitive and environmental factors. However, physiological components and environmental contents are accepted as non-neural explanations in the child's progress (Fetters & Kluzik, 1996).

Implementing clinical practices with applications based on evidence is increasingly becoming more important today. Although NDT is the most commonly used method in child rehabilitation by physiotherapists all over the world, research that presents its effects are deemed to be insufficient. There are many reasons for this. Research presenting NDT's effect was organised by AACPDM (American Cerebral Palsy Association) and as a result the difficulties and the evidence encountered were studied (Butler & Darrah, 2001).

The most prominent difficulty is that all problems, diagnosed on research that includes low incidence and high heterogeneity conditions, become complex with the change of children along with their growth and development process. Despite these obstacles, due to different practices and understandings in applying NDT and its ongoing and wide effect in CP treatment, it is important to collect information on NDT. Researchers indicate that NDT is clinically significant but that no statistical assessment can exactly present its result, partially due to the difficulties mentioned above (24). In researches where the NDT's clinical effect is attempted to be presented by practice, the NDT structure changes with time and in these researches NDT practices are usually performed with other therapy techniques and medical treatments. NDT's effect has been mostly researched in studies in which it is applied together with other rehabilitation practices such as orthesis application, Johonstone Pressure

Splint, occupational therapy, game therapy, electrical simulation, horse therapy and practices in water (Kerem & Livanelioglu, 2001, Law, 1997). The primary target of NDT is to change the central nervous system's neural based motor responses. Various aspects of the motor response have been assessed with measurement methods used in conducted researches. These are qualitative movement or physiological motor function (i.e. involuntary muscle tonus changes, spasticity, etc), reflex activity, weight transfer, postural control, trunk rotation, combined reactions, upper extremity movements and walking parameters. As a result of these researches, generally, it has been indicated that a better motor response occurred and that there were positive changes in terms of physiological motor function, movement time, step length for walking, speed and foot angle after the NDT practices (Bobath, 1971). Nonetheless, the evidence of this development in physiological motor functions and qualitative movement is not consistent (26, 31). One other very important target of NDT is to prevent or slow down deformities. The measurements of articular movement width, orthesis or surgical suggestions after the NDT practice are used for researching the degree of contractures. It has been indicated that NDT provides advantages in protecting the dynamic articular movement width in the ankle and knee (Kluzik et al. 1990). In other words, when the articular limitation was repetitively and immediately assessed after 20-25 minute NDT sessions, it decreased further. To decrease spasticity, provide normal movement experience, support functional independence during daily activities and thus indirectly support motor learning, physiotherapists use special grips and positioning within the scope of NDT. Dynamic articular movements and the child's active participation during the movement can be clinically descriptive. Motor development: standard tests have been designed for the sample activities in the field of special development; the development is compared to the normal, whereby developmental gain or age is effective. The other fields in the child's development and function and physical and physiological development in developmental theory are interrelated. Therefore, other fields of development can change when abnormal motor behaviour changes through the practice. Although NGT is said to be advantageous in cognitive, lingual, social or emotional fields for physiotherapists and families, this has not yet been statistically indicated in researches (Herndon et al., 1987, Mayston, 2008, Butler & Darrah, 2001).

Functional limitation and activity participation in practices conducted on children with CP is one of the main issues researched within the scope of "International Classification of Functioning, Disability and Health (ICF)". The standard tests used for this matter comprise activity or skill attainment items and accept developmental retardation and developmental ages as independent variables and aims to measure functional limitation/activity length and widely-used functional activities such as sitting, walking, dressing-up, playing and communicating with other people. In a study conducted on this topic, it has been proved that NGT increases the gross motor function; however, this study has not entirely put the developmental acquisition (Østensjø, 2006). It supports the expectation regarding NGT's making a greater contribution to the communication between the family and the child. Although it has been shown that in a NGT group mother sensitivity towards child is statistically significant, this effect could not be exactly presented in other groups. When considering principles of evidence-based practices in studies, it is possible to mention that the studies were conducted with groups that have low-level work force and insufficient number of cases and are heterogeneous. When the results are considered, it can be emphasized that NDT practices have positive results on postural tonus, functional independency and dynamic articular movements; however, NDT cannot be proved to be

superior to other practices and further studies are strongly required. These efforts should involve randomized studies in more comprehensive groups whereby only NDT is applied in homogeneous groups by making use of reliable and valid evaluation analyses where age, sex, severity and type of disease, socio-economic and cultural structure of family are kept under control and which indicate long-term effects.

Exercises refer to planned structured activities involving repeated movement of skeletal muscles that result in energy expenditure and seeks to improve or maintain levels of physical fitness above the intensity of activities of daily living. Several types of therapeutic exercises utilize for improving the child's motor ability as below;

Passive stretching, done manually offered in most spastic children to soft tissue tightness. Manual stretching may support increasing range of movements, reducing spasticity, or improving walking efficiency in children with spasticity. Sustained stretching of longer duration is preferable in improving range of movements and reducing spasticity of muscles around the targeted joints (Arpino et al., 2010). Static weight-bearing exercises are commonly used in order to stimulate antigravity muscle strength, prevent hip dislocation, improve bone mineral density, improve self-esteem, improve feeding, reduce spasticity, and improve fine motor function (Pin, 2007). Strength training aims to increase the power of weak antagonist muscles and the corresponding spastic agonists and provide the functional benefits of strengthening in children with CP (Damiano, 1995). Functional exercises is combining aerobic and anaerobic capacity and strength training, in ambulatory children significantly improved physical fitness, the intensity of activities, and quality of life. Training programs on static bicycles or treadmills were beneficial for gait and gross motor development without enhancing spasticity and abnormal movement patterns (MacPhail & Kramer, 1995). Electrical stimulation is proposed as a useful modality in CP due to the lack of selective muscle control required for specific strengthening programs. Neuromuscular electrical stimulation and threshold electrical stimulation are used for strengthening the quadriceps muscles in ambulatory children with diplegia who find resistive strengthening programs difficult (Kerr et al., 2004).

6. Conclusion

In physiotherapy applications of the children with CP, use the terminology “treatment” only is insufficient. Instead of this terminology, it is more accurate to use “management”. Because, physiotherapy of children with CP not only includes the treatment of the motor problems, but also takes all of the requirements of the child and a good family-child relation into consideration. During the applications, existing problems of the child should be taught as a whole of motor, cognitive, sensorial, emotional, social areas. It is very important to determine the realistic goals. The rehabilitation team should determine the short and long term targets according to the existing condition of the child and the team should control the targets in certain periods whether if they can reach those targets. If an unreal target is noticed, providing a correct connection between the condition of the child and the target and planning the strategies to reach the targets are the main principles. During the applications, planning all day, working with the family, integration to daily living activities, helping to the child, increasing the quality of life are important. Determination of the main targets during the treatment, taking the child’s personal characteristics into consideration, providing the usage of the functional abilities of child during playing are the other important main points.

7. Acknowledgement

My former colleagues from The Hacettepe University, the Faculty of Health Sciences, The Department of Physiotherapy and Rehabilitation supported me in my all working area. I want to thank them for all their help, support, interest and valuable hints. Especially I am obliged to Ayşe Livanelioğlu, Akmer Mutlu and Özgün Kaya Kara. Especially, I would like to give my special thanks to my husband Hakan Günel whose patient love enabled me to complete this work. Also I want to thank to all children with Cerebral palsy and their families.

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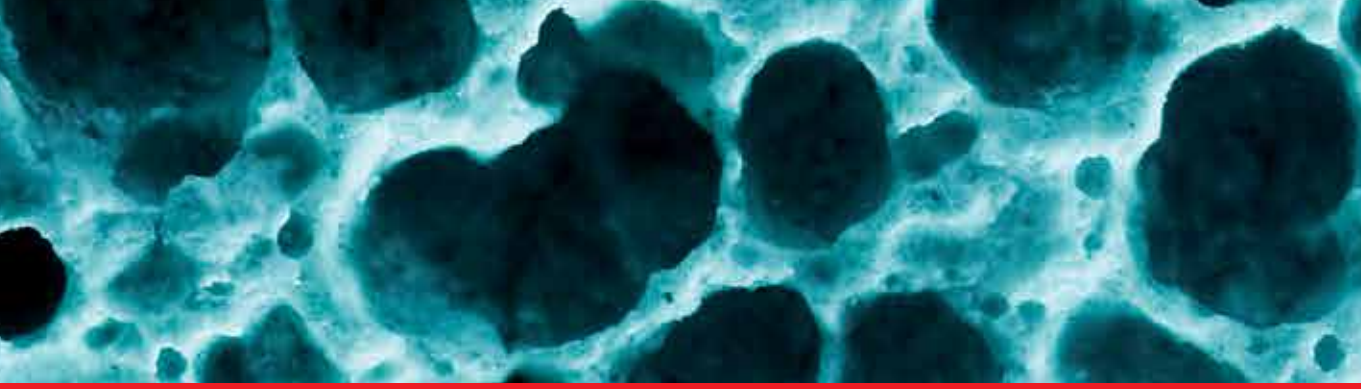

Edited by Željka Petelin Gadže

Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book "On The Sacred Disease". Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology - they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

ISBN 978-953-51-6487-6

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