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Edited by Humberto Foyaca Sibat

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Notice

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Meet the editor

Professor Humberto Foyaca Sibat graduated as a medical doctor in Havana University in 1971. He became a specialist in neurology in 1975 and second-degree specialist in 1984. He is married and has three daughters and one son. Dr. Foyaca has been an associate professor of Walter Sisulu University for more than 20 years. He also holds a PhD and Master degree in Science and is a full professor and full research investigator of the Cuban Academy of Sciences. Dr. Foyaca is a member of 15 medical societies from all over the world, he has presented more than 380 papers in different scientific events, and he published more than 75 manuscripts in peer-reviewed journals. He is the chief editor of The Internet Journal of Neurology, currently the largest electronic journal of neurology worldwide. He received and delivered many short training courses and organized many national and international conferences. Prof. Foyaca edited five books and published nine chapters for IntechOpen.

Contents

Preface

Psychogenic non-epileptic seizures (PNES) and epileptic seizures (ESs) are a very common health problem of human beings since their origin. ESs were considered as a sacred disease for thousands of years, while for the past hundred years, a real knowledge of its etiopathogenetic mechanism is better known.

This book contains a group of selected peer-reviewed chapters that were revised by members of the IJN Editorial Board and the chief editor of this project at least twice. An important number of recommendations and modifications were implemented on the chapters before they were accepted for publication.

An overview of genetic testing modalities and workflows taking into account the genetic architecture of epilepsies is given, and the practical aspects of genetic testing in epilepsies, including advantages/limitations and clinical utility of tests, are discussed.

This book aims to present in synthesized form the role of genetic, immunological, and environmental factors in autoimmune epilepsy and the treatment of PNES and ES as well. A review of the work achieved during the last years in patients with this condition provides information and experience on the diagnosis and treatment of these epilepsy types. This book reports results from a systematic search of PUBMED, looking for articles published about autoimmune epilepsy, autoantibodies and epilepsy, NMDA and epilepsy, AMPA and epilepsy, and GAD and epilepsy.

Some authors estimated the prevalence of ischemic stroke in patients presenting subarachnoid neurocysticercosis and epileptic seizures, while others deliver their results from conducted interviews, literature reviews, expert panels, and online surveys to assess the availability and quality of patient-reported data during epilepsy diagnosis and treatment, respectively. Their results highlight important data collection and design opportunities to support the diagnosis, treatment, and self-management of epilepsy.

Finally, we discuss about the treatment for pseudoseizures in a professional manner and the results of the study done on PNES in patients living in rural South Africa. Because NCC is the leading cause of epileptic seizures in developing countries where PNES is also a frequent problem, to distinguish real seizures from PNES is a challenge. Therefore, this book shows the updated information published in the medical literature and compares it with the authors' results and highlights how to differentiate epileptic seizures from PNES.

The seven chapters in this book, authored by some of the world's top neurologists and researchers in the field of central nervous system, provide a valuable update on the topic of seizures, providing a timely review of the achievements in PNES and ES, covering historic aspects, genetics, pathogenesis, clinical aspects, and imagenology, among others. Contribu-

tors from different countries have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the topics with many explanatory figures to enhance legibility and make the book useful. Countless hours have gone into writing these chapters; precious free time to be dedicated to our family, relatives, and friends has been sacrificed, but in the end, we all are very proud of this book.

Every effort has been made to check all novel information given in this book, but it is important for our readership to scrutinize last information arriving considering it is a dynamic process of learning. We all attempted to bring in valuable updated information for all issues mentioned in this book. Every effort has been made in the preparation and editing of this book to ensure that the information given is correct, but it is possible that errors have been overlooked. Finally, we like to highlight that we reviewed all controversial matters, and our medical criteria and scientist's opinions have been expressed with modesty, honesty, and respect. Nevertheless, the reader is advised to refer to other published information to check accuracy.

I would like to thank IntechOpen Publisher that unconditionally supported me in editing this book. My family has graciously tolerated the precious time spent on this project. Fortunately, Mom, Dad, my brother Francisco, and my first daughter Zayra Susana from heaven continue to inspire me. My sisters Mayra Alejandra, Lilia Teresa, and Lorna Irene supported me all the time. My second daughter Lorna Maria (33 years old) and Fatima Susana Adolfina (8 years old) encouraged me all the time to continue moving forward with persistence. My son Thabo Humberto Jorge (10 years old) pushed me to play games with him that helped me to relax and to find new ideas. My whole family contributed to this project in one way or another and they deserve my deep gratitude. My wife Lourdes de Fatima was the strongest support for this project, and without her collaboration, this project would have never happened. I also want to thank the families, relatives, and friends of all collaborators for their patience and tolerance for the lost evenings, nights, weekends, and holidays. Special thanks go to Walter Sisulu University (WSU). The new university was named in honor of an icon of the South Africa liberation struggle and close comrade of Nelson Mandela, the late Walter Max Ulyate Sisulu. Many thanks go to Dr. EN Cishe, acting director of Research Development of WSU; Professor AJ Mbokazi, dean of the Faculty of Health Sciences (WSU); Prof. Thozama Dubula, head of the Department of Medicine and Therapeutic; Dr. M Mdledle, acting governor general director of Clinical Governance of Nelson Mandela Central Hospital; and Mrs. NP Makwedini, chief executive officer of Nelson Mandela Central Hospital for the best understanding and support. I extend my deepest sense of appreciation for the support received from Dr. Roberto Morales Ojeda, minister of Public Health of Cuba, and Dr. Jorge Delgado Bustillo, deputy director of the National Unit for International Cooperation in Health.

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Chapter 1

Introductory Chapter: Seizures and Its Historical Background

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Additional information is available at the end of the chapter

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1. Introduction

Seizures are a very common problem that accompany the humanity since its origin, and epileptic seizure (ES) was considered as a sacred disease for thousands of years, while for the past hundred year, a real knowledge of its etiopathogenetic mechanism is better known.

In one of the chapters of this book, an overview of genetic testing modalities and workflows taking into account genetic architecture of epilepsies is given, and practical aspects of genetic testing in epilepsies, including advantages/limitations and clinical utility of tests, are discussed.

Other chapters of this book aim to present in synthesized form the genetic, immunological, and environmental factors' role in the autoimmunity to epilepsy, as well as the therapeutic approach that has been used to control seizures, mainly where there is a suspected anti-neuronal-antibody circulation. A review of the work achieved during the last years in patients with this condition provides information and experience in the diagnosis and treatment of this epilepsy type. In this chapter, the authors conducted a systematic search of PUBMED, for articles published between 1990 and December 2016 using the search terms "autoimmune and epilepsy," "autoantibodies and epilepsy," NMDA and epilepsy, AMPA and epilepsy, and GAD and epilepsy. The list of identified articles was complemented by additional searches for relevant articles in the reference section of the publications captured by the initial search.

In another chapter, the authors estimated the prevalence of ischemic stroke (IS) in epileptic patients presenting subarachnoid neurocysticercosis (SNCC) and IS frequency among HIV-positive patients in three NCC subgroups. Finally, to determine if the odds of ischemic stroke are elevated in SNCC patients compared to patients with intraparenchymal NCC (INCC).

They determined whether the risk for IS is elevated in HIV-seropositive patients presenting with SNCC or intraparenchymal NCC (INCC) and evaluated if and when the potential interaction varies by location of NCC in the brain. Eligible epileptic patient's seropositive status was recorded, and cross associations for the independent variables (NCC status and HIV status) and outcome variables (IS event) were performed.

The authors compared the INCC SNCC group to the reference group; the odds of IS in PLWNCC were 2.0 and 2.6 times greater patients with SNCC and INCC, respectively. The frequency of IS was greater in HIV-positive patients in all three groups, but the risk was especially pronounced when seropositive epileptic patients were both NCC groups when compared with the reference group, subarachnoid space that risk increased tree times more.

In the chapter entitled "Self-Reporting Technologies for Supporting Epilepsy Treatment," the authors conducted interviews, a literature review, an expert panel, and online surveys to assess the availability and quality of patient-reported data that is useful but reported as being unavailable, difficult for patients to collect, or unreliable during epilepsy diagnosis and treatment, respectively. Their results highlight important yet underexplored data collection and design opportunities for supporting the diagnosis, treatment, and self-management of epilepsy and expose notable gaps between clinical data needs and current patient practices.

The chapter entitled "Psychogenic Non-epileptic Seizures in Patients Living with Neurocysticercosis" analyzes the results of one study about patients presenting epileptic seizures and pseudo-seizures (psychogenic non-epileptic seizures [PNES]) and living with NCC done in rural South Africa. NCC is the leading cause of secondary epilepsy in developing countries where PNES is also a frequent problem, then to distinguish real seizures from PNES is a challenge. Therefore, the author reviewed the recent medical literature and compared it with their results and highlighted how to differentiated epileptic seizures from PNES.

2. Background history

The main clinical manifestation of NCC is ES; then the first human being presenting NCC also had ES. Probably the first human being infected by *Taenia solium* was the *Homo ergaster* [1, 2]. Therefore, the history of epileptic seizures began at the Lower Pleistocene (between 1.51 and 1.56 million years ago) when *H. ergaster* lived. *Tapeworms that plague humanity originated in carnivores such as lions, hyenas, or African dogs and jumped to humans after they began eating their prey animals on the African savannah* [2]. Modern humans share the same differences as *H. ergaster* with Asian *H. erectus*, leading the possibility that *H. ergaster* is the ancestor of later Homo population [2, 3]. In our opinion the first epileptic patient was a *H. ergaster.* Because the humans are the most important element in the *T. solium* transmission, we assumed that *H. ergaster* was the first transmitter of the tapeworms to the savage animals and from the infected animals, he got the infection with *T. solium* through their eggs and proglottids present in the contaminated water and/or food.

2.1. Ancient times

Seizure disorders, and the mysteries surrounding them, have been discussed for nearly 4000 years starting with Assyria, Akkadia, and Babylonia. Babylonians and Sumerians believed that it had supernatural causes like other diseases.

Many years after the *H. ergaster* disappeared, the habitants of earth continue being infected by *T. solium* suffered from NCC and, obviously, presenting ES. The earliest report of seizures is available in the *Sakikku*, a Babylonian cuneiform medical diagnostic text from 1067 to 1046 BC where the current description of epilepsy is named *miqtu* ("the falling disease") [4].

According to Eadie and Bladin [5] "with the probable exceptions of the absence and myoclonic seizures of today's generalized epilepsy, the Sakikku mentions probable examples of all the major contemporary classificational types of epileptic seizures. The fact the ancient and unknown author or authors of the Sakikku saw fit to bring such phenomena together in the account indicates recognition of the fundamental kinship of these phenomena. The ascribing of them all to miqtu, suggest that they were all taken to be various expressions of the same underlying disorder. Moreover, the authors (s) also distinguished between miqtu and a possible pseudo-seizure."

Historically, people with epilepsy were considered to be demonically possessed, to be witches or even insane [6]. *The history of epilepsy and its treatment in the western world dates back at least 4 millennia to the ancient civilization of the Middle East. Past and present treatments have been empirical, usually reflecting the prevailing views of epilepsy, be they medical, theological, or superstitious. Ancient physicians relied on clinical observation to distinguish between epileptic syndromes and infer their cause* [7]. In this period other peoples also worked on the field of epileptic seizures such as Atreya the father of the Indian Medicine who wrote the *Charaka Samhita* (sixth century BC) [8]. The *Huang Di Nei Ching* was written by a group of Chinese physicians between circa 770 and 221BC; they wrote on epilepsy and delivered a description about an epileptic seizure (epilepsy mania) [9].

In 400 BC Hippocrates, the father of medicine, offered another point of view on epilepsy that it was just another natural disease and could be treated through natural methods. *On the Sacred Disease* was regarded as the oldest surviving medical account of epilepsy, where he argued that the epileptic seizures were not sacred in its origins [5]. He supported the use of medicine and control of the diet in order to cure this disease based on his theories of medical methodology. While his methods were hardly scientific, he was the first to consider epilepsy to be a natural disorder and would be the only one to do so for centuries. After the Greeks the Romans took a view similar to that of the Babylonians as to the nature of epilepsy [6].

Magiorkinis et al. [10] said that "The first formal description of epilepsy as a disease should be attributed to the father of medicine, Hippocrates of Kos, in his classic treatise On the sacred disease (Περὶ ἱερῆς νούσου). In this book, Hippocrates disputes the divine origin of epilepsy by saying: "This disease is in my opinion no more divine than any other; it has the same nature as other diseases, and the cause that gives rise to individual diseases. It is also curable, no less than other illnesses."

After Hippocrates, the experience on ES in Alexandrian, Roman, Middle East, and Asian medicine did not reach higher progress, but we should highlight the work done by Diocles of Carystus, Praxagoras of Cos, Pedanius Dioscorides, and Aurelius Cornelius Celsus (circa 30AD) who wrote "Epileptic fits are not difficult to bring to an end, when they have commenced before puberty, and whenever the sensation of the coming fit begins in some one part of the body. It is best for it to begin from the hands or feet, next from the flanks, worst of all from the head" [5]. Aretaeus the Cappadocian was the first to describe visual, olfactory, and auditory auras (second century AD). Aelius (Claudius) Galenus (131–201AD) gave a definition of epilepsy: *Yet if there is not only convulsion of the whole body, but also interruption of the leading functions, then this is called "epilepsy*." Caelius Aurelianus differentiated two types of ES: deep sleep from convulsive (fifth century). Paul of Aegina, the last of Byzantine writers in the late sixth or early seventh century, also delivered a definition of ES as paraphrases of those of Galen did, but he recognized that seizures in eclampsia proceed from the uterus [5]. Nevertheless, to consider the *Ancient Chinese Medicine* among those great delivers of knowledge is mandatory, and the classification of ES in the *Zhu Bing Yuan Hou Lun* Theu in five types was a great advance [9].

2.2. Medieval times

From our historical review on NCC, we know that mysticism and dogmatism continue influence all scientific fields including medicine, and many diseases were considered as a consequence of demonic possession; then patients presenting ES were managed as warlocks and witches. Several physicians wrote about ES in this period worldwide, and almost all kept the same point of view from ancient Great and Romans. The most famous medieval Islamic writers were Abu Bakr Muhammad Ibn Zakariya al-Razi (85–925), known as Rhazes, and Abu Ali al-Husayn ibn Abd Allah ibn Sina (980AD) from Persia, known in the west as Avicenna [11]. However in this period, there were other writers with some different criteria about ES that should be mentioned: Arnold of Villanova (circa 1234–1311) who defined ES as an occlusion of the chief ventricle of the brain [12]. In 1305, Bernard of Gordon adverted to the possibility of the existence of simple partial seizures [5, 13]. In 1314, John of Gaddesden (circa 1280–1361) wrote about epilepsy in his *Rosa medicinae* considering that ES without convulsion is possible and proposed three forms of epilepsy—minor, medium, and major—assigning the synonyms true, truer, and truest. Minor epilepsy is attributed to the obstruction of arteries, medium epilepsy to the obstruction of the nerves, and major to an obstruction of the ventricles of the brain [14]. However, Antonius Guainerius (died circa 1450) considered that the presence of convulsion and foam at the mouth must be part of the clinical feature of ES [15]. According to Singer [16] Antonio Benivieni (1443–1502) wrote: "Though the disease called epilepsy is among the best known of diseases, yet many are unacquainted with it in the form of which I saw it recently in a young Aretine girl. When attacked she did exhibit the usual symptom of falling down, nor did she foam at the mouth, but she would just stand still, moving her head and neck from side to side as if trying to see something, yet dumb, deaf, and insensible. On coming to herself and being asked what she had been doing she did not know in the least."

Beyerstein [17] suggests that the curious behavior of the possessed people described in the classic Malleus Maleficarum (published in Germany in 1487) is likely symptoms of epilepsy or Tourette' syndrome. At the age 13, Joan of Arc experienced moments of ecstasy with light,

heard voices of saints, and claimed to see visions with angels, all probably symptoms of epileptic seizure [18].

The first acknowledgement of St. Valentine being a patron saint for people with epilepsy is printed in The Nuremberg Chronicle, an illustrated book printed in 1493. St. Valentine was known for healing people with epilepsy around Europe including southern Germany, eastern Switzerland, Austria, and northern Italy [19].

2.3. Brief history of ES during the renaissance and the enlightenment

In the XIV to XVII centuries (European Renaissance), the Sciences is realized from the Catholic Church's chains, and as a consequences of that, the number of writers with new criteria about ES increased remarkably, and also theories regarding the mechanism that causes the epileptic fits as well as new classifications of the disease came forth [10]. There were some peoples trying to differentiate epilepsy and demonism.

In 1549, some aspects on ES were written in the first book delivered "about neurology" (Pratensis: *De Cerebri Morbis*) according to Prestonk where the author adopted Galen's subdivision of epilepsy into three types [20].

By the end of the sixteenth century, Martinus Rulandus (1532–1602) delivered a booklet about now known as benign Rolandic epilepsy.

In the seventeenth century, Thomas Willis goes in front of the scientific revolution, and apart from his description about anatomy of the blood supply to the brain among other aspects, he wrote about ES describing the a typical tonic–clonic seizure as the characteristic epileptic convulsive phenomenon: "…The Epileptick fit or assault seems to be the only a universal and more cruel Covulsion…" [5]. Paracelsus (1493–1541 AD) dealt with epilepsy. He agrees that epilepsy may originate from the brain or the liver, the heart, the intestines, and the limbs but he also suspected that epilepsy of a sick priest derived from the presence of brain cyst [2]. Paracelsus views about the human nature and the construction of the human body from mercury, sulfur, and salt which led him to a different model for the causes of epilepsy. Ioannes Marcus Marci (1595–1667 AD), a Bohemian physician and scientist, broadened the definition of epilepsy "to any affection of the body where the victims are disordered in their minds, while the members [of the body], be it all, or some, or only one, are moved against their will" [10]. John Locke (1632–1704) worked on hysteria and epilepsy.

From the eighteenth century, we should highlight the work done by Herman Boerhaave (1669–1738), George Cheyne (1671–1743), and William Cullen (1710–1790) who wrote about spasmodic affections without fever together with tetanus and chorea or St. Vitus dance [5]. Samuel Tissot a Swiss physician (1728–1797) defined epilepsy as a convulsive illness in which every attack interferes with the senses and the understanding and is accompanied by convulsive movements of various degrees of severity involving many parts of the body [5].

Pedro de Horta a Mexican physician wrote the first book on epilepsy in the New World (1754) published in Madrid. The book contained a discussion of the distinctions to be drawn between the different medical disorders embraced by the conditions known locally as "Telele" and "Tembeleque" [21]. William Heberden, an English physician (1710–1801), included complex

partial seizures (which did not become secondarily generalized) and absence seizures in his concept of epilepsy.

2.4. Brief history of ES during the eighteenth and nineteenth centuries

Herman Boerhaave (1668–1738) provided a rather strict definition of epilepsy: "Epilepsy is the sudden abolishment of all vital functions with accompanying increase of mobility and convulsions in all body muscles," whereas he adopts the Galenic classification of epilepsy [10].

The Dutch-Austrian Gerard van Swieten (1700–1772) wrote a chapter on epilepsy in which he described extensively the clinical characteristics of various forms of the disease and discusses epilepsy in comparison with apoplexy and hysteria [22]. By law, at that time peoples presenting ES (in Sweden) is prohibited to get married (1757).

The Swiss physician Simon August André David Tissot (1728–1787) published in 1770 the first major treatise on epilepsy that is considered to be a milestone in the scientific research on epilepsy. At the same time, he refused the theory of the influence of the moon on epileptic seizures and accepted the hereditary forms of epilepsy. The Italian naturalist Felice Gaspar Ferdinand Fontana (1730–1803), in a series of experiments on stimulation of the cerebral cortex with electricity, demonstrated that convulsions could be produced by pressure on the brain, but not by irritation of the dura, as commonly believed [23, 24]. Thomas Beddoes (1760–1808) described accurately the premonitory symptoms developing before the onset of an attack. Sir Charles Locock introduced the first generation of antiepileptic drug (AED), bromides (in 1850); since then it was the only available medication for treatment of ES for the next 50 years [19]. In November 30, 1893, the Ohio Hospital for patients presenting ES was opened.

Connecticut becomes the first American state to prohibit marriage for people with epilepsy (1895). House Bill 681 denied the rite of marriage, or to live together unmarried, to individuals 45 years old or younger who either had epilepsy or were a pauper, imbecile, or feebleminded. Minimum prison sentence would be 3 years. Many states would follow with similar rules. This bill was repealed in 1953 with the passage of Public Act 254 [19].

The nineteenth century was the "golden era" of French medicine, and the English school of physicians also made a great contribution to the development of knowledge about ES. Marie Jean Pierre Flourens (1794–1867) established the basic rules regarding the irritability and sensibility of the central nervous system. The French psychiatrist Jean-Étienne Dominique Esquirol French psychiatrist (1772–1840) worked on epilepsy and insanity and identified severe from light epileptic seizures (grand mal and petit mal). Based on a large amount of clinical data, postmortem reports, and his personal experience, Antoine Baron de Portal (1742–1832) concluded that anatomical dissection did not reveal any lesions either in the brain or other parts of the body from patients affected by ES.

From the English school of physicians, numerous writers performed a great contribution to the better knowledge of ES, and the list of most famous writers is as follows: (1) James Cowles Prichard (1786–1848), Richard Bright (1789–1858), Marshall Hall (1790–1857), Robert Bentley Todd (1809–1860), Astley Cooper (1768–1841), John Russell Reynolds (1828–1896), and William Richard Gowers (1845–1915) [5].

In the late 1800, and the beginning of 1900, many American states had colonies for patients presenting ES. The first colony was created in 1896 at the Shaker colony, Sonyea, New York (Craig Colony). Some colonies had facilities for education or vocational training to epileptic patients, while other had not those facilities, and patients remained in disadvantage conditions dealing with isolation, side effects, and poor prognosis [25].

In this period, some German and Dutch physicians reached high levels of development in research on ES. Karl Friedrich Burdach (1776–1847) made a remarkable job on anatomical abnormalities observed in the brain leading to ES. Friedrich Gustav Jakob Henle (1809–1895), writing in 1853, noted that epileptic convulsions were due to increase or decrease of blood flow in the hemispheres, and Wilhelm Griesinger (1817–1868), in 1868, *employed for the first time the term "psychomotor symptoms" in epileptoid conditions* [10].

2.5. Brief history of John Hughlings Jackson

Currently, the general community of epileptologists countrywide agrees that John Hughlings Jackson (1835–1911) is the father of modern epileptology. He was a very active researcher from 1861 to 1870, and almost all of his results have been confirmed by other authors. Based on his knowledge on anatomo-pathology, he studied patients with ES. His first publication from hospital records and review of the medical literature was made in 1861; 2 years later he reported his observation on focal seizures mainly in syphilitic patients and confirmed lesion on the brain contralateral to the focal ES. Jackson believed that loss of consciousness was secondary to disorder of the very highest level of the cerebral hemisphere and the seizures started at the lower levels and then spread to higher ones through interconnecting fibers as well as to neighboring cells of the same level. Jackson said: "I do not use the term cortical epilepsy because both epileptic and epileptiform seizures are, to my thinking, cortical fits… I formerly used the term epilepsy generically for all excessive discharges of the cortex and their consequences…" He mentions, writing in 1876, a number of expressions used by patients to describe those symptoms of the so-called 'intellectual aura', some of which resemble states known in modern psychiatry and neurology as 'déjà vu" [10].

2.6. Twentieth century

In 1903, Herman Bernhard Lundborg (1868–1943) published the first description of progressive myoclonic epilepsy [26].

In 1904, William P. Spratling described his job done at Craig Colony for years as the medical superintendent and named him as epileptologist because his services were rendered to epileptics. Today he is considered the first epileptologist in history [10].

Patients with seizures have been denied many rights throughout the ages including education and work training. In 1907, legislation denying immigrants with epilepsy (as well as tuberculosis and physical disabilities) was passed.

In 1906, Santiago Ramón y Cajal (1852–1934) from Spain received the Novel Prize of Medicine as a reward of his efforts [27]. He made remarkable advances in the field of the microscopic structure of the central nervous system and described the histological structure of the neuron cell and its synapses.

In March 1907, Indiana was the first state to officially pass a eugenics law regarding to sterilization of individuals, including idiots and imbeciles, in state custody. Epileptic patients were not officially included in that statement, but in the early 1900s, terms such as idiots, imbeciles, and feeble-minded were used interchangeably when referring to people with ES. Many other states did the same and included people with ES as well. This law influenced Nazi eugenics during the Holocaust [19].

In September 1909, the ILAE held its first meeting and members from Algeria, the USA, and eight European countries attended. Ketogenic diet was used for the first time in the treatment of epilepsy in 1911 by the French physicians Guelpa and Marie. In 1912, during experimental-induced seizures, electric changes in the brain were noticed by Kaufmann, and at the same time, Alfred Hauptmann (1881–1948) synthesized phenobarbital, one of the first AED [28], whereas Walter Dandy (1886–1946) described in 1918 and 1919 pneumoventriculography and pneumoencephalography [10]. Years later, these radiographic tests were of great value in the management of peoples with ES. Everybody knows that people with ES are denied the right to serve their country during the WW I (1914–1918) and WW II (1939–1945).

In 1929, Hans Berger (1873–1941), a psychiatrist, developed the human electroencephalograph (EEG) in Germany. In 1932, Hans Berger informed about patients presenting tonic–clonic ES and an associated change on EEG in the postictal period (slow waves) and described the typical 3/s rhythmic spike-slow waves in patients with minor seizures. Its important application from the 1930s onward was in the field of epilepsy. The EEG also helped to find the origin of the ES, to differentiate different types of ES, and shows signals of brain damaged due to ES and expanded the possibilities of neurosurgical treatments, which became much more widely available from the 1950s onward in London, Montreal, and Paris [29]. The job on epileptic EEG done by Berger was completed by Frederic Andrews Gibbs (1903–1992) and Erna Gibbs (1904–1987) who in collaboration with William G. Lennox established the correlation between EEG findings and epileptic convulsions [30, 31]. Around the same time, the main progress in the history of ES is related to the development and introduction of new AED for a better management of epileptics. During the same period, H. Houston Merritt (1902–1979) and Tracy Putnam (1894–1975) discovered phenytoin and its effect on the control of epileptic seizures [32–35]. Phenytoin became the first-line AED for the control of partial and generalized tonic–clonic seizures and status epilepticus. In 1946, Richards and Everett added trimethadione to the list of AEDs mainly for the treatment of absence seizures [36].

During the 1950s, new drugs came up such as carbamazepine in 1953 [37], primidone in 1954, ethosuximide in 1958 by Vossen [38], sodium valproate in 1963 by Meunier et al. [39], and sultiame. Buchtal and Svensmark were the first ones in 1960 to measure the levels of the antiepileptic drugs in the blood [40]. In 1967, valproate came up as a new promising antiepileptic drug. Valproate was initially synthesized in 1881 by Beverly Burton in the USA and was initially employed as an organic solvent [41]. Newer AED such as vigabatrin (1989), lamotrigine (1990), oxcarbazepine (1990), gabapentin (1993), felbamate (1993), topiramate (1995), tiagabine (1998), zonisamide (1989 in Japan and 2000 in the USA), levetiracetam (2000), stiripentol (2002), pregabalin (2004), rufinamide (2004), lacosamide (2008), eslicarbazepine (2009), and perampanel (2012) were included in the list of medicines to be prescribed [42]. The research on antiepileptic

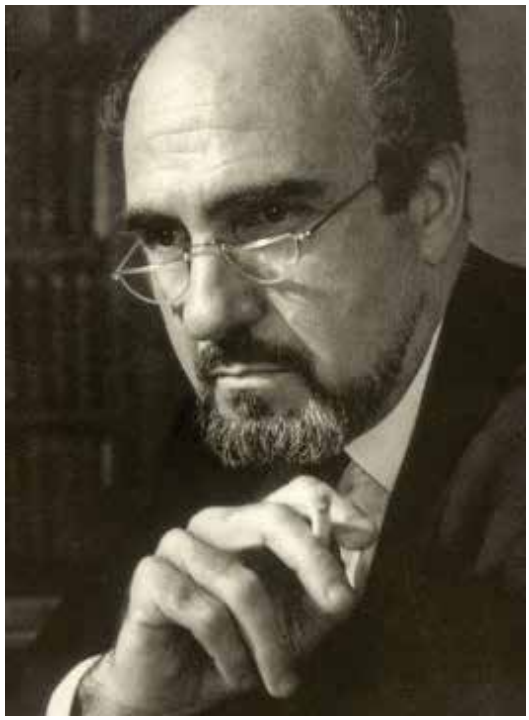

Figure 1. Henri Jean Pascal Gastaut (1915–1995) (adopted by public domain at http://www.lennox-gastaut.de/Krankheitsbild.112.0.html).

drugs is an active field, and many drugs are currently under development in clinical trials including eslicarbazepine acetate, brivaracetam, and retigabine [42].

One special space in this chapter should be dedicated to the memory of Henri Jean Pascal Gastaut (1915–1995) (**Figure 1**). He was an important and influential figure in the field of EEG whose work was intensified during the 1950s. He also worked with William Gray Walter (1910–1977) in Bristol learning the basics of EEG and discovered photic stimulation as an EEG seizure activator [42].

Gastaut also worked with Wilder Penfield (1891–1976) and Herbert Jasper (1906–1999) and investigated the role of thalamic reticular structures in the genesis of metrazol-induced generalized paroxysmal EEG discharges and developed the concept of centrencephalic seizures in 1949 [43]. Beyond any doubt Gastaut was one of the greatest European researchers in epileptology from our time.

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Chapter 2

Autoimmune Epilepsy: New Development and Future Directions

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Additional information is available at the end of the chapter

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Abstract

In recent years, there has been accumulating evidence to support an autoimmune etiology for some patients with drug-resistant seizures, typically in the context of an antibody-mediated encephalopathy; any seizure disorder that may be caused by pathogenic autoantibodies, are an example of autoimmune epilepsy. Autoimmunity is characterized by loss of immune tolerance that causes the destruction of cells and tissues. The largest complex histocompatibility system has had a strong association with autoimmune disease, although certain genes encoding cytokines and co-stimulatory molecules increase genetic susceptibility. In spite of having scientific advances in this research area, the conditions underlying mechanisms are unknown. **Goal**: this chapter aims to present in synthesized form, the genetic, immunological, and environmental factors role in the autoimmunity to epilepsy, as well as the therapeutic approach that has been used to control seizures, mainly where there is a suspected anti-neuronal-antibodies circulation. **Methods**: a review of the work achieved during the last years in patients with this condition provides information and experience in the diagnosis and treatment of this epilepsy type. For this, a systematic search of PUBMED is conducted using the search terms "autoimmune and epilepsy, auto antibodies and epilepsy, NMDA and epilepsy, AMPA and epilepsy, and GAD and epilepsy." The list of identified articles was complemented by additional searches for relevant articles in the reference section of the publications captured by the initial search.

Keywords: epilepsy, autoimmune encephalitis, NMDAr, immunotherapy

1. Introduction

Epilepsy is considered, as one disease with the highest prevalence of 1% population suffering from it. This pathology is defined as a cerebral disorder that is characterized by the predisposition to generate epileptic seizures, as well as the neurobiological, cognitive, psychological and social factors associated with this condition [1]. There is evidence that specific neuronal auto antibodies with pathogenic potential may be present in a subset of patients with epilepsy. Importantly, it has recently been shown that some patients with these serum auto antibodies and mainly in CSF are often refractory to treatment with standard antiepileptic drugs (AEDs) and, on the other hand, may respond well to immunomodulatory therapies. In this way, it has been possible to make a therapeutic approach. The autoimmune basis led to the introduction of immunotherapy (IT) in some drug-resistant syndromes [2], prompted by an intensive search for self-antibodies (Abs) in epilepsy. The findings of limbic encephalitis associated with self-Abs against neuronal plasma membrane (receptors, ion channels) and intracellular proteins have further fueled this search. As seizures are key to the infestation manifest, this disorder serves as a model for understanding epilepsy-immune system interaction [3], evoking the possibility that said antibodies could cause patients with epilepsy alone, and leading to the search for self-Acs in patients with pharmacoresistant epilepsy (PE). Recent prospective study found neuronal auto-Acs in about 10% of pediatric patients with seizures, a rate twice as high as in controls with other systemic diseases; this creates a quandary for clinicians as to when treatment should be chosen in pharmaco-resistant epilepsy patients [4].

2. Genetic and clinical heterogeneity of epilepsy

Autoimmune conditions are the result of multifactorial processes involving dysregulation of both the innate and adaptive immune system, and the possession of predisposing gene alleles, which ultimately at a certain moment in time "trigger" a sustained loss of self-tolerance resulting in an immune-mediated damage of autologous tissues [5]. The innate immune response is the host's first line of defense against invading microorganisms, while the adaptive immune responds to the infection in a time-delayed but antigen-specific manner. Adaptive immune responses are driven by specific components of bacteria or antigen, require several days to develop, and exhibit immunological memory for a lifetime, such that a second exposure to the same antigen results in an accelerated and specific response. Cell populations of the innate immune system, such as dendritic cells (DCs), which are antigen-presenting cells, promote primary T cells and B cell responses and therefore relate innate and adaptive immunity [6]. T cells that are reactive to self- antigens are largely deleted in the thymus in an active process termed thymic or central tolerance induction. Central tolerance induction occurs in both the immature thymus T cells and bone marrow for B cells. During the ontogeny of lymphocytes, T lymphocytes receptors (TCRs) that recognize high affinity, self-peptides exposed in The HLA molecules are deleted by clonal deletion, in order to avoid self-reactive clones. Only the clones whose TCRs recognize their own peptides with medium affinity, mature in secondary lymphoid organs. This shows that the HLA molecules themselves determine the TCR

repertoire. Peripheral tolerance mechanisms include clonal anergy (absence of co-stimulatory molecules), unawareness and suppression by the activation of CD4 + CD25 + FOXP3 + regulatory T cells. In the antigen recognition, the segments α1 and β1 of the HLA molecules (both polymorphic), the processed peptide and the TCR are involved [7]. In fact, some processed peptides are only exposed in certain HLA molecules. So the molecules of the HLA itself also determine which peptide can be recognized by the mature T lymphocytes TCR. The HLA molecules of an individual, determine their immune response at two levels: during negative selection in the thymus and in the selection of peptides at the periphery [7, 8]. By the other way, the new lines of AEs research focused on the genes coding for molecules involved in the central tolerance and peripheral induction. These genes found on any chromosome encode for proteins involved in the lymphocytes and molecules selection, acting as death receptors or co-stimulatory molecules. Most AEs caused the difficulty in knowing the triggering agents. The AEs caused by a mutation in a single gene (monogenic), which are small, provide clinical and experimental evidence of the contribution of different control mechanisms of self-reactivity [9].

2.1. Genetic diagnostics of epilepsies

In epilepsy, there are no studies associating autoimmunity with genetic factors; however, studies have focused on other autoimmune diseases and focuses are mainly associated with major histocompatibility system. Several alleles of classical human leukocyte antigen (HLA) genes in the MHC locus have been linked to autoimmune diseases. The genes coding for HLA molecules are located on the short arm of chromosome 6 in the region of the major histocompatibility complex (MHC). The HLA-I genes encoded by the HLAA, B, C, E, F, and G genes are expressed in all the genes encoding the class I, II, and III molecules. The nucleated cells and the platelets and HLA-II molecules are products of the HLA-DP, DQ, DR, DM, DO genes and are constitutively expressed in B lymphocytes, monocytes, macrophages, dendritic cells, endothelial cells, intestinal epithelial cells, cells early hematopoietic and activated T lymphocytes. The class III region called HLA non-classical contains a collection of approximately 20 genes. This region includes those encoding complement proteins, components involved in the intracellular processing of peptides (TAP1, TAP2) and epithelial cell surface molecules (MICA-MICB) [10, 11]. The fundamental function of molecules HLA-I and HLA-II is to bind their own and foreign peptides in order to transport them to the cell membrane. Once exposed, they are recognized by the TCR, so they have a central role in the execution of the immune response. HLA-I molecules primarily present cytosolic (such as a viral or tumor) peptides to CD8+ cytotoxic T cells, whereas HLA class II molecules generally have extracellular peptides (such as bacterial) to CD4+ helper T lymphocytes. This functional division of peptide presentation ensures the activation of T cells (CD8+ and CD4+) and therefore the appropriate immune response for each type of antigen [10]. The HLA system has two fundamental properties that make it difficult to understand, the genes involved in the predisposition to AEs: polymorphism and linkage disequilibrium (LD) [12]. I-II molecules are the most polymorphic of the whole genome. This property determines that for each loci, there are multiple alleles whose DNA sequences only differ by a few nucleotides. These local mutations are known as single nucleotide polymorphism (NSP). Genes located in the MHC region have a

high genetic association. This property is known as linkage disequilibrium (LD) and describes the tendency of certain genes to inherit together given their closeness. The above determines that the frequency of these genes (in a single haplotype) in the population is greater than their individual inheritance [13, 14]. Inside the AEs gene, the greatest association is with the molecules of the HLA. The siblings concordance with identical HLA is 15% compared to 1% for siblings with a non-identical HLA. This figure is indicative of the strong association between HLA molecules and a risk to develop an autoimmune disease. In some diseases, this association is stronger as in ankylosing spondylitis (AS), while in others, it is weaker than in the myasthenia gravis (MG) [15].

Genetic study with a cohort of 24 cases of Rasmussen (RE) autoimmune encephalitis, the human leukocyte antigen (HLA) class I and class II genes were sequenced; they got the association of three C*07 alleles: 02:01:01, DQA1*04:01:01, and DQB1*04:02:01, that increased the relative risk of RE. It has been shown that HLA-B*07:02 is a risk factor for Graves' disease. In addition, 33% of patients in that study had HLA-A*03:01:01:01, which is considered a risk factor to multiple sclerosis. 17% of patients had a combination of three HLA class II alleles that were associated with type 1 diabetes; DQA1*, 05*01:01:01, DQB1*02:01:01 and 20% patients showed a combination of HLA alleles (DQA1*01:02:01:01, DQB1*06:02:01, DRB1*15:01:01:01), that have been linked to the risk of developing multiple sclerosis [15].

The same way, anti-leucine-rich glioma-inactivated (LGI1) encephalitis was associated [16] with the DRB1*07:01-DQB1*02:02 haplotype (10 patients, 91%) in HLA class II genes, as well as with B*44:03 (8 patients, 73%) and C*07:06 (7 patients, 64%) in the HLA class I region. The prevalence of these alleles in anti-LGI1 encephalitis was significantly higher than that in the epilepsy controls or healthy controls. By contrast, anti-NMDAR encephalitis was not associated with HLA genotypes. Additional analysis using HLA-peptide binding prediction algorithms and computational docking underpinned the close relationship; this finding suggests that most anti-LGI1 encephalitis develop in a population with specific HLA subtypes [17].

2.2. Influence of environmental factors

The concordance values between monozygotic twins are indicative of the role of environmental factors in the development of autoimmunity. Within this group are infections (viruses, parasites, bacteria, and fungi), hormones and immune system regulation loss. The action mechanism proposed for these factors is based on the release of pro-inflammatory substances inducing the danger signals expression and the consequent activation of auto-reactive T lymphocyte clones.

T cell TCRs recognize different peptides in the groove of the HLA molecule as long as they maintain the same charge distribution and spatial orientation. Hence, own and foreign molecules that have this similarity are recognized by lymphocytes and produce an immune response [18]. The creation of an inflammatory microenvironment increases the presence of antigens due to tissue damage and the expression of co-stimulatory molecules. In this medium, the anergized T lymphocytes may activate and stimulate the immune response against antigens themselves [19].

Nevertheless, infections can also modify the clinical manifestations associated with autoimmune epilepsy (AE) in such a way that infections are involved in the induction and protection of AEs in genetically predisposed individuals. This dual role underlying mechanism compression offers new ways of controlling and treating these diseases [20].

3. Conventional etiological mechanisms of neural proteins as antibodies

The target antigens that play a critical role in neuronal transmission and in plasticity include the N-methyl-D-aspartate (NMDA) receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), the gamma-aminobutyric acid receptor (GABA), the glioma-inactivating leucine-rich protein (LGI1) and the contacting-associated protein 2 (CASPR2), a protein that plays a key role in the normal function of voltage-dependent potassium channels [21].

The structure of NMDA receptors (R-NMDA) are formed by combinations of different subunits: NMDAR1 (NR1), NMDAR2 (NR2), and NMDAR3 (NR3); which form a Ca++ permeable ion channel. A single gene encodes the NR1 subunit; however, transcription can generate at least eight isoforms, whereas for NR2-type subunits there are four different genes encoding NR2A, NR2B, NR2C, and NR2D7 subunits. Functional NMDA receptors are composed of heterotetramers, and formed by two dimers twisted by the subunits NR1-NR2, where in the NR1 subunit it possesses a glycine binding site and each in the NR2 subunit, a glutamate binding site, with two binding sites for glycine (S1) and two for glutamate (S2) in each receptor. The NR1-NR2 dimmer is considered the basic functional structure at each receptor, where different physiological and pharmacological binding sites are found for different ligands [22, 23]. Each ionotropic receptor subunit has similar molecular structure, which is organized into four functional domains, which are: an extracellular domain with the amino (N) terminal (DNT), a ligand binding domain (DBL), a region (M1–M4), where the M2 segment that partially enters the membrane forms the ion channel, and finally, a carboxyl domain (C) in the intracellular region (DCT) (**Figure 1(A)**) [24, 25].

In NMDARAS, IgG antibodies are directed to the N-terminal extracellular domain of the GluN1 subunit of the NMDA receptor (**Figure 1**), specifically an epitope region at GluN1 aa369 [26–28]; the cultures of dissociated rat hippocampal neurons and antibody-containing cerebrospinal fluid (CSF) from patients with NMDARAS have been used to study the molecular mechanism by which IgG antibodies cause hypo function of the NMDAR [29]; antibodies decrease the levels of synaptic NMDA receptor and disrupt NMDA receptor currents in cultured neurons. In addition, antibodies disrupt the interaction between NMDAR and the ephrin B2 receptor (EphB2R), a major stabilizer of NMDARs at postsynaptic sites, facilitating the displacement of NMDARs from the synapse [29]. The antibody does not act as a receptor antagonist, by modulating the physiological receptor binding domain, but causes capping and internalization of the receptor [30]. Antibody-mediated internalization is independent of NMDAR activity and does not occur as a compensatory response to the agonism of the receptor, suggesting that the mechanism of internalization is primarily NMDAR cross-linking by patient antibodies [29].

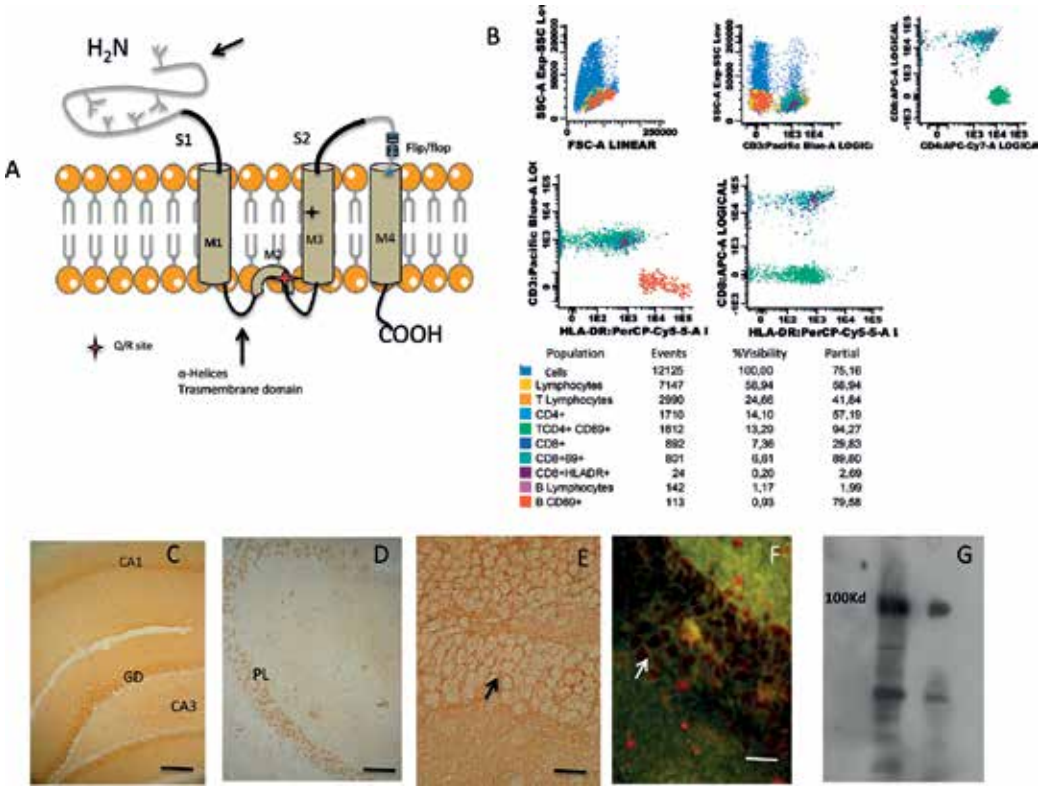

Figure 1. (A) Structure of AMPA receptor subunits. The transmembrane topology is shown, along with the flip/flop alternatively spliced exon, and the two ligand-binding domains (S1 and S2). Glycosylation sites are shown as trees in the N-terminal region; this region is associated with immune response. (B) Flow cytometry demonstrates the presence of T lymphocytes of the CD8+ class with greater activation, as well as B lymphocytes; here it can be known that the immune process has extravasated to the cerebral parenchyma, (C) and (D) the tissue based assay. Mouse brain tissue sections, such as hippocampus are stained with the patient's serum or CSF by indirect immunoperoxidase technique. (C) Shows CSF immunoreaction at the hippocampus level of the cytoplasmic and a neuronal surface in D (anti-human IgG-Px, Abcam-ab97225). (E) TBA in F, shown a reaction at neuronal surface level that colocalizes with GAD65 / 67 (Alexafluor 546, Invitrogen Molecular probes). (G) Immunoblot, CSF recognizes 100 and 50 Kd proteins(Anti-human IgG-Px, Abcam- ab97225).

Encephalitis associated with antibodies against GABAB1 receptor is generally presented as limbic encephalitis, as well as drug-refractory seizures. In a series of 15 patients, the mean age of presentation was 62 years (range 24–75) and both sexes were similarly affected. About half of the patients had an associated tumor, either a small cell lung carcinoma or a neuroendocrine lung tumor. These patients usually have antibodies to various non-neuronal proteins of uncertain significance, which suggests a susceptibility to autoimmunity [30].

In the knockout mice to the GABAB1 receptor, a variety of neurological and behavioral alterations are found, including spontaneous seizures, increased anxiety, hyperactivity, hyperalgesia and memory impairment, suggesting a dysfunction of the limbic system [31, 32].

In contrast, patients present with limbic encephalitis in conjunction with antibodies to the AMPAR were not present with seizures as frequently: only 3/10 had seizures as presenting feature with one other patient having seizures after a relapse [33].

Besides, anti-AMPA-GluR3B antibodies have been associated with many pathological effects: they activate glutamate, AMPA receptors, and are involved in the processes of "excitotoxicity." The phenomenon is associated with various pathological states of the CNS including: epilepsy, hypoxia/ischemia, and trauma. In animal and *in vitro* models, anti-NMDA-NR1 antibodies may be highly pathogenic, as they may cause a decrease in surface NMDA receptors expressed in hippocampal neurons, and also decrease the density and synaptic localization of receptors NMDA. The expression of these NR1a subunits correlates with the distribution of high-affinity NMDA receptors by agonists. Anti-NMDA-NR1 antibodies induces reduction in expression through cross-linking and internalization of NMDA receptors. Such changes may impair glutamate signaling through NMDA receptors and lead to various abnormal neuronal /behavioral/cognitive/psychiatric disorders.

Nevertheless, anti-AMPA-GluR3B antibodies induce many pathological effects that activate glutamate/AMPA receptors,which are involved in excitotoxic damage, the complement activation is modulated by regulatory proteins in which the activation plays a central role in the pathogenesis of brain damage and induces behavior and motor impairments. It has been observed in animal and *in vitro* models that anti-NMDA-NR1 antibodies can be highly pathogenic, as they may cause a decrease in surface NMDA receptors expressed in hippocampal neurons, and the density and synaptic localization of NMDA, probably by the internalization of receptors, which can impair glutamate signaling through NMDA receptors and lead to various neuronal/behavior/cognitive and psychiatric alterations. Knock-out mice to the GluR2 gene show reduced scanning and motor coordination. In these animals, the AMPA receptor-mediated synaptic transmission is reduced, but the long-term potentiation is better [34]. Knock-out mice to the GluR2 gene also exhibit increased cell death, possibly due to the excitotoxicity related to the greater insertion of the compensating homomeric GluR1 protein in AMPA receptors [35, 36].

4. Clinical features of epilepsy-associated autoimmune encephalitis

Each of the currently known neuronal cell surface or synaptic autoantibody associates with a specific syndrome or limited set off symptoms (**Table 1**). NMDAR antibody-associated encephalitis is a recently described disorder in which infrequent seizures are associated with the presence of autoantibodies directed against the extracellular domain of the NR1 subunit of the NMDAR. This disorder was first described as a clinical entity in 2005, in one in four young women who developed acute psychiatric symptoms, seizures, memory deficit, in association with the presence of an ovarian teratoma. In a study of 100 patients, it was shown that although the majority are young women (mean age 23 years), the disorder could occur in men and in children. This fact has allowed the number of pediatric cases to grow steadily and appears to represent approximately 40% of all cases [27, 37, 38].

4.1. NMDA receptor

Symptoms of anti-NMDA receptor encephalitis develop and resolve in a multi-stage process; most patients experience a prodromal similar to a viral picture, which is followed by a pattern

Epilepsy-associated antibody	Anti-LGI1 vs. LGI1 (*Channels Kv+*)	Anti-CASPR2 vs. CASPR2	LGI1 > CASPR2 (VGKC-complex) vs. LGI1 > CASPR2	NMDAR vs. Subunit NR1	GAD vs. GAD-65	$GABA_BR$ vs. $GABA_BR$	AMPA vs. GluR1/2
Gender/Age of involvement	M > F	M > F	M > F >50 years	F > M 70% childhood	F > M >20 years	M > F >40 years	F > M >40 years
Clinical manifestations	Hyponatremia. Cognitive impairment. It is associated with the presence of a thymoma or SCLC	Morvan syndrome Complication with Myasthenia gravis Not associated with neoplasias	TLE Hyponatremia and Synchronus dystonic arm posturing and grimacing facial ipsilateral associated with paraneoplasias (thymomas and lung cancer (SCLC)).	Viral pathway: fever, headache and fatigue of infectious etiology, delirium and disorientation. 10–20 days of evolution: orofacial dyskinesias, choreoatetotic movements, nystagmus, decreased consciousness and dysautonomia	Diabetes mellitus type 1, Stiff-person syndrome, cerebellar ataxia, non-paraneoplastic LE Severe cognitive impairment	LE It is associated with the presence of SCLC	LE It is associated with the presence of SCLC, thymus and breast cancer tumors
Psychiatric comorbidity	Confusion and behavior and REM sleep disorders	Cognitive impairment, memory loss and hallucinations	Sub-acute amnesia, confusion, sleep disorders, psychosis, anxiety, personality changes and depression	Personality changes, hallucinations (visual and auditory), difficulty speaking	Depression and anxiety.	Cognitive impairment, behavioral disorders such as psychosis and hallucinations	Confusion, amnesia, disorientation and psychosis
Seizure activity	GTC	GTC	FBDS GTC CPS	GTC CPS SE refractory to treatment	CPS. CTsG	CPS GTC SE	GTC CPS
Electrographic activity (EEG)	Slow focal or generalized activity	Slow focal or generalized activity	Slow focal or generalized activity	Focal or diffuse delta/theta activity and delta brush activity	Slow focal or generalized activity	Slow focal or generalized activity	Focal activity

Epilepsy-associated antibody	Anti-LGI1 vs. LGI1 (*Channels Kv+*)	Anti-CASPR2 vs. CASPR2	LGI1 > CASPR2 (VGKC-complex) vs. LGI1 > CASPR2	NMDAR vs. Subunit NR1	GAD vs. GAD-65	$GABA_BR$ vs. $GABA_BR$	AMPA vs. GluR1/2
Treatment and prognosis	Good response to immunotherapy	Good response to immunotherapy	Good response to immunotherapy	Slow response to Immunotherapy with recurrence	Refractory to treatment with AED's and immunotherapy	Good response to immunotherapy	Good response to immunotherapy with recurrence
References	[49, 54–56]	[31]	[31, 63]	[31, 55, 58, 65, 67]	[59–61]	[31, 41, 51, 57, 62, 64]	[34, 57, 61, 66]

NMDAR, N-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; AMPAR, amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA a/B R, gamma-aminobutyric acid A/B receptor; mGluR1/2, metabotropic glutamate receptor type 1/2; LE, limbic encephalitis; SPS, stiff-person syndrome; CPS, complex partial seizure; EEG, electroencephalogram; FBDS , faciobrachial dystonic seizures; GTC, generalized tonic-clonic.

Table 1. Neuronal cell surface autoantibodies, associated epilepsy, and the clinical symptoms.

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of memory alterations, behavior, cognition, developing psychotic pictures, convulsions, dyskinesia (orofacial, trunk, and limb), and autonomic respiratory instability. Most adults are initially seen by psychiatric services and may be confused with acute psychotic disturbance or drug abuse. Most children are taken to medical care due to changes in mood, behavior and/or personality, seizures, or language impairment [38–40]. Autonomic instability is a common manifestation in adults. Some patients develop severe cardiac arrhythmias that require the use of pacemakers. Signs of more frequent autonomic dysfunction in children include urinary incontinence and sleep disturbances [38]. Nuclear magnetic resonance (MRI) findings in these patients may be hyperintensities in FLAIR or T2 sequences in the cerebral cortex, cerebellar or temporal medial lobes, as well as in the corpus callosum and brainstem. In some cases, a transient increase in contrast, of the cerebral cortex, cerebellum, basal ganglia and meninges is observed.

Movement disorders are common and can be misinterpreted as a convulsive activity, the most common being dyskinesia, usually orofacial, choreoatetoid limb movements, rigidity, opisthotonos, or a combination of these. In most patients, EEG shows a slow generalized activity, disorganized without ictal discharges. These findings may overlap with ictal discharges in the EEG [41]. Niehusmann and colleagues [42] reported presence of NMDAR-antibodies in women (age range, 15–45 years), which had extra-temporal epilepsy, a reduction in level of consciousness and altered speech, as well as nystagmus, dyskinesia, dystonia, and hypoventilation. Clinical improvements in seizure frequency were seen in treatment of three patients treated with an immunomodulator such as corticosteroids and IVIg.

4.2. GABAb

GABA receptors are essential to inhibition. The presence of autoantibodies against these receptors has been associated with seizures and changes in memory and behavior. In a study with 15 patients with GABABR and LE antibodies (median age of 62 years, range 24–75 years), the clinical features where the presence of seizures, confusion and altering memory. Seizures were the predominant characteristic in 87%, and were mainly onset of temporal lobe with secondary generalization. 13% of patients presented epileptic status. CSF findings showed lymphocytic pleocytosis (n = 4) and MRI showed an increased signal, typical of LE. Clinical improvement was observed in 40% of patients who received IT alone and 20% who had IT, and 46% of patients were taken for a surgery to remove tumors. On the other hand, in a series of 15 patients, the mean age of presentation was 62 years (range 24–75) and both sexes were equally affected. About half of the patients had an associated tumor, either a small cell lung carcinoma or a neuroendocrine lung tumor. These patients often have additional antibodies to glutamic acid decarboxylase (anti-GAD) and several non-neuronal proteins of uncertain significance, suggesting a susceptibility to autoimmunity [32, 43].

4.3. AMPA receptor

Antibodies to the AMPAR have recently been described in patients with limbic encephalitis (LE). The AMPAR antibodies are the least frequent of these antibodies, however, also these patients develop a limbic dysfunction that may be associated with significant psychiatric

symptoms. The most common disorder effects were in the middle-aged women. Most patients present with a sub-acute appearance of confusion, disorientation and memory loss, and seizures may also be part of the clinical describe. About 70% of patients have an underlying tumor in the lung, breast, or thymus. AMPAR is the predominant receptor subtype in the hippocampus, and it has been found that these antibodies in patients caused a decrease in the pre- and postsynaptic GluR1/2 receptor groups in cultures of rat hippocampal neurons. Since the receptor levels have been more affected at synapses than along dendrites, the findings suggested a mechanism by which patients' antibodies disrupted the receptor traffic, moving them from synaptic sites to extra-cellular sites and intracellular pool. These effects are similar to neuronal plasticity models that decrease synaptic strength, also called long-term depression. The effects of the antibodies were shown to be reversible [42, 45].

4.4. GAD

Glutamic acid decarboxylase (GAD) is a cytoplasmic enzyme that catalyzes the conversion of L-glutamic acid to gamma-aminobutyric acid (GABA), considered the main inhibitory neurotransmitter of the central nervous system. GAD is expressed primarily in GABAergic neurons and in pancreatic β cells, and has two isoforms with different molecular weight; GAD65 and GAD67. GAD antibodies act as a marker of the underlying autoimmune disease, although it is not known how antibodies against an intracellular enzyme can directly initiate pathological events; however, it is known that anti-GAD Abs inhibit the activity of GAD, and the synthesis of GABA antibodies to GAD is associated with several autoimmune disorders, including limbic encephalitis [44, 45], type 1 diabetes mellitus [46]. Stiff Person Syndrome (SPS) [47], and cerebellar ataxia [48], as well as overlapping syndromes. Recent work highlighting the response of these patients to immunotherapy and association with forms of epilepsy related to localization suggest that antibodies may also be present with specific cell surface. This is supported by a functional study of magnetic resonance spectroscopy in patients with TLE and elevated levels of serum GAD antibodies that demonstrated significantly lower GABA levels within their cortex compared to paired control patients [44]. On the other hand, in one study with 138 patients over 18 years old, investigated with recent onset epilepsy, were prospectively studied to determine the clinical and radiological characteristics of LE, and response to treatment. Fifty-three adult patients fulfilled the criteria for LE; nine had high-titer GAD antibodies and ten had voltage-controlled potassium channel (VGKC) antibodies. Patients with GAD antibodies were younger's (range, 17–66 years) and had seizures only, whereas polymorphic limbic features were more frequent in the VGKC positive group. Patients with anti-GAD antibodies had more frequently oligoclonal bands of cerebrospinal fluid and intrathecal secretion of the specific antibody. Which after monthly, patients were treated with intravenous methylprednisolone pulses, however GAD antibodies remained elevated in 6/6 patients, however VGKC antibodies normalized in 6/9 patients ($p < 0.03$). Despite the more intense anticonvulsant treatment in the group with anti-GAD antibodies ($p < 0.01$), none of these patients were seizure free, unlike all patients with VGKC antibodies ($p < 0.001$). High-titer GAD antibodies define a form of non-paraneoplasic LE. It is a chronic non-persistent disorder, and should be included in the differential diagnosis of patients with LE and mediotemporal encephalitis [49].

4.5. LGI

Studies describing treatment of LGI1-antibody associated encephalopathy, LGI1 is a protein secreted by neurons that interact with pre- and postsynaptic receptors. LGI1 mutations have been associated with autosomal dominant temporal lobe epilepsy syndrome [50, 51]. Patients with antibodies against LGI1 develop alterations of memory, confusion, and seizures. The MRI results are typical of limbic encephalitis. Memory and cognitive deficits can be preceded by brief tonic seizures that can be confused for mimic myoclonic movements. Observational studies have provided evidence of a marked improvement with for high-dose steroids, IVIG and PLEX for patients with auto-antibodies to LGI1 and CASPR [37, 50–52]. In a retrospective study of 10 patients with high titers of VGKC-complex antibodies that had seizures and memory disorders, who received IVIG 2 g/kg/day, 100 mg prednisolone on alternate days and PLEX for 5 days, improvement was observed in frequency of seizures and cognition in six patients within 2 weeks to 12 months, correlating with reductions in antibody titers [37]. Earlier treatment, and possibly corticosteroids, appeared to provide greater benefits than before. This disorder had been included previously within the spectrum of antibodies against voltage-dependent potassium channels. Some patients develop hyponatremia and behavior or REM sleep disorders. Only 20% of cases are associated with a neoplasm, usually thymoma or small cell lung carcinoma.

5. Diagnostic approach

The laboratory diagnosis of AD depends on the identification of the clinical symptoms of the patient, their association with each disease and their correspondence with the detection of AA. For this reason, laboratory tests are of great importance for the evaluation of patients when an AE is suspected. The results can confirm the diagnosis, estimate the severity of the disease, and are useful to follow up its evolution and establish a prognosis. The presence of autoantibodies (AA) alone in a patient does not mean the diagnosis of an AD, the associated signs and symptoms help to achieve the definitive diagnosis and are of crucial importance. Analysis of CSF plays a central part in all diagnostic criteria for encephalitis, including infectious encephalitis, relevant antibodies might be found only in the CSF, because the repertoire of antibodies in the CSF and serum can be different in the same patient (e.g., NMDA receptor in CSF and serum) [52]. By other way, serological tests to detect AA have demonstrated the presence of AA in healthy individuals and in known non-EA patients and approximately half of all autoimmune encephalitis series are Ab-negative cases, so AA is a confirmatory diagnostic test, for this reason the diagnostic tests must be combined. Three basic research techniques are used for this purpose must include: tissue-based assay (TBA), cell-based assay (CBA), and immune-precipitation (IP; in-house). In the TBA, rat or mouse brains are stained with CSF or serum of patients with an indirect immunohistochemistry or immunofluorescence technique or the combination of two fluorophores, one that identifies the autoantibody and the other to the antigen and use of confocal microscopy (**Figure 1(C)–(F)**).

In the cell brain adhesion test (CBA), cells (e.g., HEK293 cells) are transfected with the respective neural antigens (receptors, channels, etc.) and incubated with the CSF or serum of patients with an indirect immunofluorescence technique. Autoantibodies to the specifically expressed receptor result in the cell membrane marking cells, similar, primary cultures of hippocampal neurons can be used, with these methods autoantibodies are displayed on the surface of the neuronal membrane [53].

For the detection of classical intracellular and cytoplasmic antibodies, the immunoblot technique is used. Immunoblotting is the method that uses Abs to detect a specific protein from a mixture of several unrelated proteins separated by molecular weight. The diagnosis of antibodies with this technique involves several steps, including protein extraction of mice brain tissue followed by (30–50 μg) spitted proteins through electrophoresis, and transfer of a nitrocellulose membrane and overlapping of the primary antibody (the serum or CSF of the patient) and secondary on the membrane labeled with enzymes (**Figure 1(G)**) or fluorescent antibodies [54]. Recently, we introduced flow cytometry and have confirmed that in those patients with AE, a large presence of activated T and B cells is observed; in some cases, the CD8+ cells are dominated and in negative cases, there is no activation of lymphocytes (unpublished data); the results suggest that this tool could provide additional information on the patient's immune response (**Figure 1(B)**). On the basis of this data, the recommendation is to include both CSF and serum for citometric testing in patients with suspected autoimmune encephalitis.

6. Concluding remarks

Recently, several reports that associate CNS disorders with autoantibodies are directed against cell surface proteins, which are likely to be pathogens. Many of these conditions have seizures as an early and prominent feature, which are commonly refractory to conventional drugs. In contrast, a good response with immunotherapy is often observed. The studies in patients coincide in clinical manifestations, but not in autoantibodies. For this reason, CSF is crucial in the identification of new antigens, including NMDAR, AMPAR, GABABR, GABAARr, mGluR5, DPPX and LGI1, and Caspr2. Serum negativity is more likely with a milder form of the disease, presenting with clinical pictures of psychosis but not requiring intensive care, particularly if the antibodies are generated predominantly in the brain, which makes it necessary to standardize the diagnostic methods in order to be safer and to offer a timely diagnosis. The effects of antibodies on children (the effects of antibodies on hippocampal synapses) are different from that of adults; this may explain some of the differences in clinical pictures between adults and children. For this reason, the selection of patients for the autoimmune evaluation requires a high level of suspicion in the initial consultation. Since there have been currently no universally agreement upon diagnostic criteria for autoimmune epilepsies, the clinical evidence, such as the high frequency of seizures, psychiatric co-morbidity and resistance to AEDs, are important indicators to decide it. More studies are needed to identify early autoantibodies and to perform preventive treatments.

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Chapter 3

Diagnostic Testing in Epilepsy Genetics Clinical Practice

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Additional information is available at the end of the chapter

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Abstract

Changing landscape of epilepsy genetic testing gives vast opportunities to both patients and clinicians. Significance of precise genetic diagnosis in patients affected by epilepsy cannot be overestimated: it not only gives the opportunities of personalized therapeutical approaches but is also associated with multiple additional benefits for patients, their families, and society. Although the burden of Mendelian and chromosomal diseases amenable to current diagnostic testing measures is unknown, recently, we have comprised a database of more than 880 human genes associated with monogenic diseases involving epilepsy or seizures, EpiGene database (http://www.kimg.eu/en/tools/epigene-database). Besides, more than 50 chromosomal syndromes are related to epilepsy or seizures. Currently, there are no recommendations or guidelines for genetic testing in epilepsy patients addressing specificities of next-generation sequencing technologies. However, as every genetic testing modality has its own characteristics of specificity/sensitivity, range of clinical indications, and possible bioethical and psychosocial implications, genetic testing in epilepsies must be properly selected and applied along with proper clinical genetics/genetic counseling services. In this chapter, an overview of genetic testing modalities and workflows taking into account genetic architecture of epilepsies is given, and practical aspects of genetic testing in epilepsies, including advantages/limitations and clinical utility of tests, are discussed.

Keywords: algorithm, diagnostic yield, clinical utility, next-generation sequencing, exome, molecular karyotyping

1. Introduction

Recent genetic revolution due to advancements in genomic testing technologies evolves into fundamental changes in clinical practice of not only clinical genetics but also other medical specialties. Changing landscape of epilepsy genetic testing gives vast opportunities

to both patients and clinicians, however, not without additional challenges. Although the burden of Mendelian and chromosomal diseases, amenable to current diagnostic testing measures, among all patients with epilepsy or seizures is currently unknown, significance of precise genetic diagnosis in patients affected by epilepsy cannot be overestimated: it not only gives the opportunities of personalized therapeutical approaches but is also associated with multiple additional benefits for patients, their families, and society. However, as every genetic testing modality has its own characteristics of specificity/sensitivity, range of clinical indications, and possible bioethical and psychosocial implications, genetic testing in epilepsies must be properly selected and applied along with proper clinical genetics/genetic counseling services. In this chapter, an overview of genetic testing modalities and workflows taking into account genetic architecture of epilepsies is given, and practical aspects of genetic testing in epilepsies, including advantages/limitations and clinical utility of tests, are discussed.

2. Diagnostic testing in epilepsy genetics clinical practice[1]

2.1. Genetic and clinical heterogeneity of epilepsy

Both traditional and genomic heritability studies unequivocally show the importance of genetic factors in epilepsy [1, 2]. Genetic factors play a role in more than half of all epilepsies [3]. Although a part of these epilepsies may not be amenable for genetic testing in current clinical practice (e.g., multifactorial or those due to somatic mutations), many monogenic and chromosomal diseases related to epilepsy or seizures may and should be diagnosed. Most of these diagnosable diseases belong to a category of rare diseases (in the European Union defined as a disease affecting less than 1 in 2000). One of the main factors delaying diagnostics of any rare disease is a low index of suspicion [4]. Indeed, for a referral to medical genetic clinic, a neurologist must raise a possibility of a genetic disorder in a patient with epilepsy or seizures first.

In any human disorder with a substantial genetic background, the choice of genetic testing modalities and workflows depends crucially on the genetic and clinical heterogeneity of a given disorder. The overall genetic heterogeneity and number of genetic nosologies involving epilepsy or seizures are largely unknown; however, epilepsy or seizures may be a symptom of many diverse conditions including channelopathies, neurodevelopmental diseases, inborn errors of metabolism, and congenital malformation syndromes [5]. Recently, we have comprised the most extensive to our knowledge database of more than 880 human genes associated with human monogenic diseases involving epilepsy or seizures, EpiGene database (http://www.kimg.eu/en/tools/epigene-database). Besides, more than 50 chromosomal syndromes are related to epilepsy or seizures (see Section 2.5). These numbers give important insights into the huge genetic heterogeneity of human disorders involving epilepsy or seizures, comparable to that of intellectual disabilities [6].

[1]Discussions about usefulness of genetic testing in multifactorial epilepsies (including pharmacogenetic testing) go beyond the scope of this chapter.

For many years the prevailing "dogma" was that epilepsy is a channelopathy [7], and the first unveiled channelopathy due to mutations in nicotinic acetylcholine receptor gene CHRNA4 became one of long-standing prototypes of genetic epilepsies [8]. Multiple channelopathies presenting with variable phenotypes are currently known (e.g., epileptic encephalopathies (due to mutations in genes HCN1, KCNA2, KCNB1, SCN8A, SLC13A5, STXBP1, and SYN1), benign neonatal seizures (genes KCNQ2 and KCNQ3), a spectrum of generalized epilepsy plus to Dravet syndrome due to SCN1A gene mutations). One of the major targets of current epilepsy genetic research is a group of disorders defined as epileptic encephalopathies; more than 70 genes have been related to this phenotype, explaining 20–25% of epileptic encephalopathy cases [9]. Relatively, homogenous clinical presentation of this epilepsy phenotype may aid in the recruitment of patients for genetic testing in both clinical setting and research. Distinct group of inherited epilepsies comprises progressive myoclonic epilepsies—an umbrella term for childhood- or adolescence-onset conditions characterized by myoclonus and relentlessly progressive neurodegeneration [10], including Unverricht-Lundborg, Lafora disease, neuronal ceroid lipofuscinoses, type 1 sialidosis, GM2 gangliosidosis, Gaucher disease, MERRF, and some other mitochondrial diseases—and other progressive myoclonic epilepsies due to mutations in genes ASAH1, CERS1, GOSR2, KCNC1, PRICKLE1, PRICKLE2, and SERPINI1. Other epilepsy phenotypes are much more heterogeneous. Surprisingly, the most extensive group of monogenic epilepsies is inherited metabolic diseases, encompassing 373 genes (42% of all genes) in EpiGene database (discussed more extensively below). The most frequent genetic epilepsy-associated symptoms are psychomotor retardation and intellectual disability (419 and 386 EpiGene diseases, respectively). Indeed, epilepsy is a frequent comorbidity (20–30% of cases) of syndromic and non-syndromic intellectual disabilities and vice versa; 30% of patients with epilepsy have intellectual disabilities [11]. Epilepsy or seizure is an accompanying symptom of a vast range of inherited neuromuscular and neurologic diseases, sometimes preceding development of other neurologic symptoms such as spastic paraplegias (SPG6, SPG11, SPG18, SPG35, SPG47, SPG49, SPG50, SPG51, and SPG52), muscular dystrophies (dystroglycanopathies due to mutations in genes B4GAT1, DAG1, FKRP, FKTN, GMPPB, ISPD, LARGE, POMGNT1, POMK, POMT1, and POMT2, congenital megaconial dystrophy (CHKB), merosin-deficient muscular dystrophy (LAMA2)), hereditary ataxias (spastic ataxia 5, ataxia with oculomotor apraxia (APTX), and ataxia-telangiectasia (ATM), spinocerebellar ataxias (SCA) SCA10 (ATXN10), SCA13 (GRM1), SCA15 (KIAA0226), SCA20 (SNX14), SCA17 (TBP), SCA12 (WWOX)), demyelinating diseases (e.g., hypomyelinating leukodystrophy due to mutations in genes AIMP1, FAM126A, GJC2, HSPD1, POLR3A, TUBB4A, leukoencephalopathy with vanishing white matter, megalencephalic leukoencephalopathy with subcortical cysts (HEPACAM, MLC1), adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease); and hereditary dystonias (dentatorubropallidoluysian atrophy, dystonia 24 (ANO3), juvenile onset Parkinson disease 19 (DNAJC6), infantile striatonigral degeneration (NUP62)). Paving embryonic neurodevelopmental processes, epilepsy or seizures are very frequent symptoms in syndromes with malformations of cortical development, including megalencephalies (AKT3, EZH2, FGFR3, and PIK3CA), lissencephalies (ARX, RELN, VLDLR, ACTB, ACTG1, DCX, DYNC1H1, KIF2A, LIS1, TUBA1A, TUBB2B, and TUBG1), polymicrogyrias (NDE1, WDR62, FH, KIAA1279, NSDHL, OCLN, GPSM2, RAB3GAP1, RAB3GAP2, RAB18,

CHD7, and SRPX2), periventricular nodular heterotopia (ARFGEF2) [12], and neurocutaneous syndromes (tuberous sclerosis (TSC1 and TSC2), Sturge-Weber syndrome (GNAQ), incontinentia pigmenti (IKBKG), neurofibromatosis (NF1 and NF2)). However, epilepsy or seizures may also be variably present in multiple other congenital malformation syndromes, including not only CNS malformations (e.g., holoprosencephaly spectrum, pontocerebellar hypoplasia, and corpus callosum agenesis) but also malformations in any other organ. More than 130 congenital malformation syndromes include epilepsy or seizures as phenotypic features (http://www.kimg.eu/en/tools/epigene-database). Five hundred thirty-seven (61%) of EpiGene disorders are autosomal recessive, 234 (27%) (autosomal dominant) and 79 (9%) (X-linked).

It is not credible that any physician would be able to recognize and differentiate about 1000 genetic nosologies involving epilepsy or seizures, especially so that most of them are very rare and/or have just recently been described. Indeed, 228 of 880 EpiGene diseases (26%) are ultrarare, described just in several patients or families. Moreover, nonspecific and overlapping symptoms are frequent characteristics of these disorders. For many genetic epilepsies, mutations in a single gene may lead to a broad range of possible phenotypes and vice versa; patients with different genetic etiologies may have the same phenotype. To complicate matters still further, characteristic MRI and/or EEG features are very rare pointers or even supporters for a specific genetic etiology [13, 14]. Therefore, in clinical practice, genetic evaluation of a patient with epilepsy or seizures is usually not an easy task.

2.2. Genetic diagnostics of epilepsies: from traditional approach

Conventional etiological evaluation of epilepsy patients was complex and traditionally included karyotype, molecular karyotyping, and individually tailored serial metabolic and molecular genetic tests [5]. Secondary invasive tests such as biopsies and cerebrospinal fluid examination, aid in diagnosis in a small percentage of additional cases [15]. The main performance characteristic of any genetic testing modality is a diagnostic yield [16]. Clinical utility of various modes of genetic testing was recently evaluated in a retrospective analysis of 110 patients with various epileptic encephalopathies [17]. Genetic causes were identified in 26% of these patients by applying biochemical genetic testing, array comparative genome hybridization (aCGH), single-gene testing, targeted next-generation sequencing (NGS) testing (gene panels of 38, 70, or 327 genes), and whole-exome sequencing (WES) in six patients. In two patients, diagnosis was made on clinical grounds and not confirmed by genetic testing (1.8%), three patients (2.7%) had microdeletions revealed by aCGH, eight patients (7.2%) had inherited metabolic disorders (IEM), and targeted NGS testing resulted in diagnosis in 14 cases (12.7%) of patients [17]. The whole diagnostic pathway leading to the final diagnosis is not analyzed in this publication; however, a comparable pathway in patients with developmental delay/intellectual disability, many of whom had epilepsy, was described by López-Pisón et al. [18]. In a total of 686 cases (69% of all cases) in whom etiological diagnosis was not established had 8 tests each on average, including 2887 biochemistry tests, 1582 metabolic tests, 516 karyotyping/subtelomeric deletion tests, and 525 single-gene testing. Indeed, with sequential targeted testing, despite considerable efforts to reach the diagnosis, final diagnosis is frequently not established leading to a long “diagnostic odyssey” arduous for both patients and healthcare

systems. Moreover, in many clinical situations, traditional approach is not only lengthy but also costly. In a study by Soden et al. before WES or whole-genome sequencing (WGS), patients had an average of 13.3 prior tests for the cost of $19,100 per family (seizures were observed in 39 of 100 patients in this study) [19]. The entire traditional diagnostic trajectory average cost was $16,409 per patient, substantially higher than the $3972 trio-WES cost, in 17 patients investigated by Monroe et al. [20]. The first and the only to date prospective comparison of cost-effectiveness of clinical whole-exome sequencing with a usual testing shows even more cost savings: in a cohort of 40 infants with neurodevelopmental disorders and congenital malformations, standard traditional testing had an average cost per diagnosis of US$21,099 compared to US$3937 for singleton WES. The use of WES early in the diagnostic pathway resulted in more than three times bigger diagnostic yield, while the price of testing was three times smaller [21]. It must be also noted that although Sanger sequencing is frequently entitled as the gold standard in genetic diagnostic accuracy, there are several recent reports about missed variants. In 9/105 families diagnosed through WES, the causative variant has not been detected by previous Sanger testing of a gene [22]. Finally, all the main professional genetic organizations, including the European Society of Human Genetics (ESHG), American College of Medical Genetics and Genomics (ACMG), and Canadian College of Medical Geneticists (CCMG), recognize that NGS testing may be a more practical approach than traditional gene-by-gene testing in certain clinical situations [23–25].

Nevertheless, traditional approach of genetic diagnostics with thorough phenotyping followed by targeted genetic testing can still be of value even in the era of NGS testing. Recently, a retrospective data analysis of 500 unselected consecutive patients coming to a university medical genetic clinic revealed a diagnostic rate of traditional approach reaching 46%. In this study, however, the reason for referral of 31% of diagnosed (14% of all) patients was a suspected specific diagnosis or a family history of a definite or suspected genetic disorder (i.e., confirmation or ruling out by a targeted genetic testing was needed only). Importantly, 72% of the diagnoses were made during the first visits (presumably, due to a highly suggestive phenotype), and further targeted testing resulted in huge expenses [26]. However, in patients with early onset epilepsy and developmental delay, standard clinical evaluation suggested a diagnosis in only 15% of them (11/71) [27]. Therefore, besides confirmation of the known family mutation, targeted testing is most suitable in cases with distinctive clinical features and minimal locus heterogeneity, for example, MECP2 gene analysis in a girl with characteristic Rett syndrome symptoms and clinical course or 15q11q13 methylation analysis in a patient with presumable Angelman syndrome. Targeted testing may also be important in selected cases where diagnosis cannot be captured by NGS (see Section 2.6). Otherwise, sequential targeted testing is largely inefficient and highly time- and cost-consuming.

2.3. To genomic testing technologies

In contrast, next-generation sequencing (NGS) technologies allow for untargeted testing of almost all genomic sequence (whole-genome sequencing (WGS)), almost all coding part of the genome (whole-exome sequencing (WES)), or simultaneous testing of a predetermined set of genes (gene panels). The most comprehensive testing methods—WGS and WES—usually allow for the most extensive differential diagnostics; however, extraction of useful

information from huge amounts of raw data is time- and resource-consuming. Besides, all the bioethical/psychosocial implications pertinent to exhaustive genomic testing technologies must be addressed properly (see Section 2.7). On the other hand, too restrictive diagnostic approach leads to missed diagnoses. In our current era of constant accumulation of knowledge in human genomic health and disease and continuous technological advances of NGS methods, creation of valid recommendations for diagnostic evaluation of human disorders with a considerable genetic background always lags behind scientific and technological achievements and is not an easy task in a constantly changing landscape. Currently, there are no recommendations or guidelines for genetic testing in epilepsy patients addressing specificities of NGS technologies [28].

Although sequencing of the first human genome took 15 years and costs approximately 3 billion US dollars, the new Illumina HiSeq X Ten System can sequence 40–50 genomes per day for approximately 1000 US dollars each [29]. However, amounts of obtained data are overwhelming. Human genome consists of roughly 3.2 billion bp and contains around 3–4 million variants (roughly, 1 out of every 1000 bases) [30]. Certainly, the vast majority of these variants are benign, determining personal particularities of any individual. Exome, the coding part of genome, comprises 1–2% of the whole-genome sequence (~65 Mb) and contains 30,000–60,000 variants [30, 31]. Human genomic variation is almost immeasurable: the most extensive to date human population exome database ExAC (http://exac.broadinstitute.org), encompassing more than 60,000 exomes, contains 7.4 million high-quality variants, a variant in one out of every eight bases on average. More than a half of these variants (54%) have been found just in one individual each [32].

Besides, extraction of useful information from the huge amounts of WGS/WES data is limited due to our limited knowledge about human genes. As of February 2015, of approximately ~19,000 protein-coding genes predicted to exist in the human genome, variants that cause Mendelian phenotypes have been identified in ~2937 (~15.5%), while the genes underlying about half of all known Mendelian phenotypes (i.e., 3152) have not yet been discovered, despite the fact that ~20% (i.e., 643) have been mapped. Moreover, ~16,063 other genes still remain candidates for Mendelian phenotypes [33]. Therefore, the major limiting factor of current genomic diagnostics is not data generation, but identification and proper interpretation of causative variants in the whole flood of "genomic noise." Multiple powerful bioinformatic approaches and tools are implemented in WGS/WES data mining; however, technologies cannot totally replace human workload. On the contrary, deep knowledge and extensive skills of multiple professionals are on a higher demand than ever in order to enable successful usage of the technological advances of NGS.

Nevertheless, hundreds of thousands of exomes and tens of thousands of genomes are already sequenced, and projects like 100K Genome Project in UK are well under way [30]. Data on diagnostic rates of WGS in epilepsy patients are limited: WGS revealed pathogenic and likely pathogenic mutations in all six (100% yield) patients with severe early onset epilepsy who had previously were refractory to molecular diagnosis by extensive genetic, biochemical, and imaging testing [34]. Other WGS studies mostly include patients with various neurodevelopmental phenotypes; however, considerable part of them have epilepsy or seizures: in 119 children WES resulted in a 33% and WGS achieved a remarkable 73% diagnostic rate, while

cumulative rate of both WES and WGS was 45% [19]. WES gave a 27% diagnostic rate (27/100 patients), while WGS in patients with negative prior WES and aCGH testing resulted in 42% diagnostic yield (21/50 patients) [35]. Indeed, WGS is the most comprehensive genomic testing mode, encompassing the most extensive mutational spectrum and bypassing many of WES limitations in mutation detection (e.g., reliable identification of deep intronic/regulatory sequence variants or tandem repeats, see Section 2.6). In a recent study of 156 cases with variable phenotypes, an estimated ~15% of causal variants identified by clinical WGS would most likely have been missed by WES [36]. However, our limited knowledge and a huge interpretative workload currently limit the use of WGS, especially in a clinical setting. In the studies mentioned above, the vast majority of data obtained from WGS, especially variants beyond the coding part of human genome, did not have any diagnostic value and could not reliably be ascribed to either benign or pathogenic [35, 36].

Meanwhile, WES gets more and more applications in the diagnostic evaluation of patients with epilepsy or seizures. Recently, a study on WES in 314 consecutive patients with unselected epilepsies has shown a diagnostic yield of 38.2% [37]. WES in 10 sporadic cases of infantile spasms was diagnosed in 40% [38]. Diagnostic output of WES in neurodevelopmental disorders, including epilepsies, was 41% in a group of 78 pediatric patients (12% of them had epilepsy) [39]. In a cohort of 500 unselected patients coming to a university medical genetic clinic, diagnostic yield of WES was 30%, while that of patients with epilepsy was 35% [40]. The output of WES may also depend on when in a diagnostic process it is used: as a first-tier test when a genetically heterogeneous disorder is suspected, as a second-tier after the initial set of tests is normal, or at the end of the whole diagnostic odyssey. In a prospective study of 80 infants with mostly neurodevelopmental disorders and congenital malformations, first-tier singleton WES resulted in 57.5% diagnostic yield compared to 13.75% diagnostic yield of standard investigations (including gene panel testing) [41].

Despite the well-recognized benefits of WGS/WES approaches, they also carry with them a high burden of interpretative workload and an increased possibility of detecting incidental findings (see Section 2.6) [42]. According to the current European Society of Human Genetics (ESHG) recommendations, it is preferable to use a targeted approach of gene panels first in order to avoid unsolicited findings or findings that cannot be interpreted [23]. Indeed, about 80% of human genes are currently not associated with a disease. In the investigation of disorders with limited genetic and phenotypic heterogeneity, gene panels may outperform WES because of better coverage, time- and cost-efficiency, and a focused approach excluding incidental findings [29]. Multiple gene panels exist for the investigation of patients with epileptic encephalopathies, cortical malformations, groups of inborn errors of metabolism, various other clinical indications, and undifferentiated epilepsy phenotypes. However, due to a huge phenotypic and genetic heterogeneity characteristic of disorders involving epilepsy or seizures, as illustrated by EpiGene database (http://www.kimg.eu/en/tools/epigene-database), gene panels may lead to smaller diagnostic yields due to their restrictiveness. Testing of 500 epileptic encephalopathy patients with a gene panel containing 65 genes gave a diagnostic yield of 10% [43], 30 gene or 90 gene panels in 349 patients with treatment-resistant epilepsies gave a diagnostic yield of 20.3% [44], a gene panel of 46 genes in 216 patients with various epilepsies gave 23% diagnostic yield [45], a gene panel trio-testing of 412 genes in 63 probands with variable epilepsies gave 23.8% diagnostic yield [46], and a combined approach of 46 gene

panel and targeted exon-level aCGH in 400 patients with early onset epilepsy and developmental delay gave 18% diagnostic yield [27]. Comparisons of gene panel testing studies are hindered by a huge phenotypic and gene panel variability in all these studies. Indeed, Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/) database lists more than 60 epilepsy gene panels from several to 377 genes in size (as of 09/04/2016), and the most comprehensive commercially available epilepsy gene panels include from 100 to more than 400 genes, with a proportion of genes associated with epilepsy in animal or association studies only and up to 4% of included genes currently not related to epilepsy or seizures at all [47]. Moreover, there is a high inconsistency in both gene numbers and compositions of gene panels even though applied for similar groups of patients with epilepsy. In a clinical setting, selection of the most appropriate gene panel in a given patient may be challenging because of overlapping, not-full-blown, atypical clinical presentations [42]. Finally, gene panels rather quickly become outdated because of newly discovered genes [41]. A possible solution to these problems is the use of "virtual" gene panels applied to WES data. Such an approach gives a flexibility in "virtual" gene panel selection and, in cases of negative findings, further possibilities to eventually proceed to a much more untargeted analysis of the whole WES data. Besides, carefully selected and applied to WES sequencing data, "virtual" gene panels can act as a supplementary filtering system aiding in time-efficient and better variant calling in terms of exclusion of both false-positive (by filtering out non-epilepsy-related genes) and false-negative (by inclusion of epilepsy-related genes which could be missed in the whole flood of variants) findings. Recently, we have created a web tool for a customized gene panel creation according to the phenotype (http://www.kimg.eu/generator). Application of this tool to 405 patients with various phenotypes increased diagnostic sensitivity from 25.4 to 29.7% [42] comparing to the whole WES data analysis.

2.4. Diagnoses not to miss: treatable inborn errors of metabolism

Metabolic epilepsies represent an unquestionable area of precision medicine where timely diagnosis and specific treatments tailored to the inherited metabolic defect may markedly improve both the seizures and associated comorbidities as intellectual disability [48]. Regrettably, diagnosis of these and other potentially treatable epilepsy-related diseases is still often delayed [49]. The reasons for that may be insufficient testing due to a low index of suspicion, phenotypic variability and nonspecificity, complexity and limited availability of metabolic testing, and invasiveness of some of the diagnostic methods.

More than 370 inborn errors of metabolism (IEM) can present with epilepsy or seizures, and more than 90 of these disorders have disease-specific treatments leading to a much more better prognosis, improved control of both seizures and comorbid symptoms, and complete avoidance of antiepileptic drugs if diagnosed timely (**Table 1**; http://www.kimg.eu/en/tools/epigene-database). However, traditional diagnostics of IEM may be cumbersome as it involves a range of metabolic tests performed in specialized laboratories. Urine and/or plasma specimen are mostly used; however, in some IEM characteristic metabolites can mainly or only be investigated in cerebrospinal fluid (CSF). Histological and/or biochemical investigations of biopsies (e.g., skin, conjunctiva, or muscle) can aid in the diagnostics of certain other IEM. Selection of tests is usually based on a diagnostic hypothesis and requires specialized

Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
1. Disorders of amino acid and peptide metabolism				
1.	Glycine encephalopathy (GCE)	Hyperglycinemia Hyperglycinuria Elevated CSF glycine Elevated CSF/plasma glycine ratio	*AMT* *GCSH* *GLDC*	#605899 #605899 #605899
2.	Argininemia	Hyperarginemia Diaminoaciduria (arginuria, lysinuria, cystinuria, ornithinuria) Orotic aciduria Pyrimidinuria Increased CSF amino acids (arginine, ornithine, aspartate, threonine, glycine, and methionine)	*ARG1*	#207800
3.	Argininosuccinic aciduria	Increased citrulline (P) Increased glutamine (P) Argininosuccinic aciduria Orotic aciduria	*ASL*	#207900
4.	Citrullinemia, classic	Increased citrulline (P) Increased glutamine (P) Decreased arginine (P) Orotic aciduria	*ASS1*	#215700
5.	3-Methylglutaconic aciduria, type I (MGCA1)	Metabolic acidosis Increased 3-methylglutaconic acid (U) Increased hydroxyisovaleric acid (U)	*AUH*	#250950
6.	Maple syrup urine disease (MSUD)	Increased branched chain amino acids (leucine, isoleucine, valine) (P) Branched chain ketoaciduria (alpha-keto isocaproate, alpha-keto-beta methylisovalerate, alpha-keto isovalerate) Increased alloisoleucine(P) Positive urine DNPH screening test	*BCKDHA* *BCKDHB* *DBT*	#248600 #248600 #248600
7.	Homocystinuria due to cystathionine beta-synthase deficiency	Homocystinuria Methioninuria	*CBS*	#236200
8.	Carbamoyl phosphate synthetase I deficiency, hyperammonemia due to	Decreased citrulline (P) Decreased arginine (P) Decreased orotic acid (U)	*CPS1*	#237300

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Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
9.	Glutaric acidemia I	Glutaric aciduria	*GCDH*	#231670
10.	Hyperinsulinemic hypoglycemia, familial, 6 (HHF6)	Hyperinsulinemic hypoglycemia Hyperammonemia	*GLUD1*	#606762
11.	17-Beta-hydroxysteroid dehydrogenase X deficiency	Increased 2-methyl-3 hydroxybutyrate (U) Increased tiglylglycine (U)	*HSD17B10*	#300438
12.	Isovaleric acidemia (IVA)	Isovaleric acidemia Isovaleric aciduria Isovaleryl glycinuria	*IVD*	#243500
13.	Homocystinuria-megaloblastic anemia, cblG complementation type (HMAG)	Homocystinuria Hyperhomocysteinemia Hypomethioninemia	*MTR*	#250940
14.	Homocystinuria-megaloblastic anemia, cblE complementation type (HMAE)	Homocystinuria Hyperhomocysteinemia Hypomethioninemia	*MTRR*	#236270
15.	N-Acetylglutamate synthase deficiency (NAGSD)	Increased glutamine (P) Decreased or absent citrulline (P) Normal orotic acid (U)	*NAGS*	#237310
16.	Ornithine transcarbamylase deficiency, hyperammonemia due to	Decreased citrulline (P) Decreased arginine (P) Increased glutamine (P) Increased asparagine (P) Increased orotic acid (U) Increased ornithine (P)	*OTC*	#311250
17.	Phenylketonuria (PKU)	Hyperphenylalaninemia Phenylpyruvic acidemia	*PAH*	#261600
18.	Propionic acidemia	Increased propionate Increased 3-hydroxypropionic acid Increased 3-methylcitric acid Hyperglycinemia Hyperglycinuria	*PCCA* *PCCB*	#606054 #606054

Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
19.	Phosphoglycerate dehydrogenase deficiency (PHGDHD)	Decrease serine (fasting) (P) Decreased serine (C) Normal-to-decreased glycine (fasting) (P) Decreased glycine (C)	*PHGDH*	#601815
20.	Phosphoserine aminotransferase deficiency (PSATD)	Decreased serine (P, C) Decreased glycine (P, C)	*PSAT1*	#610992
21.	Phosphoserine phosphatase deficiency (PSPHD)	Decreased serine (P) Decreased glycine (P)	*PSPH*	#614023
22.	Citrullinemia, type II, adult-onset (CTLN2)	Citrullinemia	*SLC25A13*	#603471
23.	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	Hyperornithinemia Hyperammonemia Homocitrullinuria	*SLC25A15*	#238970
24.	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCLD)	Hypoketotic hypoglycemia	*HMGCL*	#246450
2. Disorders of carbohydrate metabolism				
25.	Fructose intolerance (hereditary)	Hypoglycemia Fructosemia	*ALDOB*	#229600
26.	Glut1 deficiency syndrome	Decreased CSF/plasma glucose ratio	*SLC2A1*	#614847
27.	Hyperinsulinemic hypoglycemia, familial, 1 (HHF1)	Hypoglycemia Hyperinsulinemia	*ABCC8*	#256450
28.	Hyperinsulinemic hypoglycemia, familial, 5 (HHF5)	Hypoglycemia, postprandial Hyperinsulinemia, fasting Elevated serum insulin-to-C-peptide ratio	*INSR*	#609968
29.	Hyperinsulinemic hypoglycemia, familial, 2 (HHF2)	Hypoglycemia Hyperinsulinemia	*KCNJ11*	#601820
3. *Disorders of fatty acid and ketone body metabolism*				

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Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
30.	Multiple acyl-CoA dehydrogenase deficiency (MADD)	Neonatal acidosis Hypoglycemia Glutaric aciduria Glutaric acidemia Ethylmalonic aciduria	*ETFA* *ETFB* *ETFDH*	#231680 #231680 #231680
31.	Neurodegeneration due to cerebral folate transport deficiency	Decreased methyltetrahydrofolate (MTHF) (C)	*FOLR1*	#613068
32.	3-Hydroxy-3-methylglutaryl-CoA synthase-2 deficiency (HMGCS2D)	Hypoketotic hypoglycemia	*HMGCS2*	#605911
4. Disorders of energy metabolism				
33.	Coenzyme Q10 deficiency, primary, 4 (COQ10D4)	Increased lactate (P, C)	*ADCK3*	#612016
34.	Coenzyme Q10 deficiency, primary, 1 (COQ10D1)	Lactic acidosis	*COQ2*	#607426
35.	Coenzyme Q10 deficiency, primary, 5 (COQ10D5)	Lactic acidosis	*COQ9*	#614654
36.	Encephalopathy, ethylmalonic (EE)	Lactic acidosis Ethylmalonic aciduria Methylsuccinic aciduria Increased C4 and C5 acylcarnitine esters (P) Increased isobutyryl glycine (U) Increased 2-methylbutyryl glycine (U) Increased thiosulfate (U)	*ETHE1*	#602473
37.	Cerebral creatine deficiency syndrome 2 (CCDS2)	Low creatine (C) Low creatinine (C)	*GAMT*	#612736
38.	Cerebral creatine deficiency syndrome 3 (CCDS3)	Decreased guanidinoacetate (GAA) (P, U)	*GATM*	#612718
39.	Pyruvate dehydrogenase E1-alpha deficiency (PDHAD)	Lactic acidosis Increased pyruvate (P, C, U) Increased lactate (P, C, U)	*PDHA1*	#312170
40.	Pyruvate dehydrogenase E1-beta deficiency (PDHBD)	Lactic acidosis	*PDHB*	#614111

Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
41.	Pyruvate dehydrogenase E3-binding protein deficiency (PDHXD)	Lactic acidosis Increased pyruvate (P) Increased alanine (P)	*PDHX*	#245349
42.	Coenzyme Q10 deficiency, primary, 3 (COQ10D3)	Increased lactate (P)	*PDSS2*	#614652
5. Disorders of the metabolism of sterols				
43.	Cerebrotendinous xanthomatosis (CTX)	Increased cholestanol (P) Increased 7 alpha-hydroxylated bile alcohols (U)	*CYP27A1*	#213700
44.	Smith-Lemli-Opitz syndrome (SLOS)	Decreased cholesterol (P) Increased 7-dehydrocholesterol (P)	*DHCR7*	#270400
45.	Bile acid synthesis defect, congenital, 1 (CBAS1)	Increased serum bilirubin Abnormal liver function tests Decreased serum cholesterol	*HSD3B7*	#607765
6. Disorders of porphyrin and heme metabolism				
46.	Porphyria, acute intermittent (AIP)	Increased delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) during acute attacks (U)	*HMBS*	#176000
47.	Porphyria variegata	Increased fecal protoporphyrin and coproporphyrin Increased porphyrins (U) Increased porphobilinogen (PBG) and delta-aminolevulinic acid (ALA) during acute attacks (U)	*PPOX*	#176200
48.	Porphyria, acute hepatic	Hemolytic anemia Elevated urinary delta-aminolevulinic acid and porphyrins	*ALAD*	#612740
49.	Coproporphyria, hereditary (HCP)	Increased coproporphyrin isomer III:I ratio (HCP, feces) Increased harderoporphyrin excretion (feces, harderoporphyria)	*CPOX*	#121300
7. *Disorders of lipid and lipoprotein metabolism*				
50.	Sjogren-Larsson syndrome (SLS)	Fatty alcohol: NAD+ oxidoreductase deficiency in leukocytes and fibroblasts	*ALDH3A2*	#270200
8. *Congenital disorders of glycosylation and other disorders of protein modification*				

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Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
51.	Congenital disorder of glycosylation, type IIc (CDG2C)	Neutrophilia, both basal and during infections Isoelectric focusing of serum transferrin (type II)	*SLC35C1*	#266265
10. Lysosomal disorders				
52.	Aspartylglucosaminuria (AGU)	Aspartylglucosaminuria	*AGA*	#208400
53.	Metachromatic leukodystrophy	Increased protein (C) Increased sulfatide (U)	*ARSA*	#250100
54.	Krabbe disease	Increased protein (C)	*GALC*	#245200
55.	Gaucher disease, type III	Gaucher cells in bone marrow	*GBA*	#231000
56.	Fabry disease	Bone marrow contains lipid-laden macrophages Increased globotriaosylceramide (GB3) (P, U) Increased globotriaosylsphingosine (lyso-GB3) (P)	*GLA*	#301500
57.	Mucopolysaccharidosis, type IIID (MPS3D)	Heparan sulfate (U)	*GNS*	#252940
58.	Mucopolysaccharidosis, type IIIC (MPS3C)	Heparan sulfate (U)	*HGSNAT*	#252930
59.	Mucopolysaccharidosis, type II (MPS2)	Dermatan and heparan sulfate (U)	*IDS*	#309900
60.	Mucopolysaccharidosis, type IIIB (MPS3B)	Heparan sulfate (U)	*NAGLU*	#252920
61.	Niemann-Pick disease, type C1 (NPC1)	Foam cells on bone marrow biopsy "Sea-blue" histiocytes Foam cells in visceral organs and CNS Foam cells contain polymorphic cytoplasmic inclusions consisting of lamellar osmiophilic membranes on electron microscopy	*NPC1*	#257220
62.	Niemann-Pick disease, type C2 (NPC2)	Foam cells on bone marrow biopsy "Sea-blue" histiocytes Foam cells in visceral organs and CNS Foam cells contain polymorphic cytoplasmic inclusions consisting of lamellar osmiophilic membranes on electron microscopy	*NPC2*	#607625
63.	Mucopolysaccharidosis, type IIIA (MPS3A)	Heparan sulfate (U)	*SGSH*	#252900
10. Peroxisomal disorders				
64.	Adrenoleukodystrophy (ALD)	Very long-chain fatty acids (P, U, C)	*ABCD1*	#300100

Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
11. Disorders of neurotransmitter metabolism				
65.	Succinic semialdehyde dehydrogenase deficiency (SSADHD)	Increased 4-hydroxybutyric acid (U, P, C) Increased gamma-aminobutyric acid (U, P, C)	*ALDH5A1*	#271980
12. Disorders in the metabolism of vitamins and (nonprotein) cofactors				
66.	Epilepsy, pyridoxine-dependent (PDE)	Increased pipecolic acid (U, P, C) Increased alpha-aminoadipic semialdehyde (P, U, C)	*ALDH7A1*	#266100
67.	Hypophosphatasia, infantile	Phosphoethanolaminuria Increased inorganic pyrophosphate (P, U) Decreased alkaline phosphatase (P)	*ALPL*	#241500
68.	Biotinidase deficiency	Increased beta-hydroxyisovalerate, lactate, beta-methylcrotonylglycine, beta-hydroxypropionate, methylcitrate (U)	*BTD*	#253260
69.	Hyperphenylalaninemia, BH4-deficient, B (HPABH4B)	Hyperphenylalaninemia Decreased homovanillic acid and 5-hydroxyindoleacetic acid (C) Decreased neopterin and biopterin (U, C)	*GCH1*	#233910
70.	Holocarboxylase synthetase deficiency	Increased beta-hydroxyisovalerate, beta-methylcrotonylglycine, beta-hydroxypropionate, methylcitrate, lactate, tiglylglycine (U) Normal serum biotin concentration	*HLCS*	#253270
71.	Methylmalonic aciduria and homocystinuria, cblF type	Methylmalonic acid (U, P) Homocystine (P, U) Cystathionine (P, U) Decreased adenosylcobalamin Decreased methylcobalamin	*LMBRD1*	#277380
72.	Methylmalonic aciduria, cblA type	Methylmalonic acid (P, U) Long-chain ketonuria Hyperglycinemia Decreased adenosylcobalamin Normal serum cobalamin (vitamin B12)	*MMAA*	#251100

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Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
73.	Methylmalonic aciduria and homocystinuria, cblC type	Homocystine (P, U) Methylmalonic acid (P, U) Decreased methionine (P) Cystathionine (P, U) Decreased adenosylcobalamin Decreased methylcobalamin Normal serum cobalamin	*MMACHC*	#277400
74.	Methylmalonic aciduria and homocystinuria, cblD type	Megaloblastic anemia Homocystinuria Homocystinemia Methylmalonic acid (P, U) Decreased methionine (P) Decreased adenosylcobalamin Decreased methylcobalamin Normal or mildly reduced serum cobalamin	*MMADHC*	#277410
75.	Molybdenum cofactor deficiency	Increased xanthine (U) Increased hypoxanthine (U) Increased S-sulfocysteine (U) Increased taurine (U)	*MOCS1* *MOCS2*	#252150 #252160
76.	Homocystinuria due to deficiency of N(5,10)-methylenetetrahydrofolate reductase activity	Low to normal methionine (P) Homocystinemia Homocystinuria	*MTHFR*	#236250
77.	Pyridoxamine 5-prime-phosphate oxidase deficiency	Normal to increased glycine (P) Normal to increased threonine (P) Decreased arginine (P) Increased vanillactic acid (U) Decreased homovanillic acid (C) Decreased 5-hydroxyindoleacetic acid (C) Increased 3-methoxytyrosine (C) Increased glycine, threonine, taurine, histidine (C) Decreased arginine (C) Decreased pyridoxal (C) Decreased pyridoxal 5-prime-phosphate (C)	*PNPO*	#610090

Inherited metabolic disease		Diagnostic metabolites	Gene	OMIM number
78.	Hyperphenylalaninemia, BH4-deficient, A (HPABH4A)	Hyperphenylalaninemia Decreased homovanillic acid and 5-hydroxyindoleacetic acid (C) Increased neopterin (U, C)	*PTS*	#261640
79.	Hyperphenylalaninemia, BH4-deficient, C (HPABH4C)	Hyperphenylalaninemia Decreased homovanillic acid and 5-hydroxyindoleacetic acid (C) Increased biopterin (U, C)	*QDPR*	#261630
80.	Salla disease (SD)		*SLC19A2*	#249270
81.	Thiamine-responsive megaloblastic anemia syndrome (TRMA)	0	*SLC19A3*	#607483
82.	Folate malabsorption, hereditary	Megaloblastic anemia, folate-responsive Decreased folate (P, C) Decreased methionine (P) Increased formiminoglutamic acid (U)	*SLC46A1*	#229050
83.	Dystonia, dopa-responsive, due to sepiapterin reductase deficiency	Decreased 5-hydroxyindoleacetic acid (C) Decreased homovanillic acid (C) Increased sepiapterin (C) Increased biopterin (C) Increased dihydrobiopterin (C) Decreased HVA, 5-HIAA, and vanillylmandelic acid (U) Normal urinary pterins No hyperphenylalaninemia	*SPR*	#612716
13. Disorders in the metabolism of trace elements and metals				
84.	Menkes disease	Decreased copper and ceruloplasmin (P)	*ATP7A*	#309400
85.	Wilson disease	Decreased ceruloplasmin (P) Increased copper (U)	*ATP7B*	#277900

Table 1. Treatable inborn errors of metabolism (IEM) associated with epilepsy or seizures.

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knowledge in IEM. Unfortunately, characteristics of seizure semiology, EEG, or head magnetic resonance imaging/spectroscopy (MRI/MRS) can only seldom guide differential diagnostics of these IEM [13, 48, 50–52]. Besides, there is a huge phenotypic diversity: epilepsy or seizures are usually accompanied by other signs and symptoms; multisystem involvement is common. Seizures can be the main and the first symptom (e.g., in pyridoxine-dependent epilepsy) or a late presentation (e.g., in some of lysosomal storage diseases). Intermediary metabolism defects can present with symptomatic seizures during acute crises only [48, 53]. Consequently, diagnostics of IEM is sophisticated, time-consuming, and sometimes invasive and requires a high degree of specialization, experience, and investments into the diagnostic laboratory equipment and human resources (**Table 1**).

Molecular genetic tests are usually performed for the confirmation of IEM diagnosis and/or genetic counseling purposes [52]. However, recent emergence of NGS technologies provides us entirely new diagnostic possibilities. Indeed, previously unsuspected IEM were frequently diagnosed in patients with epilepsy through NGS studies [19, 54], and, vice versa, other genetic diseases were diagnosed in patients with suspected IEM [55]. Noninvasiveness is a further advantage of NGS tests. Therefore, NGS testing might be considered as a primary test and as the most comprehensive screening test for these IEM.

Many IEM present with acute symptoms and metabolic testing in this setting can give the only opportunity for timely diagnosis. However, with ever progressing technological advancements, application of NGS methods can be comparably time-efficient and gives very high diagnostic yield rates. In a study by Soden et al. [19], accelerated whole-genome sequencing has been performed in 15 acutely ill patients in 50 hours (7 of them presented with seizures) with a remarkable diagnostic rate of 73%, while turnaround times of whole-exome sequencing (applied mostly for outpatients) were on average of 16 days. About 20% of all diagnosed patients (9 patients of 45 diagnosed) were diagnosed with IEM [19].

2.5. Chromosomal disorders with epilepsy or seizures

Several hundreds of chromosomal disorders are associated with epilepsy or seizures including aneuploidies (e.g., ~10% of Down syndrome patients have epilepsy), chromosomal rearrangements (e.g., balanced translocations and disrupting known epilepsy-associated genes), and structural variants (syndromic and non-syndromic deletions, duplications, and inversions) [56]. In most of these disorders, epilepsy or seizure is a variable feature, and most of these chromosomal disorders are associated with developmental delay/intellectual disability (DD/ID), autism, and/or congenital malformations (CM). Historically, G-banding karyotype was used for the detection of aneuploidies and large-scale chromosomal rearrangements with an average diagnostic yield in patients with DD/ID and/or CM not exceeding 3% (excluding Down syndrome; [57]). Fluorescent in situ hybridization (FISH) technique was mostly used for the diagnosis of known, recognizable microdeletion and microduplication syndromes (e.g., 4pdel (Wolf-Hirschhorn), 17pdel (Miller-Dieker), 15q11q13del maternal (Angelman), and 18qdel (de Grouchy), all including seizures), and subtelomeric FISH/subtelomeric MLPA allowed for identification of subtelomeric gains or losses with additional ~3–6% of diagnoses [58, 59]. The major breakthroughs came with the advent of microarrays that have evolved from rather crude

bacterial artificial chromosome (BAC)-based platforms to the contemporary platforms allowing copy number variation (CNV) analysis down to an exon level. These methods increased diagnostic rates in patients with ID/DD and/or CM by ~15% [60] and allowed for elucidation of multiple other microdeletion/microduplication syndromes associated with epilepsy or seizures (**Table 2**). Besides, NGS approaches for CNV variant calling (e.g., by using depth-of-coverage analysis-based tool CoNIFER [61] have been developed. Importantly, these methods are restricted to unbalanced chromosomal rearrangements solely; therefore, they do not abolish completely the need for karyotyping. For example, a small part of patients with ring 14

1q21.1del/dup	14q23.3del
1q31.3q41dup	15q11.2del
1q41q42.12del	15q13.2q13.3del
1q43q44del	15q13.3del
2q23.1del/dup	15q26.1del
2q23.3q24.2del	15q26.3del
2q24.1del	16p11.2del/dup
2q24dup	16p13.11del
2q24.3del/dup	16p12del
3p25.3del	16p11.2dup
5p15.31p15.2del	16q22.1del/dup
5q11.2del	17p13.3del
5q14.3q15del	17p13.1del
6q22.1del	17p11.2del
6q25.3q27del	17q11.2del/dup
6q26q27del	17q21.31del/dup
7q11.23q21.12del	19p13.2del
7q11.23dup	20p13del
7q22.2q22.3del	20q13.33del
8p23.3p23.1del	21q22del
8q22.2del	22q11.2del
9p24.1del	Xp22.33del
9q22.3del	Xp11.4dup
9q34.3del	Xq11.11del
14q12q22.1del	Xq27q28dup

References: 1. Leu et al. [110]; 2. Nevado et al. [111].

Table 2. Microdeletion and microduplication syndromes, associated with epilepsy or seizures.

and ring 20 chromosomal syndromes do not have any chromosomal material loss [62, 63]. It was estimated that <1% of all diagnoses will be undetected by array-based investigations due to balanced chromosomal rearrangements [64]. Moreover, different ranges of CNV size are typically captured by array-based and NGS-based methods. Although WGS may capture the whole spectrum of CNVs (and other structural variations), costs and large amounts of data requiring analysis and interpretation currently limits its use [65, 66].

Currently, copy number variation is defined as a genomic segment of at least 50 bp that differs in copy number based on two or more genome comparisons (the smaller elements are known as insertions or deletions, indels) [65]. Copy number variation of human genome is even more extensive than single-nucleotide variation (a median of 8.9 Mb of sequence is affected by structural variants in comparison to 3.6 Mb of single-nucleotide polymorphisms [67]). As of 2014, the most extensive general population of CNV database of genomic variants (DGV) contains more than 2.3 million variants [68], and the bulk of structural variations identified in population controls are low-frequency variants (e.g., 65% of variants detected in 2504 individuals had VAF <0.2% [67]). Together with a limited knowledge on human pathological copy number variation and functional importance of these genome elements, it creates huge challenges in CNV data interpretation [69, 70]. Although the American College of Medical Genetics and Genomics provides some guidelines in CNV analysis [70], interpretation and reporting, multiple various workflows, and strategies exist [60, 69, 71], and diagnostic outputs may substantially differ even in the same cohort of patients investigated by the same professionals over just several years [72]. Currently, the most extensively investigated are heterozygous de novo or inherited dominant CNVs. However, autosomal recessive, imprinting, and X-linked disorders (as much as 10% of all identified causative CNVs in ID were X-linked in a study by Hehir-Kwa et al.) may also be uncovered [69, 73]. Although the pathogenic potential of 1–500 kb small CNVs has not been well elucidated and may not be reported in some laboratories performing aCGH (2010 consensus statement on diagnostic chromosomal microarray testing recommends a resolution of ≥400 kb as a balance of analytical and clinical sensitivity), small CNVs may account for a neurodevelopmental disease phenotype in at least 2% of patients, and this range of CNVs is of increasing importance due to spreading NGS-based CNV calling methods [74]. Although noncoding copy number variation is usually discarded as nonrelevant or uninterpretable, intergenic or intronic structural variation may affect gene regulation through position effect and disturbance of regulatory sequences or normal chromatin folding [75]. Moreover, somatically acquired structural variation may also play a role [76].

Since 2009, importance of CNVs in various epilepsy phenotypes has been shown in multiple studies. The biggest diagnostic yields have been achieved in patients with epilepsy and various brain malformations: pathogenic and likely pathogenic CNVs had 23.7% of 76 patients [77] and 22.5% of 169 patients [78]. Microarray testing has been informative in 3.4–8% of patients with epileptic encephalopathy [79, 80], 10.9% in 247 cases with epilepsy and associated ID/DD and/or CM [81], and 5% in 805 patients with unselected epilepsy phenotypes [82]. Both recurrent CNVs at 15q13.3, 15q11.2, 16p11.2, and 16p13.11 and rare CNVs may play a significant role as one of the major risk factors for common epilepsies, including genetic generalized epilepsy [83, 84], absence epilepsies [85, 86], and Rolandic epilepsy [87]; however, lack of knowledge on the whole phenotypic expression and penetrance of these CNVs present considerable challenges for genetic counseling.

2.6. Next-generation sequencing testing in epilepsies: current problems and limitations

There are two main groups of limitations and problems that must be taken into consideration while applying NGS technologies in a diagnostic testing: technological problems/limitations and psychosocial/bioethical implications (discussed in Section 2.7).

Although WGS interrogates almost the whole genome and WES—a coding part of the genome—diagnostic rate of WGS in patients with epilepsy and other phenotypically and genetically diverse neurodevelopmental disorders is seldom above 70%, while the rate of WES usually does not exceed 50%. Some types of mutations are reluctant to WGS (e.g., epigenetic mutations, structural chromosome rearrangements, tissue-restricted somatic mosaicism). Although our knowledge of WGS-reluctant human molecular pathology is very limited, there are several recent examples of such pathology discovered in patients with epilepsy. Postzygotic tissue-restricted somatic de novo mutations in *AKT3*, *MTOR*, and *PIK3CA* have been identified as the cause of cortical malformation syndromes associated with severe epilepsy [88], and somatic mutations in *DCX*, *LIS1*, *FLNA*, and *TUBB2B* genes as the cause of double cortex syndrome, periventricular nodular heterotopia, and pachygyria [89]. Recently found biallelic mutations in the box C/D snoRNA U8 gene *SNORD118* as a cause of the cerebral microangiopathy leukoencephalopathy with calcifications and cysts are an example of a pathogenic genomic variation, not amenable to current WES variant filtering practices restricted to coding regions and canonical splice sites [90].

Deep intronic, intergenic, regulatory sequence variants (noncoding parts of genome), tandem repeats, mtDNA variants, CNVs, variants in GC-rich, repetitive, and homologous regions of exome may not be detected in WES [91]. However, at least some of the technological limitations of WES technologies may be solved. Capturing of mtDNA variation (e.g., by using MitoSeek tool; [92]) and CNV variant calling (see Section 2.5) may be incorporated into the method and WES data analysis pipeline. Although detection of very large or small (one to two exons) deletions may be limited, sensitivity of identifying CNVs containing three or more exons has been estimated to be 76%, with a specificity of 94% [61]. As both CNVs and mtDNA variations [93] play a substantial role in the etiology of genetic epilepsies, these amendments are crucially important in this patient group. Unequal coverage of exome leading to missed variants (mostly in GC-rich, repetitive, and homologous regions) is a well-known problem [31, 91]. Therefore, when testing a limited number of genes in disorders with a limited genetic heterogeneity (~50–300 genes comprising about 0.5–2 Mb), gene panels, possibly supplemented with Sanger sequencing for poorly covered sequences, may be a better approach [29]. However, as it was recently shown in a retrospective study, 99.7% (1491/1533) of variants detected in gene panel testing had sufficient coverage for detection in WES [94]. Therefore, for disorders with extensive genetic and phenotypic heterogeneity, the minimal false-negative rate due to unequal coverage may be outweighed by a substantially larger diagnostic yield of WES due to a comprehensive nature of this technology. Sanger sequencing of potentially causative variants is also currently used for the confirmation of NGS testing. However, as it was shown by several groups, high-quality (≥500 Q) NGS variants do not require Sanger confirmation and restriction of Sanger confirmation to low-quality single-nucleotide variants, and all insertions/deletions <10 bp may reduce Sanger confirmation workload by 70–80% and enable cost savings [95].

Finally, the biggest part of false negatives in WES may be accounted for current variant filtration, annotation, and interpretation practices; therefore, rate of false negatives have a potential to diminish with accumulating information and bioinformatic/technological improvements [96, 97]. Although too stringent criteria can lead to false negatives, most likely they are unavoidable in a current setting of clinical practice. False-positive diagnoses can potentially have more devastating consequences for the family (e.g., through erroneous application of prenatal testing); therefore, all doubtful variants are usually ascribed to variants of unknown significance (VUS): it is easier to specify earlier suspected diagnosis than to refute previously established diagnosis [24].

There are some other non-laboratory-dependent problems potentially leading to missed or misinterpreted variants. One of the major steps in variant annotation process is assessing variant frequency in the general population. However, population databases cannot be assumed as containing data of healthy people only [24]. Besides, the prevalence of reported severe disease-causing variants in population controls points of the fact that incomplete penetrance and wider than appreciated expressivity are more inherent to genetic pathology than usually appreciated. One more problem potentially leading to a wrongful diagnosis is an erroneous annotation of variants and genes in databases and published data. Recently, several genes including *CACNA1H*, *SCN9A*, *EFHC1*, *CLCN2*, *GABRD*, and *SPRX2,* at first ascribed to various monogenic forms of epilepsy, have later been refuted as causative [9]. Finally, lots of very rare pathogenic variants are currently hiding in "private" databases of various laboratories. As both normal and pathogenic variation of human genome is almost endless (see Section 2.3), very large collaborative efforts for sharing both phenotypic and genotypic data of patients must be employed for the elucidation of these ultrarare variants and for ascribing them to certain phenotypes. Recently, the Epilepsy Genetics Initiative has created a database to house the clinically sequenced exomes (and, in due course, sequenced genomes) and phenotypic data of individuals with epilepsy; one unique purpose of which is to allow ongoing iterative reassessment of unsolved cases [49].

2.7. Building new healthcare practices in a responsible way

Incidental findings are not a new issue in clinical practice, for example, unanticipated findings in radiological imaging or even surgery, sometimes leading to dramatic changes in patient care, are well-known examples. However, all-inclusive nature of genomic testing, especially WES and WGS, means that the generation of a certain amount of unanticipated or incidental findings is unavoidable, currently confronted in 1–8% of all tested individuals [98]. Incidental findings in genetic testing have several definitions including more general "unexpected positive findings" [98] and deliberate search for pathogenic variants not related to the primary diagnostic question [99]. Some of these findings are "actionable," that is, measures may be implemented for preventing/alleviating the consequences of imminent genetic disorder. In other cases, no such measures exist. In any case, many psychosocial/bioethical issues may arise; therefore, all the main professional genetic organizations, including ESHG, ACMG, and CCMG, provide perspectives on how to handle unsolicited/incidental/secondary findings [23, 25, 98, 100].

Uncertainty of medical information, including pathogenicity assessments of laboratory or instrumental investigation results and prognostication, is also not a new issue in medicine. In genomic testing, a significant number of variants of unknown clinical significance (VUS) that

cannot reliably be ascribed to either benign or pathogenic are generated. It is presumable that over time due to accumulating knowledge of benign and pathogenic human genome variation a considerable proportion of these VUS will receive their proper meaning. However, as a normal mutation rate will continue to generate a nearly infinite spectrum of variants, the challenge of VUS is going to persist; therefore, in clinical genetic practice, professionals must prepare their patients for the possibility of uncertainty due to VUS [23].

2.8. Clinical utility of genetic and genomic testing in epilepsies

Establishment of exact etiological diagnosis, where it is possible, is a standard of care in nowadays clinical practice. Precise genetic diagnosis has a huge impact on the individuals tested, their families, and community, as it allows timely medical interventions, informed reproductive choices, and avoidance of additional testing. In some cases it enables avoidance of inappropriate or detrimental treatments as illustrated by epilepsy due to *POLG1* gene mutations where valproates are contraindicated due to a threat of fatal hepatic failure [101]. Precise diagnosis can also determine the eligibility for clinical trials or enable engagement into appropriate patient support groups [102]. Psychosocial benefits of ending the diagnostic odyssey may also be substantial [103]. Finally, accurate prognostic information can be used by families for obtaining appropriate social and educational services and making personal and financial plans.

Undoubtedly, the most important benefits that may be enabled by exact genetic diagnosis are disease course-changing specific treatments. With timely diagnosis, there is an opportunity to provide life-saving and disability-preventing specific treatments to some epilepsy patients. Specific therapies have been initiated or adjusted in 6–8% of diagnosed patients in some studies [19, 22]. A significant group of treatable metabolic epilepsies provide one of the most veritable examples of precision medicine applications (see Section 2.4). Recent examples of specific treatments also include individuals with *KCNT1* mutations treated with quinidine, children with *KCNQ2* mutations treated with ezogabine (retigabine), individuals with *GRIN2A* mutations treated with memantine, and patients with mTORopathies treated with everolimus [49]. Fueled by novel epilepsy of genetic discoveries leading to further elucidation of pathogenetic disease mechanisms, the list of precision medicine applications in monogenic epilepsies will likely expand in the future. However, the first prerequisite to specific treatment applications in all these cases is an exact genetic diagnosis. Moreover, as currently up to one-third of all epilepsy cases are refractory to current treatments, new discoveries in monogenic forms of epilepsy may also fuel research and novel treatment target discoveries in common epilepsies.

In reaching diagnosis, comprehensiveness and untargeted approach of NGS technologies, especially WES, may be of special importance. It allows for elucidation of diagnoses in atypical, unusual, and not-full-blown (e.g., in young patients) phenotypes where phenotype-driven diagnostic hypothesis and targeted testing are impossible [19, 104]. Indeed, compatibility of a phenotype to that described in literature (the "first case bias") is one of the main factors in diagnostic hypothesis both raising and ascribing of pathogenicity to a novel variant. However, as of February 2015, 706 genes or ~24% of all genes associated with a Mendelian phenotype in OMIM database were responsible for at least two "clinically discrete" phenotypes [33]. Comprehensiveness of WES is also important for diagnostics of more than one genetic disease in a patient; such cases comprised four of 105 diagnosed patients in a study by Sawyer et al. [22]

and 4.6% of patients in a study by Yang et al. [105]. NGS testing may be the only opportunity for diagnosis in life-limiting disorders or in postmortem setting when DNA samples can be limited [41]. Finally, novel disease genes are also not an unusual finding in a clinical practice with WES or WGS testing and were found in 3.3–8.1% of patients in various studies [37, 40, 102, 104] and 23% of patients in FORGE study [22]. Importantly, each successful discovery opens horizons for diagnostic, preventive, and therapeutic opportunities for the corresponding disease [33]. The most common reasons for patients not to receive a diagnosis prior to WES in FORGE study were a significant genetic heterogeneity of the interrogated disorder, atypical presentation, missed diagnosis by other methods, and novel and ultrarare disorders [22].

2.9. The role of a clinical geneticist

Given all the complexities of genetic diseases' clinical presentation and phenotype evaluation, choice of the right genetic testing strategies, interpretation of genetic testing results and their communication to patients and families, genetic counseling regarding further risks and possibilities for prenatal diagnostics, and finally, sensitive and respectful consideration of all the psychosocial/bioethical aspects related to genetic diseases and genetic/genomic testing, the role of a clinical geneticist in the whole pathway of genetic diagnostics of a patient with epilepsy or seizures is undisputed. In the contemporary clinical genetic practice, geneticists must possess not only proper clinical skills but also abilities to use a vast range of bioinformatic tools and databases and have a deep knowledge of not only clinical genetics but also multiple genetic and genomic testing specificities.

Success of both targeted genetic testing and untargeted NGS approach is crucially dependent on the completeness and accuracy of phenotype evaluation [24, 26, 106]. Given the vast phenotypic variability of human monogenic and chromosomal disorders involving epilepsy or seizures, illustrated by EpiGene database (http://www.kimg.eu/en/tools/epigene-database), phenotyping of patient may include not only neurological examinations and tests but also thorough assessment of dysmorphic features, cutaneous signs, congenital malformations, variable symptoms of any other organ or organ system impairment, results of prior laboratory/radiological and other testings, information on cognitive functioning, etc. Family history/genealogy data may be helpful. Contrary to expectations of some people, with the advent of NGS testing, importance of thorough phenotyping did not diminish [106]. On the contrary, the final stages of variant annotation (gene level) and accurate variant interpretation are crucially dependent on the full phenotypic picture of a patient. Besides, as in many cases, phenotype-driven diagnostic hypothesis is not raised; a constant contact between laboratory and clinics with possibilities to perform a "reverse phenotyping" or "genotype to phenotype" correlation of identified variants is very important. Indeed, diagnostic yields were lower in studies where exome sequencing and interpretation of results were done in laboratories separate from clinical units (e.g., gene panel of 447 genes in 148 patients with a suspicion of mitochondrial diseases gave a diagnostic yield of only 9.4% in a separate laboratory [107] in comparison to 39% yield in a group of 109 patients tested with a gene panel of 238 genes in a laboratory connected to clinical unit [55]). In a recently published study, discordance rate in the initial interpretation of causal variants between laboratory and clinical geneticists was approximately 10% [108]. Finally, standardization and automation of phenotyping may be facilitated by tools like PhenoTips [109].

3. Diagnostic testing in epilepsy genetic clinical practice: proposed workflow

Currently, there are no recommendations or guidelines for genetic testing in epilepsy patients addressing specificities of NGS technologies [28]. We propose a simplified diagnostic workflow based on expected diagnostic yields and cost-effectiveness in various clinical situations encountered in epilepsy genetic clinical practice (**Figure 1**). The choice of a diagnostic route that is the most appropriate in a given clinical situation requires not only deep knowledge of

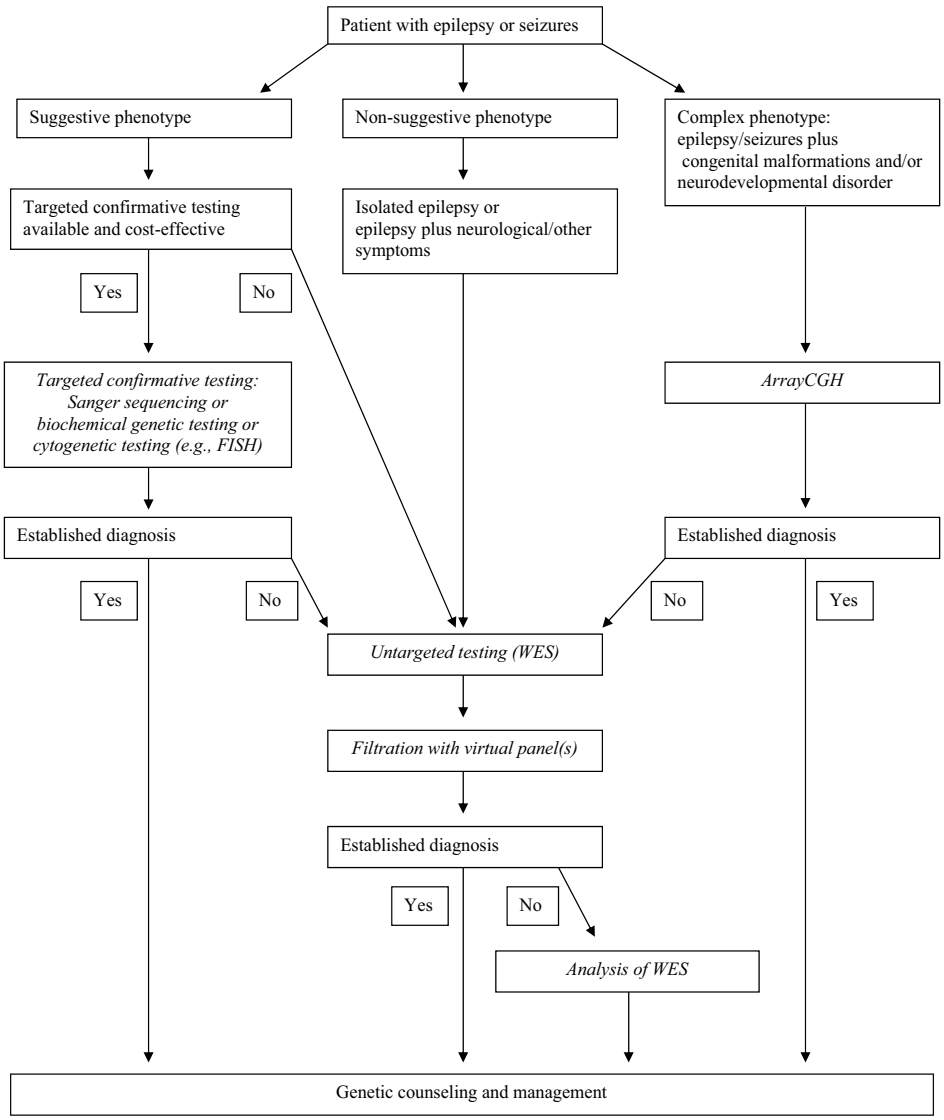

Figure 1. Provisional diagnostic workflow in patients with epilepsy or seizures.

a genetic architecture and a molecular pathology of a disorder; multiple technical specificities and limitations/disadvantages of diagnostic methods must be taken into consideration.

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Chapter 4

Self-Reporting Technologies for Supporting Epilepsy Treatment

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Additional information is available at the end of the chapter

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Abstract

Epilepsy diagnosis and treatment relies heavily on patient self-reporting for informing clinical decision-making. These self-reports are traditionally collected from handwritten patient journals and tend to be either incomplete or inaccurate. Recent mobile and wearable health tracking developments stand to dramatically impact clinical practice through supporting patient and caregiver data collection activities. However, the specific types and characteristics of the data that clinicians need for patient care are not well known. In this study, we conducted interviews, a literature review, an expert panel, and online surveys to assess the availability and quality of patient-reported data that is useful but reported as being unavailable, difficult for patients to collect, or unreliable during epilepsy diagnosis and treatment, respectively. The results highlight important yet underexplored data collection and design opportunities for supporting the diagnosis, treatment, and self-management of epilepsy and expose notable gaps between clinical data needs and current patient practices.

Keywords: health tracking, patient self-reporting, clinical data indicators, neurocognitive, neurophysiological, implications for design

1. Introduction

Health tracking technologies such as wrist-worn seizure detection devices stand to play an increasingly important role in epilepsy diagnosis and treatment as tools that can assist patients with reporting physical [1] and psychiatric symptoms [2]. Neurologists rely on patient self-reporting to document a wide range of symptoms and triggers [3, 4] such as medication

intake, sleep, exercise, missed meals and stress levels. In practice, most patients struggle with reporting these types of information [5], and these reports are known to be highly inaccurate [6–10].

These shortcomings present two sets of challenges for technology developers and healthcare providers alike. First, the type, priority, and characteristics of clinically relevant patient data are not well documented. This presents problems for technology developers, who must understand these needs for establishing appropriate technology design requirements. Second, the performance of health tracking devices is not well explored with respect to clinical seizure reporting needs. This presents problems for healthcare providers, who require an understanding of current reporting capabilities for recommending appropriate patient self-reporting tools.

In this chapter, we present our research with clinicians to first establish clinical patient self-reporting needs with respect to clinical decision-making during epilepsy diagnosis and treatment, and second to investigate the extent that the performance of current seizure detection and classification devices may be suitable for addressing these needs.

Our study included a literature review and interviews with clinicians to identify relevant epilepsy-related symptoms and triggers; a card sorting session to prioritize these symptoms and triggers; a technology review of seizure detection devices; and finally, a pair of online surveys was administered for establishing further characteristics of clinical patient self-reporting needs during epilepsy diagnosis and treatment, respectively.

Our results include a consensus on the types, priorities, and characteristics of clinical patient self-reporting needs during anti-epileptic drug (AED) selection and treatment along with a comparison of seizure detection devices and patient self-reporting performance. These findings are intended to provide a useful reference for both developing future patient self-reporting tools and to highlight the extent that current technologies may be suitable for addressing the clinical needs that we identified within the practice. Finally, we conclude with a discussion of technology recommendations that could stand to benefit mainstream epilepsy treatment.

The main contribution of this work is a "roadmap" for developing technologies that support epilepsy treatment. The results include:

1. Identification of the **type, priority,** and **characteristics** of self-reported data that clinicians need from patients as a reference for technology developers.
2. Evaluation of current device and patient seizure reporting performance as a reference for providers.
3. Identification of **self-reporting challenges** associated with current reporting as a starting point for developing future patient self-reporting and data collection tools.

Moreover, our study demonstrated the importance of stakeholder engagement. The role of clinical patient self-reporting is important yet often undocumented in literature. In our findings, we help to address this gap by presenting specific data collection strategies to help

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providers to collect high priority patient self-reports that are not well supported by current health reporting mechanisms and technologies. This research is unique in that we investigate both the information needs of neurologists during clinical treatment and the performance statistics that technologists need for guiding development efforts.

2. Related work

2.1. Patient self-reporting challenges

Health information can also be challenging for patients to collect and therefore be unreliable even when available, or it may not be collected frequently enough to be informative [9, 11]. Handwritten and electronic patient "seizure diaries" tends to be either incomplete or inaccurate [5, 12]. In practice, many patients (30–50%) fail to report seizures during the day [6–9] while most patients fail to report seizures at night (85.8%) [9]. Eyewitness accounts often disagree on important details of how a seizure presents [9, 13], and observation is often difficult at night [5, 14]. Reminding patients to fill in reports may be ineffective as consciousness can be impaired both during and following a seizure [9]. These collective challenges present problems for clinicians as important patient information is often unavailable, unreliable, or not collected frequently enough to be informative during diagnosis and treatment [9, 11].

The **types** and **priorities** of patient self-reporting information are therefore important to understand for informing care along with the following self-reporting **characteristics**:

1. **Reporting availability:** Self-reports may not be available due to patient non-compliance, inability to document or observe the requested data [9], or limited awareness regarding the types of information that would be most relevant to collect in preparation for appointments.
2. **Reporting usefulness:** Self-reports may not be useful for clinical management. For example, patients may be unsure of what data to collect and fail to report important indicators [15] while devices may report data in a manner that requires considerable interpretation for answering clinical questions.
3. **Reporting reliability:** Self-reports may not be reliable due to issues such as recall bias [16]. Moreover, self-reporting performance can be difficult to assess given the absence of readily quantified measurements or validated study designs [5].
4. **Reporting difficulty:** Self-reporting may be too difficult or burdensome for patients to collect between appointments [17]. Neurologists often ask patients to document and report data such as the time, date, and a description of symptoms before, during, and after clinical presentations of symptoms [5, 18–20].
5. **Reporting frequency:** Finally, patient health data must be sampled or collected at an appropriate frequency for clinical interpretation. For example, clinicians require frequent and detailed seizure and developmental reports when treating patients with infantile spasms [24].

2.2. Health tracking design challenges

Health tracking technologies could help answer these questions but many practical challenges remain [17]. Health tracking priorities among clinicians and the patient's role in self-reporting are each often under-specified in the literature. There is considerable interest in behavioral surveillance [21] as input for both assessing chronic conditions and evaluating self-management during treatment [22].

These advancements stand to greatly inform traditional diagnosis and treatment, but current health tracking measurements only touch on a small subset of health indicators that are relevant for patient care. The Chronic Care Model [23] is helpful in describing the role of clinical systems, healthcare communications, and self-management in patient care, but it is not instructive in terms of describing what clinical, self-management, and electronic health record (EHR) information is most important to keep track of for achieving positive long-term outcomes.

Current developments can be leveraged for greatly enhancing the capabilities of the existing systems. For example, inertial-based seizure detection wristbands are increasingly capable of detecting convulsive seizures [24]. Most patients have access to smartphones with increasingly powerful sensing capabilities [9, 10]. Well-designed health tracking [25] and health reporting tools [26] have the potential to greatly reduce the burden placed on patients to collect clinically significant health information [27]. It is, therefore, important for researchers to establish an understanding of clinical information needs and health tracking performance for developing appropriate and effective health tracking tools.

3. Methods

In this section, we present a multiphase, sequential mixed method study design. The study included a total of 16 clinicians who specialized in pediatric and adult epilepsies.

Our study included two main parts: The first part of the study investigated the **types, priorities,** and **characteristics** of useful clinical indicators during epilepsy diagnosis and treatment, respectively; while the second part investigated the **performance of current seizure detection technologies** as compared with current patient self-reporting.

3.1. Part 1: establishing self-reporting types, priorities, and characteristics

The first step was establishing the **types, priorities,** and **characteristics** of useful patient indicators that clinicians need during diagnosis and treatment. This included

- Interviews and a literature review to identify symptoms and triggers.
- Interviews with subject matter experts to identify five **characteristics of** self-reporting challenges.

The complete list of symptoms and triggers is available upon request. The resulting findings are intended to provide technology developers with insights for anticipating clinical patient self-reporting needs.

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3.1.1. Investigating self-reporting needs

We conduct interviews over a 2-month period. The interviews included one-on-one meetings with one nurse practitioner specializing in pediatric epilepsy at the Children's Healthcare of Atlanta (CHOA), Georgia and two attending specializing in adult epilepsy at Emory University Hospital, Georgia. These meetings highlighted important patient self-reporting characteristics that we would later include in our online survey.

Next, we conducted a literature review to generate a list of patient symptoms and triggers that clinicians might find as useful feedback during diagnosis and treatment. Inclusion criteria for the symptoms included any health indicators that described a specific aspect of the condition such as duration and quality; while triggers included any factors that were known to impact the likelihood of symptoms such as physical activity, sleep quality [28], and self-management behaviors [29, 30]. The literature review resulted in a list of 48 symptoms and 11 triggers that may be of interest during either diagnosis or treatment.

3.1.2. Investigating self-reporting priorities

The next step was to establish the clinical priority of these symptoms and triggers during diagnosis and treatment. A one-hour card sorting session was conducted with six pediatric epilepsy care specialists at CHOA. Informed consent was obtained from all participants. The participants included four nurse practitioners and two epileptology attendings.

The card sorting was conducted as follows. First, we printed the list of symptoms and triggers from the literature review on two separate stacks of notecards. The same card sorting exercise was conducted twice, with one stack of cards being sorted in terms of usefulness to prioritize data needs during diagnosis, and the second stack of cards being sorted to prioritize the same data during treatment. Each card contained a single symptom or trigger, and each set of notecards was shuffled beforehand.

The clinicians were asked to order the notecards in terms of "most-to-least" useful patient-reported symptoms and triggers during diagnosis and treatment, respectively. Notecards of equal importance were stacked on top of one another. New note cards were added to both piles if the clinicians believed we had overlooked any important symptoms and triggers from our literature review. Likewise, irrelevant or difficult to understand notecards were discarded from both piles, as shown in **Figure 1**.

The priority ranking for each card was then computed transcribing the notecards into a three-columned Excel spreadsheet that contained: (1) symptom/triggers names, (2) notecard positions during diagnosis, and (3) notecard positions during treatment, respectively and then summing the two sorted card indices for diagnosis and treatment as shown in Eq. (1).

$$\text{Priority ranking} = \text{diagnosis card index} + \text{treatment card index} \tag{1}$$

The spreadsheet was then sorted by our resulting priority ranking column from least to greatest for establishing a list of clinical data indicators that were considered important during both diagnosis and treatment. It should be noted that the exercise could have been accomplished

Figure 1. Expert panel card sorting exercise with four nurse practitioners and two epileptology attendings who specialized in diagnosing and treating pediatric epilepsy.

by using a single set of notecards, however, we opted to use two sets of cards to avoid having to document the cards before moving onto the second sorting session.

3.1.3. Establishing self-reporting consensus

Next, we conducted an online survey with the aim of further understanding several practical characteristics of these clinical data collection needs. The survey was administered to 6 clinicians over a 5-week period and included the following 5 questions for each of the "top 20" highest ranked symptoms and triggers:

1. Availability	Is this information available?
2. Reliability	Is this information useful?
3. Usefulness	Is this information reliable in your opinion?
4. Difficulty	Is it easy or hard for patients to report?
5. Frequency	How frequently would you ideally like this information to be collected?

The survey had two pages and was designed to take less than 15 min. The first page included demographics questions. The second page contained a 20 row by 5 column table of multiple-choice questions with symptoms and triggers as rows and questions as columns.

3.2. Part 2: investigating seizure reporting performance and capabilities

The second part of our study specifically investigated clinical patient self-reporting needs surrounding patient seizure reporting. This included:

- Interviews and a literature review to identify aspects of seizure reporting.
- Technology review and a meta-analysis to present common performance statistics.

Moreover, we discussed our findings with clinicians. This feedback highlighted several important yet underexplored data collection opportunities for supporting diagnosis, treatment, and self-management.

The findings are intended to help providers to assess the extent that current seizure detection devices may be suitable for complementing patient self-reporting capabilities.

3.2.1. Investigating seizure reporting needs

Interviews, a literature review, and an online survey were conducted as background for establishing clinical seizure reporting needs during diagnosis and treatment.

The interviews included two fellows and one attending at the Emory School of Medicine and provided us with an opportunity to discuss seizure reporting practices among current patients and caregivers. The literature review included 27 papers and focused on identifying seizure reporting needs for informing clinical decision-making. The most common clinical information needs were seizure frequency, duration, type, and ability to observe seizure progression over time.

Next, we administered an online survey among an additional group of clinicians to further assess the perceived importance and accuracy of these seizure reporting measures. The survey was administered to 10 epileptologists at Emory (5 residents, 1 fellow, and 4 attendings) and included 23 Likert scale ratings. The Likert ratings were presented on a scale from 1 to 5 with 1 being "not important" and 5 being "most important" while ratings of self-reporting accuracy ranged between <20 and >80% with 5 even intervals. The respondents were also asked which type of patient reporting error would be the most detrimental during treatment and then given three choices: (a) patient over reporting, (b) patient underreporting, or (c) both errors are equally detrimental.

The online survey results highlighted the need for a follow-on technology review. Most notably, while survey respondents indicated a strong need for more accurate patient and caregiver seizure movements and seizure counts, limited research was available regarding the applicability of current technologies for addressing these needs. In addition, the literature did not specifically compare patient self-reporting to system performance [37].

3.2.2. Evaluating seizure reporting technologies

The technology review addressed these shortcomings by evaluating the performance of current systems for detecting and counting seizures, characterizing patient seizure motion, and comparing performance against that of current patient self-reporting capabilities.

Inclusion criteria included all systems that had been evaluated within a home or clinical setting. Exclusion criteria included vagus nerve [31] and brain stimulation [32] systems that required permanent surgeries and electroencephalogram (EEG) systems that can be burdensome for patients during long-term use [33, 34].

The first step was to choose performance measures that would address two sets of findings from our earlier research. First, our survey respondents showed no consensus regarding the relative impact of over or under reporting seizures. Second, our interviews with clinicians indicated that most patients and caregivers report seizures themselves without the help of seizure detection devices [3, 5]. It was, therefore, important for us to choose performance metrics that would both quantify over and under reporting as well as support comparison between seizure reporting systems and patient self-reporting rates from the literature [9].

To address these requirements, we evaluated each system in terms of three statistics: precision, recall, and F-score. Recall or sensitivity is the fraction of all seizures that were detected. High recall values reflect a low chance of under reporting or missing a seizure. Missed seizure events are problematic as untreated seizures can have serious long-term health consequences.

$$\text{Recall} = \frac{\text{true positives}}{\text{true positives} + \text{false negatives}} \tag{2}$$

Precision is the fraction of all relevant seizures that are detected. High precision values reflect a low chance of over reporting seizures or triggering false alarms. Low false alarm rates are important to avoid changing already effective medication.

$$\text{Precision} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \tag{3}$$

The F-score balances over and under reporting and is expressed as:

$$\text{F} = \frac{2 * \text{precision} * \text{recall}}{\text{precision} + \text{recall}} \tag{4}$$

In practice, notable inconsistencies between studies required making several assumptions. Many systems did not report precision and recall directly. In some cases, these rates had to be calculated based on information in the papers. Next, several studies presented statistics in terms of only those patients with seizures (PWS) [38–40] while other studies reported statistics for all patients in a study [41–43]. Including all patients meant that some patients without seizures might also contribute false positives. To address this discrepancy, we recomputed precision to include only those false positives from patients with seizures. For example, Poh et al. [41] reported performance for all patient and precision subsequently increased 24.54% when calculated among only those patients with seizures.

Next, we calculated patient self-reporting performance based on previous studies [18]. In this case, we assumed perfect self-reporting precision. Blum et al. [7, 9] evaluated seizure awareness among 31 patients with partial and generalized type epilepsies and observed that patients never falsely reported seizures. Next, we calculated based on observations from a similar study from Hoppe et al. [9] in which 91 patients with focal type epilepsies failed to report 32.0% of seizures during the day and 85.8% of seizures while asleep at night. This resulted in a precision of 100% for both day and night time reporting, recall values of 68.0 and 14.5% and F-scores of 0.25 and 0.81 for day and night time reporting, respectively.

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4. Results

4.1. Part 1: self-reporting types, priorities, and characteristics

This section summarizes our key research findings. **Figure 2** presents the type, priority, and characteristics of important information that clinicians need patients to report along with notable perceived patient self-reporting challenges and agreement between participants.

4.1.1. Self-reporting types

The first step for our analysis was establishing the types of patient self-reported data that clinicians need from patients. The bottom row of **Figure 2** shows a sorted list with highest to lowest priority clinical information needs.

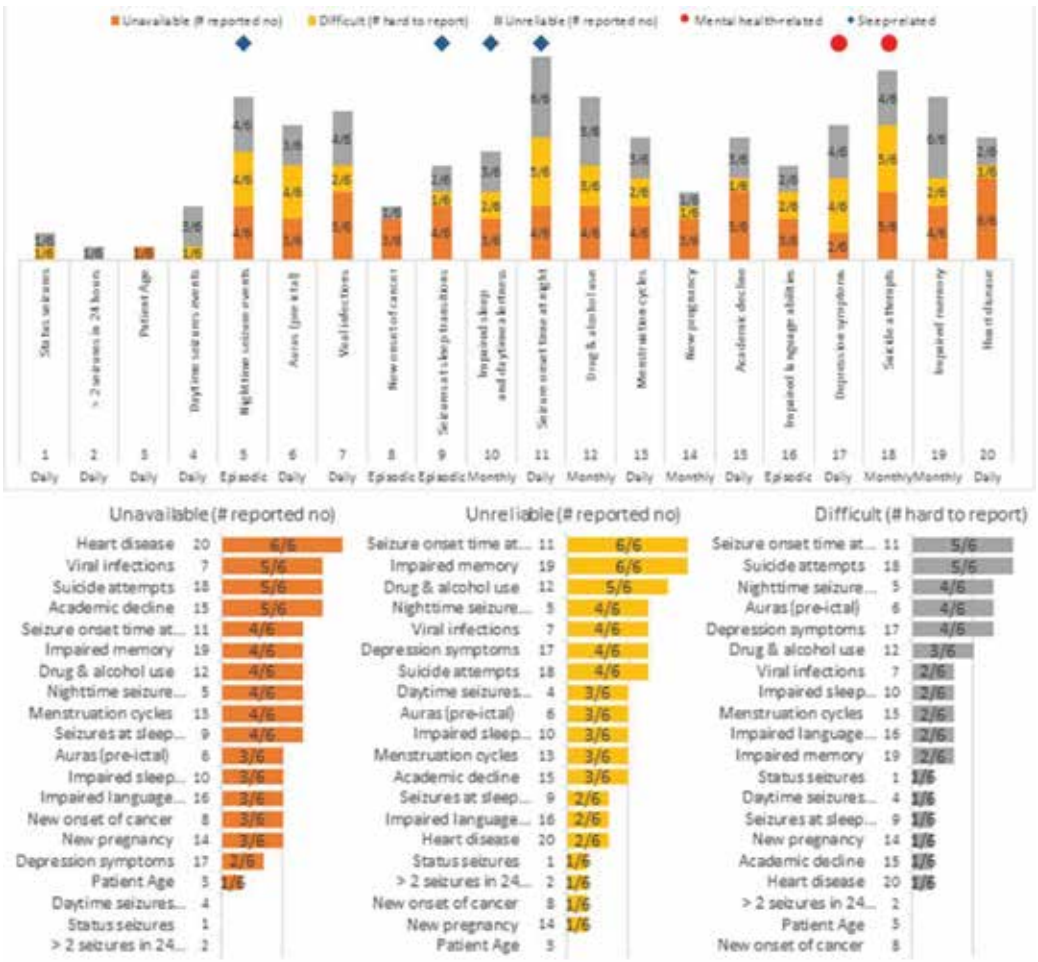

Figure 2. "Top 20" types, priorities, and characteristics of neurocognitive self-reporting needs (top row) and specific self-reporting challenges (sorted from greatest to least importance) (bottom row).

4.1.2. Self-reporting priorities

Next, we investigated the priority of the patient self-reported data that clinicians need from patients. The "top 20" highest priority symptoms and triggers are shown in **Figure 2**.

4.1.3. Self-reporting characteristics

The online survey established a consensus regarding several important self-reporting characteristics. The top row of **Figure 2** shows clinician perceptions regarding the "top 20" highest ranked symptoms and triggers in terms of availability, reliability, difficulty and desired frequency; while the bottom row shows the same characteristics but categorized in terms of "unavailable", "difficult" for patients to collect" or "unreliable", respectively.

4.1.4. Self-reporting challenges

Next, we identified the pair of symptoms and triggers with the highest number of critical clinical responses. The most frequent clinician survey responses are shown in **Table 1**.

The first row in **Table 1** highlights patient reporting challenges associated with information access. This includes the symptom or trigger with the greatest number of "unavailable" and "difficult" responses. The second row, further accounts for problems associated with data collection performance. This includes the symptom or trigger with the greatest number of "unavailable", "difficult", and "unreliable" responses, respectively. The results highlight "suicide attempts" and "seizure onset time at night" as two important unmet clinical needs.

4.1.5. Self-reporting themes

Mental health and sleep-related symptoms and triggers each appeared among the "top 20" highest ranked symptoms and triggers. Icons above the bar graphs in **Figure 2** denote mental health-related symptoms and triggers such as "depression symptoms" with red circles and sleep-related symptoms and triggers such as "impaired sleep and daytime alertness" and "impaired sleep quality" with blue diamonds.

4.2. Part 2: seizure reporting technology review capabilities

This section summarizes our research findings and highlights how inaccurate patient and caregiver seizure reporting impacts clinical decision-making for prescribing and adjusting

	Epilepsy
Unavailable + dfficult	Suicide attempts
Unavailable + difficult + unreliable	Seizure onset time at night

Table 1. Most frequent clinician reported survey responses.

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AEDs. Here our key findings were that limited technologies exist for supporting the process of characterizing patient seizure type, and while most seizure detection devices are more accurate than patients for nighttime reporting, these devices must be made more accurate to be beneficial for daytime use.

The results in **Figure 3** provide a comparison of seizure detection device and patient self-reporting capabilities on an F-score axis between 0 and 1. The results also account discrepancies in study population size by computing performance for only those patients with seizures (PWS) as opposed to all patients that participated in each study. The following subsections describe inertial systems, video systems, and multimodal systems.

4.2.1. Inertial systems

Inertial systems utilize one or more wrist and/or chest-worn motion sensor [36, 44] and detect seizure-like convulsions as intense, repetitive limb, and torso movements with F-scores ranging from 0.133 to 0.990. These systems offer the benefit of being able to measure motion under blankets for nighttime use [36] and typically measure limb motion using an accelerometer [42], and/or gyroscope [45]. The two highest performing research systems in our review were from Schulc et al. [45] and Dalton et al. [46]. Schulc et al. [45] instrumented patients with a

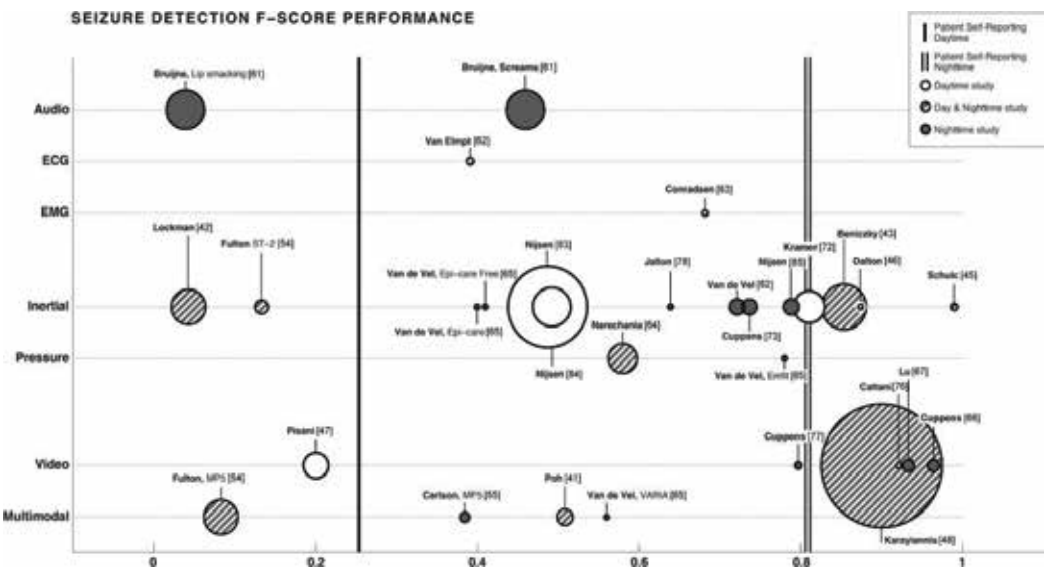

Figure 3. Seizure reporting performance comparison: multiple types of non-EEG seizure detection systems are compared against patient self-reporting on a continuous F-score scale from 0.0 to 1.0, read left to right, where 0.0 is worst and 1.0 is shows the best performance. Each seizure detection system is represented as a circle for given class technology. The circle texture indicates the time of day that the system was evaluated and diameter reflects the relative number of patients that had at least one seizure during each study. Self-reporting performance is shown using vertical lines. Daytime performance is shown as a vertical white line with a black border while nighttime performance is shown as a solid black line, respectively.

single sensor on the forearm (98.00% precision, 100.00% recall) while Dalton et al. [46] instrumented patients with a pair of wrist-worn sensors (84.0% precision, 91% recall). The highest performing commercial product is Epi-care Free. Epi-care Free is a single wrist sensor with similar performance (81.95% precision, 89.74% recall) [43]. High false positive rates remain a challenge as rhythmic activities such as brushing teeth [42, 43] and exercise [41] are often responsible for triggering false alarms.

4.2.2. Video systems

Marker and markerless video systems been developed for detecting and classifying a range of seizure types [39] with F-scores between 0.201 and 0.964. These systems had lower overall performance than other alternatives such as inertial systems, but modern computer vision techniques are making these systems increasingly flexible and attractive for long-term use.

Markerless video systems can be trained to reliably detect patient seizure movement without the need to wear sensors on the body. For example, while prior systems were restricted to specific settings such as specific Neonatal Intensive Care Units [47, 48], more recent systems such as the one from Cuppens et al. [77] use image features that are more robust to lighting and viewpoint changes and thus applicable to different bedrooms.

Marker-based video systems, by contrast, require patients to wear active or passive markers for measuring patient motion but provide among the few examples of systems that also classify types of detected seizures [35, 38, 51]. Rémi et al. [35] used an infrared camera and retroreflective markers to track and classify different types of patient limb movements during seizures. The video recordings were analyzed to track the position of each marker over time. The relative movement of these markers between video frames was then used to discriminate between motor characteristics during different types of convulsive seizures.

4.2.3. Multimodal systems

Multimodal systems utilize inputs from multiple types of sensors thereby improving seizure detection performance with F-scores ranging from 0.083 to 0.560. Poh et al. [41] showed that electrodermal activity (EDA), in conjunction with an accelerometer, could detect seizures better than using accelerometry alone [41]. EDA measures autonomic arousal and could play a role in detecting seizures with subtle motor movement. In addition, future research may highlight differences between EDA responses on both wrists and legs for differentiating generalized and partial seizures, and for characterizing seizure laterality [52].

The MP5 system [54, 55] consisted of an under mattress microphone and accelerometer according to Ref. [56], although performance was comparatively poor (average F-score = 0.234). More recently, Pavlova et al. showed that respiration can complement video EEG during seizure diagnosis [57]. Heart rate variability [58], EDA, and respiration may enable systems to recognize life-threatening postictal depression following seizures [59, 60].

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4.2.4. Audio, ECG, EMG, pressure systems

van Elmpt et al. [62] used ECG measurements for detecting the onset of heart rate changes associated with seizures and achieved competitive performance with inertial sensors (F-score = 0.391). Heart rate was observed to increase (tachycardia) at the onset of seizures and decrease following seizures (postictal bradycardia). Muscle activated sensors have been used to detect seizures [63], however, no further efforts have been made, perhaps due to adhesive EMG sensors being cumbersome to wear for long periods of time.

Mattress pressure pads have achieved mid-level performance for generalized tonic clonic (GTC) seizures [64, 65] with F-scores ranging from 0.580 to 0.78. These sensors present the added benefit of not requiring patients to wear sensors and increased privacy over having a camera installed in bedrooms. Most mattress systems, however, report false positive rates that are notably higher than inertial and video-based systems [66], due to pillows dampening pressure readings or the patient sitting up in bed [64].

4.2.5. Seizure reporting comparison between devices and patient self-report

Table 2 presents a set of statistics for comparing each system to patient [9] seizure reporting performance. Each row contains an F-score along with precision, recall, and number of patients with seizures and modality or type of system and is sorted by descending F-score for reference. Next, **Table 3** presents statistics for comparing performance between each type of system. Each row includes the mean, standard deviation, minimum and maximum values together with two sets of p-values from a one-sided t-test. The p-values report the likelihood that each type of system would achieve a higher average F-score performance than that of patient self-reporting [9]. It should be noted that the t-test could not be computed for EMG and ECG as we only evaluated a single system from each of these categories.

Systems	F-score	Precision	Recall	PWS	Modality
Schulc [45]	0.990	0.980	1.000	3	Inertial
Cuppens [66]	0.964	0.931	1.000	5	Video
Lu [67]	0.933	0.933	0.933	5	Video
Cattani [76]	0.921	0.932	0.910	1	Video
Karayiannis [48]	0.900	0.900	0.900	54	Video
Dalton [46]	0.874	0.840	0.910	5	Inertial
Beniczky [43]	0.854	0.814	0.897	20	Inertial
Kramer [72]	0.811	0.714	0.938	15	Inertial
Cuppens [77]	0.797	0.850	0.750	3	Video
Nijsen [85]	0.788	0.650	1.000	7	Inertial
Van de Vel, Emfit [65]	0.780	0.780	0.780	1	Pressure
Cuppens [73]	0.737	0.600	0.952	7	Inertial

Systems	F-score	Precision	Recall	PWS	Modality
Van de Vel [82]	0.721	0.578	0.957	7	Inertial
Conradsen [63]	0.682	0.750	0.625	2	EMG
Jallon [78]	0.639	0.717	0.577	2	Inertial
Narechania [64]	0.580	0.430	0.890	13	Pressure
Van de Vel, VARIA [65]	0.560	0.560	0.560	1	Multimodal
Poh [41]	0.508	0.349	0.938	7	Multimodal
Nijsen [84]	0.492	0.350	0.830	18	Inertial
Nijsen [83]	0.487	0.350	0.800	36	Inertial
Bruijne Screams [61]	0.459	0.300	0.980	17	Audio
Van de Vel, Epi-care Free [65]	0.410	0.410	0.410	1	Inertial
Van de Vel, Epi-care [65]	0.400	0.400	0.400	1	Inertial
van Elmpt [62]	0.391	0.900	0.250	3	ECG
Carlson MP5 [55]	0.385	0.278	0.625	4	Multimodal
Pisani [47]	0.201	0.117	0.714	12	Video
Lockman [42]	0.133	0.072	0.875	6	Inertial
Fulton MP5 [54]	0.083	1.000	0.043	15	Multimodal
Fulton ST-2 [54]	0.043	1.000	0.022	15	Inertial
Bruijne Lip smacking [61]	0.039	0.020	0.980	17	Audio
Self-reporting					
Daytime reporting [9]	0.810	100.00	68.00	91	Patient
Nighttime reporting [9]	0.253	100.00	14.50	91	Patient

Table 2. System and patient self-reporting performance comparison.

Modality	Mean	SD	Min	Max	Right-tail hypothesis test	
					p-Value day	p-Value night
Inertial	0.598	0.282	0.043	0.99	0.008	1
Video	0.786	0.292	0.201	0.964	0.426	0.997
Pressure	0.68	0.142	0.58	0.78	0.209	0.927
EMG	0.682	0	0.682	0.682	–	–
Multimodal	0.384	0.214	0.083	0.56	0.014	0.846
Audio	0.249	0.297	0.039	0.459	0.114	0.494
ECG	0.391	0	0.391	0.391	–	–
All systems	0.585	0.288	0.039	0.99	0	1

Table 3. System F-score and p-value statistics by modality.

The resulting tables can then be used for more closely examining system performance with respect to under and over reporting. High recall systems with low precision [41, 61] seldom miss seizures for addressing the concern of underreporting yet tend to overcompensate and over report seizures due to false alarms. High-precision systems with low recall [54, 62] have the opposite problem and address the concern of over reporting seizures at the risk of missing seizures. High F-score systems [45, 66, 67] have high-precision and recall values and therefore perform well without over or under reporting.

5. Discussion

5.1. Part 1: self-reporting types, priorities, and characteristics

The multiphase structure of our study was instrumental in translating our interviews, literature review, and expert panel findings into effective online survey questions. The key findings included the types, priorities, and characteristics of self-reported data that clinicians need from patients as shown in **Figure 2**.

The remainder of this section highlights notable patient self-reporting challenges as well as subsequent feedback after sharing these findings with clinicians.

5.1.1. Self-reporting availability

Many symptoms and triggers were reported as "useful" but "unavailable" as shown in orange in **Figure 2**. "Academic decline" was said to be unavailable (five out of six respondents). These findings highlight the need for patient data that may already be collected but unavailable to clinicians. Improved interoperability between electronic health records (EHRs) and electronic grading systems could alert clinicians to changes in patient grades during appointments.

5.1.2. Self-reporting difficulty

There were several symptoms and triggers that were reported as "difficult" for patients to report as shown in yellow in **Figure 2**. Notably, "Seizure onset at night" and "excessive sleep movements" were said to be "difficult" to report among most epilepsy specialists (five out of six respondents). These findings highlight the inherent difficulty of patient data collection while sleeping or unconscious. Introducing automated wrist-worn devices such as the Empatica E4 [68] and ActiGraph Link [69] could stand to increase patient self-reporting performance by detecting events such as seizure and unusual sleep movements, while also reducing patient and caregiver data collection burden.

5.1.3. Self-reporting reliability

Next, many symptoms and triggers were reported as being useful but unreliable when self-reported as shown in gray in **Figure 2**. All epilepsy specialists (six out of six respondents) agreed that patient and caregiver reports of patient "memory impairment" were "unreliable".

These findings suggest a need for more reliable and simple patient data collection tools. For example, introducing automated data collection tools could help to increase reliability for clinicians by making data collection more accurate and consistent. The forward auditory Digit Span task, WISC-R subtest [70] could be administered as a smartphone unlock screen for periodically assessing short-term memory.

5.1.4. Self-reporting desired frequency

Finally, the majority response for desired patient self-reporting frequency is shown in each column of **Figure 2**. Epilepsy clinicians desired daily reports for over half of all "top 20" indicators (11 out of 20 items). New onset "viral infections" and "status seizures" require immediate medical attention for managing seizure control medications.

Finally, "episodic" patient self-reporting was most frequently desired by psychologists. Many patient behavior changes are highly context driven such as "loss of interest in activities". These findings have implications for displaying patient health dashboards for clinicians within these respective specialties as episodic changes may be more difficult to anticipate than daily, weekly, and monthly data collection on a pre-defined schedule.

5.1.5. Self-reporting challenges

Mental health indicators and patient seizure reports may not always be available to clinicians during pediatric epilepsy treatment.

Most notably, suicide attempts were reported as useful, unavailable, and difficult for patients to collect at monthly intervals by all but one clinician. Medication side effects can often trigger depression and there is a high prevalence of depression among patients with epilepsy. If symptoms are known, then clinicians can consider prescribing a seizure control medication that may be less effective but help to stabilize mood. The main challenge for clinicians is that this type of data is often not available or difficult to collect depending on the patient's age and caregiver situation. For example, a primary caregiver may be knowledgeable of the patient's mental health but a patient may be accompanied by an uninformed family member.

The onset of nighttime seizure reports was also reported as useful, unavailable, and difficult for patients to collect at daily intervals by most clinicians. All respondents indicated that patient reports were unreliable due to age and cognition. This reliability is important for treating and thereby helping to reduce the risk of a condition called sudden unexpected death in epilepsy (SUDEP).

These results suggest the need for more reliable and easy to use mental health and seizure reporting tools. For example, automated weekly or monthly validated mental health surveys such as the Personal Health Questionnaire PHQ-9 [71] could be emailed or assessed in clinic on a tablet to increase reliability when it comes to screening for suicide attempts and depression. Finally, clinicians could suggest that patients wear seizure detection wristbands at night for detecting and reporting convulsive type seizures [41].

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5.2. Part 2: seizure reporting performance and capabilities

Interviews and our literature review and card sorting exercise with clinicians helped us characterize the types of information that neurologists deem to be the most important during typical stages of epilepsy treatment, how likely they are to have access to this information, and the perceived accuracy of patient reports.

Most neurologists reported having access to EEG reports and verbal descriptions of seizures during treatment. However despite this information, neurologist also expressed a need for more and more detailed characterization of patient movement during seizures and more accurate seizure counts over time.

These needs were then further reflected in our literature review as we explored current methods for characterizing motion during seizures and compared existing patient seizure counting performance to current seizure detection systems. Moreover, our online survey results highlighted two important self-reporting challenges. First, there are limited recording and annotation tools available for characterizing patient motion during seizures. Second, seizure detection systems tend to have false positives and therefore over report seizures. Introducing video capture systems that are triggered by wearable seizure detection sensors may prove beneficial in both cases. More accurate seizure data could, therefore, present new opportunities for informing clinical decisions.

5.2.1. Self-reporting needs

Neurologists reported mixed reliance on patient and caregiver reports when making decisions during treatment. In our questionnaire, 70% of neurologists rated patient and caregiver self-reporting as playing a significant role when determining the best course of AED treatment (4 or greater on a scale of 5), however there was considerable in terms of how frequently these initial self-reports included patient movement characteristics during seizures (SD = 1.10) and/or described the evolution of the seizure over time (SD = 0.78). This finding suggests that, while neurologists perceive self-reporting as important, they also emphasize the need for evaluating the validity of patient reports.

5.2.1.1. Informing initial AED selection

Neurologists from our survey indicated that support for characterizing patient seizure type could be beneficial for selecting the most suitable initial AED based on the patient's seizure symptoms. The survey respondents ranked seizure type and movement characterization as the most important information during the initial diagnosis and AED selection phase. Most respondents had access to EEG reports (7/10) and MRI reports (5/10) and verbal accounts of seizures (80%). Less than one-third of neurologists had access to hospital records, imaging records, blood work, seizure diaries, and video of patient seizure events. Most notably, while all neurologists (10/10) expressed a desire for supplemental video only 3/10 respondents had regular access to such video for informing diagnosis and treatment.

These findings stress a need for capturing additional patient information prior to diagnosis and have implications for patient and caregiver data collection efforts. MRI and EEG may not be available for first-time general practitioner referrals. Initial outpatient EEG sessions tend to be short, ~20 min. Moreover, even with routine activation procedures such as patient hyperventilation, photic stimulation, and sleep withdrawal, many patients may not show symptoms during a single visit and require further observation. It may, therefore, be helpful for patients to collect additional seizure observations such as video recordings prior to initial appointments.

5.2.1.2. Informing AED adjustment

Neurologists ranked seizure frequency as the most important patient self-reported information available to them (100% rated 5 out of a scale of 5) for making AED adjustments. Most neurologists (8/10) estimated that patients failed to report between 40 and 60% of seizures overall (given 5 uniform ranges between 0 and 100%). This estimate agreed with Hoppe et al.'s findings that 55% of patients failed to document 55% of seizures overall [9]. Most neurologists also agreed that an ictal description of a seizure is the most difficult for a patient to report, and 66% of the surveyed neurologists said that patients or caregivers report less than 60% of their seizures. It may, therefore, be helpful to introduce seizure detection devices that address specific patient challenges such as nighttime reporting.

5.2.2. Seizure reporting shortcomings

Major shortcomings of current seizure classification and detection technologies include (1) limited capture and playback solutions for characterizing seizure type and (2) inaccurate seizure detection for counting seizures and limited support for identifying seizure types that do not exhibit limb movement.

5.2.2.1. Limited tools for AED selection

The prospect of developing motion characterization tools for informing initial AED selection remains largely unexplored. Efforts have been limited to active and passive motion tracking as additional feedback for EEG technicians [38, 51]. To date, existing research and commercial systems have not focused on the problem of motor characterization for initial partial versus generalized seizure characterization. There is, therefore, a need to utilize additional video and motion tracking technologies for informing AED selection.

5.2.2.2. Inaccurate seizure counts for AED adjustment

Neurologists from our survey agreed that accurate seizure counts are the most important feedback. In our review, inertial seizure detection systems [43, 45, 46, 72] achieved higher performance than embedded mattress devices [55, 65] and multimodal devices [41]. Inertial devices also tend to support daytime use, while mattress and video systems are often limited nighttime use within bedrooms [47, 65].

High false positive rates remain a problem. More accurate seizure counts could better inform AED treatment. We contend that false positives remain a problem despite studies with higher

precision, but fewer numbers of patients [45, 46, 73]. In turn, more work is needed for reducing false positives among all classes that we surveyed. **Table 3** shows that many of the best performing systems utilize video with an average F-score of 0.79 (SD = 0.29) while audio-based systems performed the worse with an average F-score performance of 0.25 (SD = 0.30) with precision as low as 2% for detecting audible lip smacking [61]. High p-values above 0.05 in **Table 3** suggest that mean F-scores for each type of system share a greater than chance probability of performing better than self-reporting at night while low p-values suggest that systems will perform worse than patients during the day on average.

Most systems performed better than patient reporting during the night but notably worse than patients during the day. In our review, all but two systems achieved higher F-score performance at night while only four inertial systems performed better during the day. The average F-score for all systems was 0.59 (SD = 0.29); this reflects a notable improvement over patient self-reporting at night (F-score 0.25) yet remains significantly worse than self-reporting during the day (F-score 0.81). Inertial systems are shown to perform well across both day and nighttime studies [41, 43], however, as noted more work must be done for reducing false alarms during daily activities [40].

High-performance variability was observed between the same types of systems. These discrepancies can largely be explained by the following four contributing factors:

1. **Day versus night:** Many systems were only evaluated at night [55, 65, 73], or strictly during the day, [36] while others were evaluated during the night and day [41–43]. Nighttime studies tended to perform better than daytime studies with an average F-score of 0.62 as compared to 0.56 during studies that included daytime monitoring. This makes direct comparison difficult because daytime seizure detectors must also distinguish non-seizure events such as exercise and teeth brushing which were less prevalent at night. For example, Van De Vel et al.'s [65] evaluation of the Emfit pressure mat highlighted false positives when sitting up in bed, Pisani et al. [47]'s video analysis confused random infant movements, Lockman et al.'s inertial wristband [42] reported false positives during rhythmic activities such as brushing teeth and pen tapping while Poh et al. [41] reported similar false positives during dice rolling and video game activities.
2. **Alerting versus reporting:** Many systems are primarily designed for alerting caregivers rather than accurately reporting seizure counts. Existing commercial systems are designed for alerting caregivers to ongoing seizures [43, 53, 67]. The caregiver is often burdened with adjusting system-specific threshold settings for minimizing false positives [51, 74–75]. This, in turn, may result in missing facial tics and other less apparent symptoms.
3. **Patient age:** We observed considerable variation between the age and number of patients enrolled in studies. For example, Cuppens et al. [73] and Lockman et al. [42] each developed similar inertial-based systems, however, Cuppens et al. [73] studied patients aged 5–16 while Lockman et al. [35] studied ages 3–85. It may be reasonable to expect that differences in muscle development and limb length between these age groups could have resulted in slightly different movement characteristics during seizures.
4. **Patient count:** The number of patients with seizures also varied between studies with a single patient having seizures at night. For example, seven studies had less than four

participants [45, 62, 63, 65, 76–78]. Van De Vel et al. [65] and Narechanie et al. [64] each evaluated pressure sensing mattress inserts, however, Van De Vel et al. [65] included only 1 patient with an F-score of 0.78 while Narechanie et al. [64] included 51 patients with a perfect F-score of 1.0 for reporting seizure counts at night.

5.2.2.3. Limited diversity of seizure types

Most patients have focal types seizures (70%>50%) [80, 81]; however, only some but not all focal seizures involve limb movement. This presents a challenge as most systems to date are limited to measuring seizures based on limb movements. More reliable metrics or a combination of metrics should be studied for capturing non-motor seizure symptoms.

To date, there has been limited work on detecting seizures using non-inertial and video sensors. Bruijne et al. analyzed [61] audio for detecting "lip smacking" and "screams" however; the performance was among the poorest of all the systems that we evaluated (F-score = 0.04). To the best of our knowledge, there are no non-EEG devices for detecting symptoms (e.g. subtle face or hand movement during partial seizures or behavioral arrest).

Inertial seizure detection wristbands [43] and nighttime video recording could provide a promising short-term solution for increasing the accuracy of patient reporting. Most patients are seen by a general practitioner and are later referred to see a neurologist [79]. This gap presents an opportunity to equip patients with data collection systems for detecting and recording patient seizures in the home prior to an initial neurology visit. For example, the open source OpenSeizureDetector [52] inertial wristband could be used in conjunction with an already available and bedroom instrumented camera such as the SAMi [49] or OpenSeizureDetector [50] detect seizures and trigger video recording. In turn, neurologists could review video for characterizing the seizure prior to treatment. Movements during seizures could be captured and reviewed.

Finally, seizure reporting video annotation tools could enable patients, caregivers, and neurologists to label the start and stop of seizure events could improve seizure detection performance over time and address the problem of having to manually adjust thresholds as in commercial products [42, 43] as the system will be trained for a particular individual.

6. Conclusions

The role of clinical patient self-reporting is important yet often undocumented in literature. Health tracking technologies such as wrist-worn seizure detection devices stand to play an increasingly important role in epilepsy treatment and diagnosis as data collection tools that can help patients and caregivers to collect self-report seizure counts and other high priority health indicators for informing clinical decision-making.

In this paper, we conducted a multiphase study that included interviews with clinicians, two literature reviews, a card sorting exercise and online surveys for investigating clinical patient self-reporting needs within the context of epilepsy diagnosis and treatment. In our work with clinicians, we identified a need for more reliable mental health reporting

and sleep indicators during epilepsy treatment. In our technology review, we surveyed seven types of seizure detection sensing modalities and identified a strong need for more accurate and reliable seizure reporting and motion characterization during diagnosis and treatment.

The key challenges faced by technology developers and providers are:

1. Identifying the specific types, priorities, and characteristics of data that clinicians need from patients.
2. Establishing the extent that current health tracking devices are suitable for addressing these needs is similarly unknown.

The findings from our research highlighted important patient self-reporting needs among a diverse set of clinicians for epilepsy diagnosis and treatment and in turn, may provide clinicians and technology developers with a useful reference for aligning development efforts with clinical information needs within epilepsy treatment. High false positives remain a problem for seizure detection devices; however low-cost hardware may be able to mitigate these issues. For example, inertial sensors [42] and the bedroom instrumented camera [49] could be sent home with patients prior to treatment; such a combination of tools could be vital information aiding neurologist in how best to treat the patient.

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Chapter 5

Psychogenic Nonepileptic Seizures in Patients Living with Neurocysticercosis

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Additional information is available at the end of the chapter

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Abstract

Very little is known about psychogenic nonepileptic seizures (PNES) in patients with cysticercosis in the brain. We review the available medical literature on PNES in patients with neurocysticercosis and found no reports on this matter apart from our publications. Based on our previous experiences with patients presenting neurocysticercosis and associated epileptic seizures and/or PNES, we compared our results with the current advances published up to date. We also discuss the available information about epidemiology including frequency and prevalence, the role of sexual abuse on the ethiopathogenesis of PNES, clinical diagnosis and its differential diagnosis, laboratory investigations and video electroencephalogram, methods to induce PNES, medical treatment, and psychological intervention.

Keywords: psychogenic nonepileptic seizures, epileptic seizures, epilepsy, neurocysticercosis, epidemiology, diagnosis, video electroencephalogram, treatment and ethical aspects

1. Introduction

Neurocysticercosis (NCC) is a parasitic disease of central nervous system (CNS) caused by the larval stage (cysticercus cellulosae) of the pig tapeworm *Taenia solium*. This parasite is the most common helminthes to produce CNS infection in humans. The presence of acquired epilepsy in a person from an endemic region for cysticercosis or even in one living in close contact with patient who have taeniasis should suggest a diagnosis of cysticercosis of the CNS; the NCC

may remain asymptomatic for months to years, and sometimes its diagnosis is made incidentally when CT/MRI scan is done. Symptoms and signs are related both to the parasite and to the inflammatory-immunological response of the host but in almost all symptomatic patients, headache and epileptic seizure (ES) are the most frequent problem. NCC is the most common cause of acquired epilepsy worldwide and most of the patients taking first line antiepileptic drugs (AED) respond very well [1]. For interested people, other aspects concerning to NCC are available online [2].

NCC is a common parasitic disease of the brain in developing countries. The clinical and pathologic features of NCC vary depending on the inflammatory/immune response around cysticerci, their number, size, and localization. Inflammation around degenerating cysticerci may have severe consequences, including focal encephalitis, edema, and vasculitis. NCC can cause a wide variety of clinical syndromes from chronic meningitis and cranial nerve palsy to spinal infarction and symptoms due to either as mass effect or, particularly in racemose disease, raised intracranial pressure.

Almost all patients living neurocysticercosis (PLNCC) have epileptic seizures (ES) due to this zoonotic parasitic infection [2]. However, an important number of those epileptic patients also present psychogenic nonepileptic seizures (PNES) because epileptic and nonepileptic seizures are not mutually exclusive phenomena and may coexist in the same patient. PNESs are defined as change in behavior or consciousness resembling epileptic seizures but which have a psychological origin. PNESs are categorized as a manifestation of dissociative or somatoform (conversion) disorders. Predisposing, precipitating, and perpetuating factors should be carefully assessed individually. The complex process of communicating the diagnosis to patients and their relatives using a multidisciplinary approach is an important and effective therapeutic step than should be performed by good skilled physician. Video-EEG (vEEG) recording of an event is the gold standard for diagnosis [3], but in many developing countries where NCC is endemic, this technology is not available.

To distinguish ES from PNES, an accurate clinical assessment is mandatory apart from other technologies. Frontal lobe seizures can be mistaken for PNES, though these tend to have shorter duration, stereotyped patterns of movements, and occurrence during sleep in spite of vEEG technology. Sometimes, elevated blood levels of serum prolactin following most tonic–clonic or complex partial ES can support a diagnosis, but because the frequency is false positive, it is not a gold standard test. The psychological mechanisms underlying PNES are poorly understood, and there is a lack of well-established, evidence-based treatments [4].

To differentiate PNES from ES in PLNCC is an important challenge for neurologists, epileptologists, internists, and pediatricians but even more for general practitioners and family doctors. PNESs, also known as nonepileptic attack disorders, are events resembling an epileptic seizure but without the characteristic electroencephalophic anomalies associated with epileptic seizures. They are common in neurological settings and often associated with considerable distress and disability.

Brown and Markus described PNES (nineteenth century), as *seizure-like attacks not related to an identified central nervous system lesion*, and are currently classified as a conversion disorder,

according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [4]. While a universally accepted and unifying etiological model does not yet exist, several risk factors have been identified. Management of PNES should be based on multidisciplinary collaboration, focusing on modifiable risk factors. The first priority in the management of PNES is patient engagement that is challenging given the demonstrated low rates of treatment retention [4]. The differential diagnosis of PNES firstly involves ruling out epilepsy as the cause of the seizure episodes, along with other organic causes of nonepileptic seizures, such as syncope, migraine, vertigo, stroke, faking ES, and malingering.

Are psychogenic nonepileptic seizures just another symptom of conversion disorder?

Some authors argue that the etiological and mechanistic distinctions they support, particularly when bolstered by additional data, give reason to sustain a separation between these conditions [5].

In 2003, an international consensus group of clinician-researchers in epilepsy, neurology, neuropsychology, and neuropsychiatry from the International League Against Epilepsy Nonepileptic Seizure Task Group collaborated with the aim of developing clear guidance on standards for the diagnosis of PNES. Because the gold standard of vEEG is not available in many countries, and for every patient, the group delineated a staged approach to PNES diagnosis. Using a consensus review of the literature, this group evaluated key diagnostic approaches. These included history, EEG, ambulatory EEG, vEEG/monitoring, neurophysiologic, neurohumoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis. Levels of diagnostic certainty are developed including possible, probable, clinically established, and documented diagnosis, based on the availability of history, witnessed event, and investigations, including vEEG. The aim and hope of this report are to provide greater clarity about the process and certainty of the diagnosis of PNES, with the intent to improve the care for people with epilepsy and PNES [6].

There is no general scientific consensus as to what causes PNES. However, some physicians [7] *believe* that *the condition may be triggered by psychological problems (irrespective of whether the patient shows any obvious psychological distress or pathology). It is estimated that 20% of seizure patients seen at specialist epilepsy clinics have PNES.*

Other author [8] believes that *PNES can significantly affect an individual's quality of life, the health care system, and even society. The first decade of the new millennium has seen renewed interest in this condition, but etiological understanding and evidence-based treatment availability remain limited. After the diagnosis of PNES is established, the first therapeutic step includes a presentation of the diagnosis that facilitates engagement in treatment.*

To date, only very narrow aspects of ethical dilemmas in PNES have been explored, but without doubt, the most important ethical values at stake include trust, transparency, confidentiality, professionalism, autonomy of all stakeholders, and justice.

> *Recently, Gul and Ahmad [9] "demonstrated cognitive impairment in terms of the interrupted ability to switch between emotion and non-emotion face categorizations in patients with PNES. In contrast, healthy individuals exhibited efficient switching between these face categorizations. They also found in patients with PNES, an asymmetric relationship between*

emotion and age tasks, while this asymmetry was absent in the healthy group. Their results demonstrated that patients with PNES used expressive suppression to regulate their emotions more frequently than the control group and on the other hand, patients with PNES less frequently reappraised their cognitions than healthy individuals. This is the first study demonstrating the presence of switching deficits in terms of inferior cognitive control of emotion in patients with PNES as compared to healthy individuals".

PNESs are relatively common, accounting for 5–40% of visits to tertiary epilepsy centers. Inpatient vEEG monitoring is the gold standard for diagnosis as mentioned before, but additional positive predictive tools are necessary given vEEG's relatively scarce availability. Robbins et al. [10] investigated *if the number of patient-reported allergies distinguishes between PNES and epilepsy, using electronic medical records, ICD-9 codes, and text-identification algorithms to search EEG reports, and they identified 905 cases of confirmed PNES and 5187 controls with epilepsy but no PNES. Patients with PNES averaged more self-reported allergies than patients with epilepsy alone (1.93 vs. 1.00, $p < 0.001$).* They concluded that *"long allergy lists may help identify patients with PNES and hypothesize that a tendency to inaccurately self-report allergies reflects a maladaptive externalization of psychologic distress and that a similar mechanism may be responsible for PNES in some patients with somatic symptom disorder".*

Many patients with PNES dismiss the idea that their seizures are psychogenic, especially if the correct diagnosis comes after many years of treatment for epilepsy [11].

Outcomes in PNES are generally poor: 71% of PNES patients continue to have seizures 4 years after diagnosis and 56% are dependent on Social Security assistance. Neurologic and psychiatric factors associated with poor outcome include:

- history of epilepsy
- abnormal MRI
- presence of a psychiatric diagnosis
- age > 30
- duration of illness (the longer the patient has been treated for epilepsy, the worse the prognosis) [11].

In Diagnostic and Statistical Manual of Mental Disorders, fifth edition, "PNES do not have a unique classification as they can be found within different categories: conversion, dissociative, and somatization disorders. The ICD-10, instead, considers PNES within dissociative disorders, merging the dissociative disorders and conversion disorders, although the underlying defense mechanisms are different" [12].

Last year, some authors conducted 140 empirical studies on the following aspects of PNES: life adversity, dissociation, anxiety, suggestibility, attention dysfunction, family/relationship problems, insecure attachment, defense mechanisms, somatization/conversion, coping, emotion regulation, alexithymia, emotional processing, symptom modeling, learning, and expectancy, and they concluded that:

> *"physical symptom reporting is elevated in patients with PNES; trait dissociation and exposure to traumatic events are common but not inevitable correlates of PNES; also, concluded that there is a mismatch between subjective reports of anxiety and physical arousal during PNES; and inconsistent findings in this area are likely to be attributable to the heterogeneity of patients with PNES"* [4].

The main goal of this chapter is to compare our finding from 2003 with recent investigation on PNES to identify new knowledge and challenges.

1.1. Our study

In 2003, we studied 32 rural patients from the poorest regions in Mthatha (South Africa), diagnosed as epilepsy due to NCC presenting PNES. We found that the common clinical characteristics of this series and its psychological profile were duration of events, history of sexual abuse in females, absent of focal neurological signs, vocalization in the middle of the seizures, and lack of postictal symptoms were very useful for its differential diagnosis and the possible difference between the clinical features and psychological profile of those patients and others without PNES. Finally, some advices for the management of this condition by family doctors were delivered [13].

As mentioned [14–16], PNES *are sudden changes in behavior that resemble epileptic attack but lack organic cause and are also known by conversion seizures, dissociative seizures, hysterical seizures, psychogenic seizures, and nonepileptic seizures.* They are quite often misdiagnosed and represent the opposite end of the spectrum from seizures that mimic psychiatric disorders without organic cause and an expected EEG changes. Accurately distinguishing PNES from EP and other illnesses is difficult because of the breadth and overlap of symptoms seen in each condition and the frequent co-occurrence of PNES and epilepsy [14].

There is a general consensus about subjects with PNES that exhibited trauma-related profiles which differed significantly from those of epileptic comparison subjects and closely resembled those of individuals with a past medical history of traumatic experiences [15–17]. As we published, PNES patients frequently report a history of physical and sexual abuse, and traumatic experience is considered part of the mechanism for producing dissociation and may be a manifestation of dissociative disorders, especially when a history of sexual or physical abuse is documented [18]. In our region, sexual abuse is more frequently seen among members of the same family.

At the present moment, there exists a controversy regarding the significance of dissociation and conversion in the pathogenesis of PNES. Soon after the elimination of the term "hysterical neurosis" from the current diagnostic systems, these kinds of seizures were diagnosed as either Dissociative Disorders (ICD-10) or in the DSM IV as Somatoform disorder, most often conversion type.

> *"The significantly higher incidence of dissociation in the patients with PNES suggests dissociation in the pathogenesis of these seizures"* [13].

Significant advances have been made in the diagnosis and treatment of epilepsy before 2003. With the introduction of vEEG monitoring, physicians are now able to reliably differentiate epilepsy from other conditions that can mimic it, including PNES. Many new AEDs have become available in recent years. The ketogenic diet is another treatment option in certain types of epilepsy and the vagus nerve stimulator, approved in 1997, represents another treatment modality for refractory epilepsy, and finally epilepsy surgery is an effective treatment for those patients with uncontrolled epilepsy.

Our study was performed at the former Transkei which was one of the three administrative authorities of the so-called independent South African homelands (Ciskei, Transkei, and the Cape Provincial Administration under different apartheid governments). It is currently named as region D and E of Eastern Cape Province, and it is also one of the poorest region of the country. That region serves as a labor reservoir for other wealthier provinces, with men leaving behind women and children, while they seek and find employment elsewhere. Our region has the most elevate indices of poverty and underdevelopment and shows a remarkable limited access to employment, cash income, primary education, safe and clean water, proper toilet facilities, proper refuse disposal, electricity, and telecommunication. Some communities still do not have easy access to any health care facility.

The aim of this study was to identify a psychological profile of a group of patients with epilepsy NCC-related presenting PNES and to detect the possible difference between the clinical features and psychological profile of patients affected by PNES and ES NCC-related and those patients in whom EPs are associated with NCC only and have been reported earlier [19–25].

We included female and male patients [13]. In this region, people beyond age of 13 are considered as adults. Therefore, people aged 13 years and older who had all developed EP fulfilling the International League Against Epilepsy criteria for epilepsy and the radiological criteria for calcified NCC (considering multiples intraparenchymal calcifications measuring between 2 and 10 mm in patients from endemic regions as pathognomonic) were selected, and others experienced more than one attack of PNES per month. Patients were excluded due to the following reasons: seizures caused by clear precipitants such as alcohol or hypoglycemia; we also excluded patients with previous medical history of head injury, syncope, stroke, brain tumor, cortical dysplasia, hyponatremia, hypomagnesaemia, hyperparathyroidism, cardiac arrhythmias, heart failure, and history of medication taken on the past 6 months such as theophylline, meperidine hydrochloride, isoniazid, antipsychotic drugs, alkylating agent, beta-lactam antibiotics, tricycle antidepressants, acyclovir, beta-blockers, and decongestants; also pregnant or breastfeeding women and patients with any medical condition that might interfere with the interpretation of the results of this study. At screening, all patients had a physical examination, including a detailed neurological examination done by one of us (FSH), routine laboratory test including hematology, urinalysis, urea, and electrolytes, glucose, plain skull X-rays, CT scan of the head, and a 32-channel digital EEG (Nihon Khoden) for 30 minutes recording using opening and closing the eyes and 3 minutes hyperventilation as activating maneuver.

Seven patients presented PNES that we could not distinguish clinically from EP; therefore, their anticonvulsant medication was rapidly tapered to provoke seizure; if the seizure did not develop, other serial maneuvers including 24 hours' sleep deprivation followed by

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hyperventilation and suggestion with intravenous saline injection were done. Diagnosis of PNES was considered when their seizures did not change the background EEG activity under observation plus others clinical features of PNES. All patients granted written informed consent before entering the study [13].

All patients presented radiographic signs of active and/or calcified NCC on CT scan (**Figure 1**), and signs of other stage of the parasite were also observed but the predominant finding was no less than five calcified lesions fulfilling the radiographic criteria for calcified NCC at the brain parenchyma. In this series, 37% of patients (all women) were on disability grant program for epilepsy, and that cash income was the only way for alleviating their requirements and poverty; however, evidence of malingering on this group was not be identified [13].

About 85% of the studied female patients were single mothers or married women living alone with their children, while their husband was working in gold mines very far away from home and only contact between them happened on December every year.

A total of 17 female patients from our series complained of a previous history of sexual abuse, and 14 of them physical abuse as well. Members of their own family raped 10 women, and 11 mentioned other members of their families that have had been raped during their early youth. According to information obtained from this group, some families suffered deeply when one of their members was raped and six people (not included in this series) were also murdered. Usually their father or the mother became chronically depressed, alcoholic, and their socioeconomic situation became remarkably deteriorated; for five patients to talk about this topic was rejected, and each refused to accept psychiatry or psychological referral because of financial or

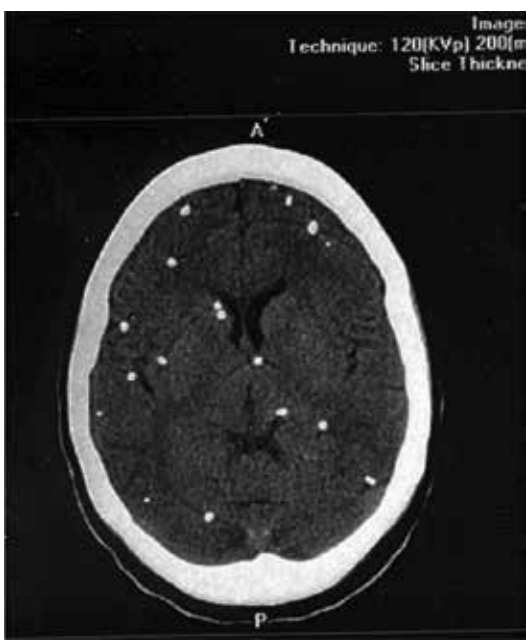

Figure 1. Bilateral calcified NCC lesions on CT scan of the brain.

transportation's problems (25%) because they did not consider it necessary (18%) or for other reasons. About 38% got injuries on both group including tongue biting [13].

Maximal duration of tonic-clonic ES was 95 seconds and for PNES was 904 seconds, and minimal duration was 45 seconds for EP and 18 seconds for PNES. See **Table 1**.

Psychic manifestations were present in different group: frontal lobe epilepsy (FLE), tonic-clonic generalized (TCG), partial complex motor seizure (PCS), and PNES: Rocking: PNES = 47, FLE = 63; PCS = 18, TCG = 5; Kicking: PNES = 60, FLE = 75, PCS = 21, TCG = 0; Cursing PNES = 54, FLE = 35, PCS = 47, TCG = 0; Babinski: PNES = 0, FLE = 65, PCS = 76, TCG = 83; Pelvic thrusting: PNES = 57, FLE = 0, PCS = 63, and TCG = 5; and other dissociative symptoms of depersonalization and deserialization were present only in patients with PCS/PNES (see **Tables 2** and **3**).

No changes of the background activity on the EEG during provocative saline infusion and the occurrence of PNES were seen.

In general, patients complained of PNES revealed higher percentage of Somatoform Disorders and Cluster B Personality Disorders. The occurrence of PNES mimicking generalized tonic-clonic ES was documented only on illiterate peoples.

Three patients complained of auditory hallucinations, two had focal complex motor seizures as well, and the third one presented TCG seizures and paranoid schizophrenia; all presented calcified NCC on the basal ganglia without active or calcified lesion of NCC on the temporal lobe. EEG under provocative saline solution done in two patients did not show changes on the background activity during the test (**Figure 2**).

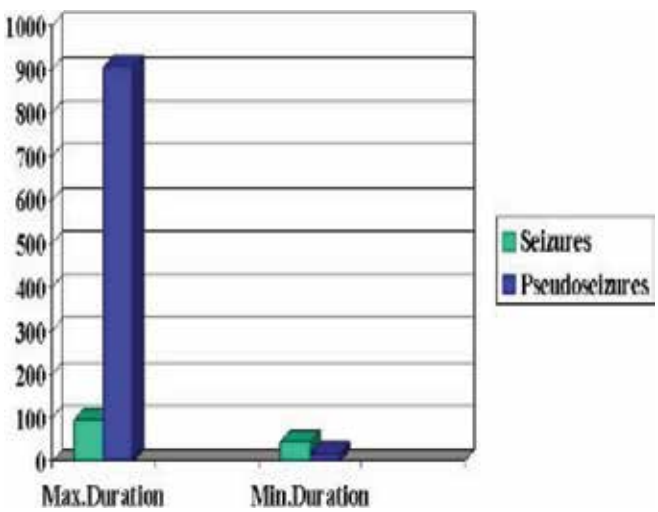

Table 1. Duration of the events in seconds.

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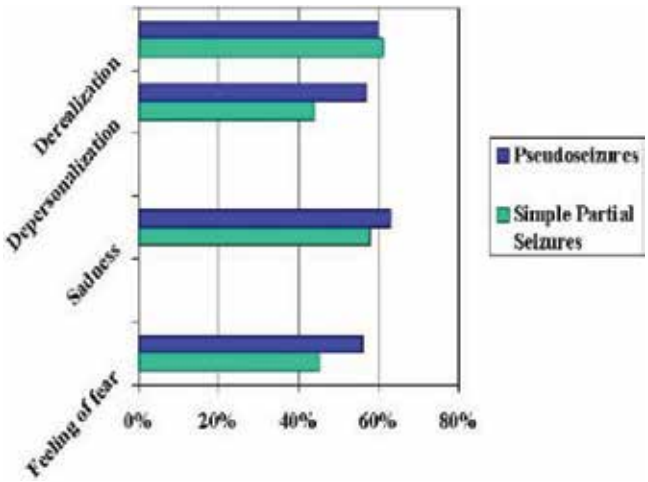

Table 2. Psychic manifestations in both groups.

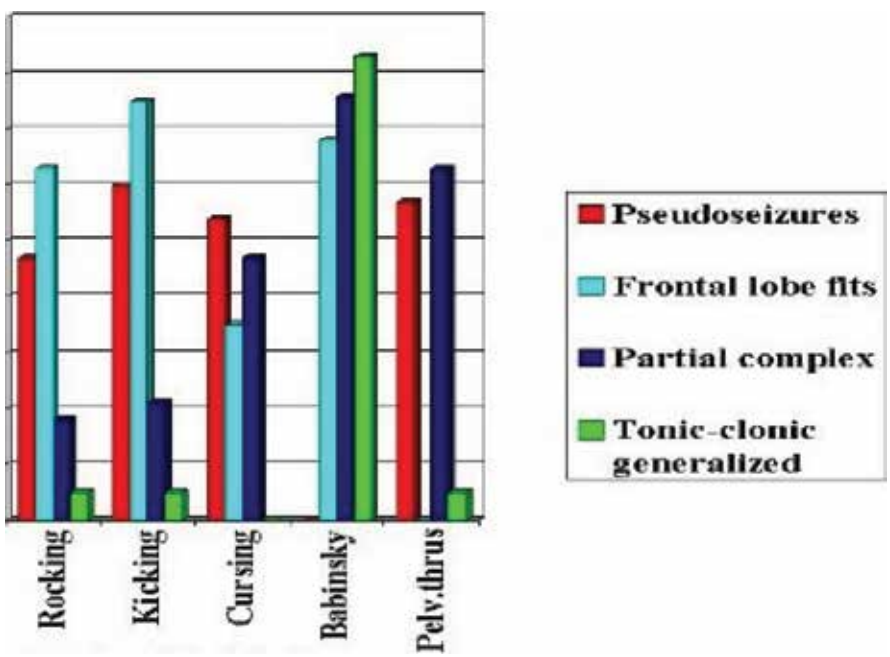

Table 3. Frequency of clinical signs during the event.

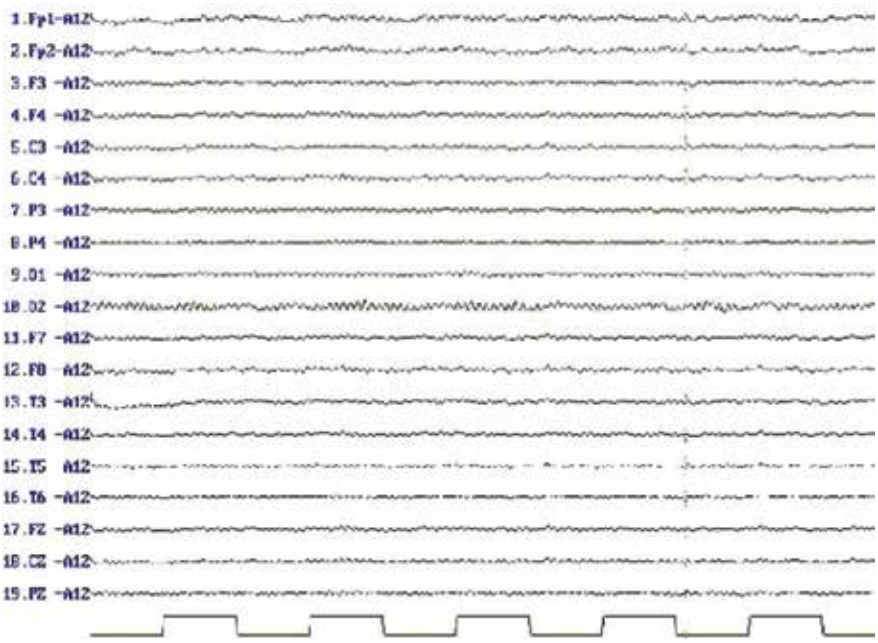

Figure 2. No changes of the background activity on the EEG during provocative saline infusion and the occurrence of PNES.

In Transkei, ES are the commonest clinical expression of calcified NCC followed by headache as it had been reported by us previously [19–40], but the associated PNES is related with other functional disturbances which were not usually present in patients with epilepsy and NCC alone, although some cases have been reported [41–43].

In temporal lobe epilepsy, some symptoms such as reactive automatisms and subjective abnormal sensations are difficult to differentiate from dissociative symptoms of depersonalization, derealisation, and alteration of consciousness, which can be misinterpreted as symptoms of ES; for the other hand, some nonspecific EEG abnormalities and possibly structural NCC findings can contribute to reinforce this diagnostic impression; therefore, when they are present, despite the absent of other reliable diagnostic tools, both "organic" and "functional" disturbances should be treated at the same time [13].

> *"Bilateral motor seizures with retained consciousness are rare and often mistaken for PNES* [42]. *When a realistic threat of physical or sexual assault to a member of their family involved in the problem is revealed, is important the role for family therapy skills in the evaluation and treatment of PNES"* [43].

Some patients did not improve from the occurrence of PNES probably because of lack of more specialized treatment, and others did not discontinue their treatment including AED, in spite of our personal agreement, probable because of fear to loss their disability grant among other reasons and also because of ignorance, superstitions, and poor health education. Many patients

found solace in becoming and remaining neurological ill; thus, defense mechanism of denial, dissociation, introjections, identification, and symbolization contributed to the patient's symptom picture and to their adaptation to traumatic life events.

> *"Bringing the unconscious psychotic elements into conscious awareness is an important aspect of the treatment of dissociative disorders* [44] *and may be assayed by family physician if there is no other choice".*

Using AED in patients with PNES before its confirmation was a common problem in other series [45] but not for us because all patients from our series also presented ES and then were treated accordingly.

> *"Auditory hallucinations, are paradigmatic symptoms of the schizophrenic patients, and can be present in disorders such as: Alzheimer's disease, epilepsy, deafness, tumors of the temporal lobe, and toxic psychosis, usually due to disturbances of the left temporal lobe, limbic, and paralimbic areas. We could not have demonstrated the source of the hallucinations in our series but based on our observations we have hypothesized that hallucinations could be secondary to hyperactivity of the basal ganglia (thalamus and striatum) since that mechanism was before-published"* [46].

Malingering is an accusation, and the people have intentional and obvious goals, such as to get financial benefits or avoidance of duty or school, to reach better position in penitentiary, evasion of criminal prosecution, obtaining of drugs or compaction among other. These goals may resemble secondary gain in conversion symptoms but with the distinguishing feature being the conscious intent in the production of the symptoms.

Why more ladies than gentlemen in our series? Because there are more females than males living in Transkei (due to temporal migratory reasons) and also because women are more susceptible than men to develop this kind of somatoform disorder therefore increased incidence and prevalence of PNES is expected. Charcot and Freud [47] *emphasized the sexual aspects of the seizure as has the current interest in childhood sexual abuse.* Major mood disorders and severe environmental stress, especially sexual abuse, were common problems among our patients and they were considered in every case. From case studies and review of the medical literature, we believe that PNES in women express rage, fear, and helplessness against the dominant and abusive male rather than sexual conflicts. *Emphasizing the aggressive component of seizures does not minimize the traumatic effects of sexual abuse but rather includes it as leading to rage and helplessness* [13].

We performed EEG under provocative suggestion and intravenous (IV) normal saline solution in a small number of patients only because we consider that deceptive diagnostic tests are justified only in exceptional situations [13]. The use of provocative IV normal saline solution in that way is fundamentally deceptive, requiring the physician to intentionally and directly lie to the patient and causing the patient to believe that the administered solution caused his seizures, provocative saline infusion compromises the fiduciary obligation of truthfulness, is inimical to patient autonomy, is undignified, and risks grave harm to patient trust in physicians; however, if no deceptive alternatives are not available and the difficulty of distinguishing malingerers cannot be solved,

then we have not choice and deceptive diagnostic testing should be implemented. Without such deception, the test might be useless [48].

From our personal experience, sometimes those patients have to be treated by family physicians. Under those circumstances, we strongly recommended being very patient, very kind, and also very gentle, we advise do not accuse anybody of malingering or deliberately faking the seizures under any circumstances and always advised to get counseling. We suggest do not forget they inability for controlling their PNES and for proper socialization and its impact on their families, friends, and other members of the community. We learned that it is a good practice to understand their disabilities and frustrations and to identify their hopes. It is very important to define the underlying causes and the triggering factors for PNES such as rage, fear, and panic among others and to contribute in the healing process of emotional hurts and their emotional control; to provide an ideal psychological support and to address an adequate management of stress, emotional upset, or physical illness are also recommended; do not named those patient as hypochondriac and to explain clearly why they are unaware of the source contributing to the events, when it will be appropriated [13].

> *"When patients are having PNES to keep them safe, just as would be done when they are having ES is strong recommended, if the diagnosis of PNES is clear-cut then leaving the patient alone until it is over, keeping the environment calmed and free of starling noises is the best choice".*

When the clinical event of PNES is over, try to elicit some kind of respond from the patient. Never use suggestions by hypnotic procedures if you have not enough expertise.

Physical abuse on patients having PNES must be damned forever. It is very successful to encourage patients for exploring their own feelings and assisted in learning to cope with the feelings in new ways. Patients with history of attend to suicide were not suitable for this group. If there is not a good response in a due time, the diagnosis must be revised.

The clinical differentiation of PNES from epileptic attacks in patients with NCC is particularly difficult and sometimes almost impossible, if 24-hour video-EEG monitoring techniques are not available, but duration of events, history of sexual abuse in females, focal neurological signs, vocalization in the middle of the seizures, and lack of postictal symptoms can be very useful for its differential diagnosis. However, if the patient presents PNES, temporal lobe epilepsy, other types of epileptic seizures because of NCC, and some associated conditions such as factitious disorder and malingering, then confirmation PNES cannot be reached. *Under exceptional circumstances those patients can be treated by their family physician if some specialized advices are adjusted*.

In summary, we review the commonest clinical features in PLNCC presenting PNES and epileptic seizures in our series of patients. To differentiate ES from PNES or vice versa, clinical psychiatric and neurological knowledge are mandatory; however, if both manifestations are present on the same patient other diagnostic tool should be required. We conclude that:

> *"Some features are more or less likely to suggest PNES but they are not conclusive and should be considered within the broader clinical picture. Features that are common in PNES but rare*

in epilepsy include: biting the tip of the tongue, seizures lasting more than 2 minutes (easiest factor to distinguish), seizures having a gradual onset, a fluctuating course of disease severity, the eyes being closed during a seizure, and side to side head movements. Features that are uncommon in PNES include automatisms (automatic complex movements during the seizure), severe tongue biting, biting the inside of the mouth, and incontinence. If a patient with suspected PNES has an episode during a clinical examination, there are a number of signs that can be elicited to help support or refute the diagnosis of PNES such as: normal size of the pupils, pupillary reflexes, cutaneous plantar reflexes, and caloric test" [13].

2. PNES at the present moment

2.1. Definition

Despite the terminology of "*pseudo seizures*" is obsolete, some authors still using that at the present moment and define PNES, as paroxysmal episodes that can be similar to ES and can be misdiagnosed very often by general physician and medical officers. It is important to highlight that PNES are psychological disorders such as emotional or stress-related events

"Paroxysmal nonepileptic episodes can be either organic or psychogenic. Good examples of organic nonepileptic paroxysmal symptoms are migraine, syncope and transient ischemic attack (TIA). The terminology on the topic has been variable and, at times, confusing. Various terms are used, and apart from pseudo seizures, another such as: nonepileptic seizures, nonepileptic events, and psychogenic seizures" [49],

and PNES, followed by nonepileptic event(s), psychogenic attack(s), nonepileptic attack(s), and psychogenic nonepileptic attack(s) in Google and PubMed Google and in PubMed using multiple search terms (https://www.google.com and http://www.ncbi.nlm.nih.gov/pubmed). The broad spectrum of synonyms used to refer to PNES in the medical literature reflects a lack of internationally accepted and uniform terminology for PNES. In addition to "seizure(s)," lay people use the word "attack(s)" to describe PNES [49, 50].

PNES has been the preferred term in the literature, but in practice, the term "seizures" is confusing to patients and families [49]. Other authors consider that PNESs are the most common paroxysmal event misdiagnosed as epilepsy, and they significantly affect quality of life, functional status and use of medical resources [51, 52].

By definition, PNES is a psychiatric disorder; more specifically, it is a conversion disorder, which falls under the diagnostic category of somatic symptom disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The specific *DSM-5* criteria for conversion disorder are:

One or more symptoms of altered voluntary motor or sensory function:

- Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.

- The symptom or deficit is not better explained by another medical or mental disorder.
- The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

According to the *DSM-5* classification, neurological symptoms that are found, after appropriate neurological assessment, to be incompatible with neurological pathophysiology can fall under conversion disorder, factitious disorder, or malingering [49].

The immobility, loss of independence, and anxiety that occurs during the monitoring process using vEEG can be difficult for older adults [53]. PNES is also a remarkably challenging and complex medical condition that gives rise to a number of ethical issues with which even the most skilled clinician struggles [54].

> *"Seizures can be divided into three major categories: epileptic seizures (ES), PNES, or physiologic nonepileptic events"* [55].

Like epileptic seizures, PNES present as paroxysmal time-limited, alterations in motor, sensory, autonomic, and/or cognitive signs and symptoms, but unlike epilepsy, PNES are not caused by ictal epileptiform activity. In contrast to ES, which are a manifestation of excessive and hypersynchronous discharges in the brain, PNES have psychologic underpinnings and causes. Physiologic non-epileptic evoked seizures are neither epileptic nor psychogenic, rather they are events associated with systemic alterations that produce an ictus (e.g., convulsive syncope or hypoglycemic seizure) [56, 57]. PNES occur across cultures worldwide. Events described as PNES and occurring in a similar context to PNES seen in industrially developed countries are reported from threshold or developing countries, as well. PNES therefore seem to represent a fairly universal human condition. The semiology is described similarly across ethnicities and cultures [57].

As is very well known, functional neurological disorder (conversion disorder) is a neurobehavioral condition frequently encountered by epileptologist, neurologists, and family physicians.

> *Observational research studies "suggest that PNES and Functional Movement Disorders may represent variants of similar (or the same) conditions given that both groups exhibit a female predominance, have increased prevalence of mood-anxiety disorders, frequently endorse prior abuse, and share phenotypic characteristics"* [55].

Physical and neurologic findings are usually normal, but the examination can also uncover suggestive features. For example, overly dramatic behaviors, give-way weakness, and a weak voice or stuttering can be useful predictors. Psychological features suggestive of psychogenic episodes include anxiety, depression, inappropriate affect or lack of concern (*la belle indifference*), and multiple and vague somatic complaints suggestive of somatization disorder, and abnormal interaction with family members [49].

2.2. Gender

PNES are more prevalent among women worldwide and we also find similar results in our series. However, Asadi-Pooya et al. [57] investigated the potential differences in demographic

and clinical characteristics of PNES between women and men from Iran in 2013 and they did not observe any significant differences between women and men with PNES with regard to demographic, clinical, and semiological characteristics. Likewise, seizure characteristics and semiology were very similar in both genders. It appears that an Islamic lifestyle (in Iran) has little influence on the sex ratio and clinical manifestations of PNES compared with the Western studies. For the other hand,

> *Gale et al.* [58] *compare males with PNES to females with PNES and to males with epilepsy and they concluded that gender difference in PNES seizure semiology was associated with whether or not clinically significant somatic symptoms were present; males with elevated somatic symptoms were much more likely to have motor PNES*.

However, they did not find evidence of greater psychopathology in males with PNES compared to females. Gender differences in the behavioral manifestation of PNES in the context of presence or absence of somatization may have implications for diagnosis and treatment.

2.3. Epidemiology

PNES is by far the most frequent nonepileptic condition seen in general hospital, neurological institutions, and epilepsy clinic, where they represent 20–30% of referrals. About 50–70% of patients become seizure free after diagnosis, and about 15% also have epilepsy [49]. Similar to conversion disorders, PNES typically begin in young adulthood and occur more frequently in women (approximately 70% of cases) than in men as we found in our study. Although very rare, PNES can also occur in elderly peoples. According to most authors (ourselves included), the combination of ES and PNES occurs in around 10% of patients with PNES. Some cautious should be taken in diagnosing PNES when the onset is in early childhood or elderly peoples. In young age groups, nonepileptic physiologic events may be more common than other organic conditions. Recurrent hospital admissions with apparent seizure status or daily convulsive events suggest PNES, especially when reported by a well and fully conscious patient [59].

> *Studies on the prevalence of PNES show variable but clinically significant results, from 5 to 33% of outpatients receiving treatment for epilepsy, and from 10 to 58% of inpatients treated for refractory epilepsy present PNES* [60].

According to Gates [55] such *a significant difference in results may be explained by differences in diagnostic criteria for PNES. A female preponderance of up to 80% has been observed in studies of patients with PNES* [50–62]. PNES is present in children and elderly people, but many patients' ages range between the 1920s and 1930s [62–64].

The incidence of PNES in our population was 6.45/100,000/year higher than in previous studies.

Duncan et al. [65] found an incidence of 4.90/100,000/year which is also high and the median diagnostic delay was 0.6±0.2 year. About 50% of their patients diagnosed early became spell free immediately or soon after diagnosis. There were high rates of psychological morbidity, medically unexplained symptoms, and economic dependence before or at the time of onset, and the early outcome was predicted by employment status.Other authors consider that

PNESs are diagnosed in at least 10–40% of the patients seen for long-term monitoring of epilepsy, and it is no surprise that patients with PNES are often treated for epilepsy [66].

PNES and psychogenic movement disorders (PMD) are among the most common psychogenic neurologic disorders.

PNES are common at neurological institutions and epilepsy clinics, where they are seen in 20–30% of patients referred for refractory seizures. PNES are probably also common in the general population, with an estimated prevalence of 2–33 cases per 100,000 population, which makes PNES nearly as prevalent as multiple sclerosis or trigeminal neuralgia [49].

2.4. Sexual abuse

Chen et al. [67] performed a systematic review and meta-analysis in some series of patients about sexual abuse and lifetime diagnosis of psychiatric disorders.

> *The search yielded 37 eligible studies, 17 case-controls, and 20 cohorts, with 3,162,318 participants. There was a statistically significant association between sexual abuse and a lifetime diagnosis of anxiety disorder (OR, 3.09; 95% CI, 2.43–3.94), depression (OR, 2.66; 95% CI, 2.14–3.30), eating disorders (OR, 2.72; 95% CI, 2.04–3.63), posttraumatic stress disorder (OR, 2.34; 95% CI, 1.59–3.43), sleep disorders (OR, 16.17; 95% CI, 2.06–126.76), and suicide attempts (OR, 4.14; 95% CI, 2.98–5.76).*

Therefore, a history of sexual abuse is associated with an increased risk of a lifetime diagnosis of multiple psychiatric disorders [67]. Patients having PNES present a high prevalence of traumatic life events; therefore, psychosocial factors are thought to play an important role in the etiology. Neurobiological factors may also contribute to the development of seizures, as a subgroup of patients is characterized by cognitive impairment and subtle structural and functional brain abnormalities [68].

Antecedent sexual trauma or abuse is thought to be important in the psychopathology of psychogenic seizures and psychogenic symptoms in general. A history of abuse may be more frequent in convulsive rather than limp type of PNES [49].

2.5. Psychogenic nonsyncopal collapse vs. PNESs

> *Heyer et al.* [69] *characterized the clinical features of tilt-induced psychogenic non-syncopal collapse (PNSC) from a cohort of young patients and to compare the semiology between PNSC and EEG-confirmed PNES and concluded that PNSC events were briefer than PNES events (median: 45 versus 201.5s, p<.001). Negative motor signs (head drop, body limpness) predominated in PNSC (85% versus 20%, p<.001), while the positive motor signs of convulsion occurred more often with PNES (90% versus 30%, p<.001). Behavioral arrest (25% versus 32.5%, p=.46) and eye closure (85% versus 72.5%, p=.21) did not differ between PNSC and PNES. Patients with PNSC were more likely to be tearful before (30% versus 7.5%, p=.02) and after (62.5% versus 7.5%, p<.001) an event.*

In spite of overlap exists, the features of PNSC generally appear similar to neutrally mediated syncope, while the features of PNES generally appear similar to ES.

2.6. Diagnosis

The patient's history may suggest the diagnosis. Several clues are useful in clinical practice and should raise the suspicion that seizures may be psychogenic rather than epileptic. Misdiagnosis of epilepsy is frequent and occurs in approximately 25% of patients with a previous diagnosis that does not respond to AED. Therefore, many cases of misdiagnosed epilepsy are eventually shown to be PNES.

> *Other paroxysmal conditions are occasionally misdiagnosed as epilepsy, but PNES is by far the most commonly misdiagnosed condition, accounting for >90% of misdiagnoses at epilepsy centers* [49].

> *Despite the ability to diagnose PNES with near certainty by using vEEG monitoring, the time to diagnosis is long, about 7–10 years. This delay indicates that neurologists may have an insufficiently high enough index of suspicion for PNES* [49, 70].

Approximately 80% of patients with PNES have been treated with AEDs before the correct diagnosis is made. A psychogenic etiology should be considered when AEDs have no effect whatsoever on the reported frequency of seizures [49].

> *Given the substantial economic costs and mental health burden of misdiagnosis, it is imperative to establish early identification, correct diagnosis, and effective treatment of PNES in order to provide the greatest opportunity for remission of events, improved psychological functioning, and social-vocational outcome* [65].

> *The great majority of PNES are classified as mental disorders in the current medical nosologies (only malingered seizures are not considered a mental disorder).*

> *The average delay from first seizure to diagnosis of psychogenic non-epileptic seizures (PNES) is over 7 years. The reason for this delay is not well understood. We hypothesized that a perceived decrease in seizure frequency after starting an anti-seizure medication (ASM) may contribute to longer delays, but the frequency of such a response has not been well established* [3].

Earlier diagnosis also reduces unnecessary doctor's visits and missed school/working days. The implementation of continuous education programmers for healthcare providers in particular could contribute positively to the diagnostic process of PNES for patients [71, 72].

> *In 2014 Elliot and Chariton* [73] *studied 689 patients presenting some events leading to a diagnosis, 47% (n=324) with PNES only, 12% (n=84) with PNES & Epilepsy and 41% (n=281) with Epilepsy only. Five biological predictors of a PNES only diagnosis was found; number of years with events (OR=1.10), history of head injury (OR=1.91), asthma (OR=2.94), gastro-esophageal reflux disease (OR=1.72) and pain (OR=2.25). One psychological predictor; anxiety (OR=1.72) and two social predictors; being married (OR=1.81) and history of physical/*

sexual abuse (OR=3.35). Two significant biological predictors of a PNES & Epilepsy diagnosis were found; migraine (OR=1.83) and gastro-esophageal reflux disease (OR=2.17).

The importance of considering the biopsychosocial model for the diagnosis and treatment of PNES or PNES with concomitant epilepsy based on these finding is certain.

Clinicians need to take a detailed time-consuming history from parents and when possible from the patient to identify warning signs suggestive of PNES. Such as: *an inconsistent seizure history, gradual and slow onset, as well as long duration of seizures and lack of seizure occurrence when the patient is alone. Recognizing signs suggestive of PNES is particularly difficult in the 35–44% of patients that have comorbid epilepsy* [73, 74]. The diagnosis and management of PNES is often challenging and fraught with discord and disagreement between patients, parents, and physicians [70].

In neuropsychiatric diseases, disturbances of the autonomic nervous system (ANS) are common. Heart rate variability (HRV) is useful to assess for disturbances of both sympathetic and parasympathetic activity, whereas electrodermal activity (EDA) can assess sympathetic activity. Parasympathetic HRV parameters are typically decreased in posttraumatic stress disorder (PTSD), while EDA is increased. Nevertheless, in major depressive disorder (MDD) and dissociation, both parasympathetic and sympathetic markers are decreased. Using HRV, ANS abnormalities have also been identified in PNES, indicating lower parasympathetic activity at baseline [75]. Other authors also use HRV in order to compare maximum autonomic activity of ES and PNES as biomarkers for distinguishing these types of clinical episodes. However, the great variation of autonomic response within both groups makes it difficult to use these HRV measures as a sole measurement in distinguishing epileptic seizures from PNES [76].

PNES can be suspected in patients with a psychosocial history with evidence of maladaptive behaviors or associated psychiatric diagnoses. To pay special attention during mental status assessment, especially to the patient's general demeanor, the appropriateness of his or her level of concern, over dramatization, and hysterical features is strong recommended. Certain symptoms and signs suggest ES. These include significant physical injuries, in particular, tongue biting on the lateral side, the duration of the seizures, and an ictal cry are highly specific to generalized tonic-clonic seizures and are helpful signs when present [49].

Once the PNES diagnosis and underlying psychological problems have been ascertained by the neurologist and mental health professional, a communication process relaying the diagnosis in a manner that promotes early acceptance of PNES and the treatment plan is imperative to preserve the best outcome possible for the patient [72].

Conducting the vEEG and mental health evaluation during the current hospitalization prevents additional delays in diagnosis. In areas where EEG video monitoring is not available, clinicians can be used a staged approach for diagnosis developed by the task force of the International League Against Epilepsy, these included: history, EEG, ambulatory EEG, vEEG/monitoring, neurophysiologic, neurohumoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis [6, 77]. The task force proposed the following four categories of certainty for PNES diagnosis:

- Documented PNES – confirmed by clinical history plus EEG video monitoring.
- Clinically established PNES – defined by clinical history, clinician witness, and EEG recording of habitual events without video.
- Probable PNES – determined by clinical history, clinician witness of video or live events, and a normal EEG.
- Possible PNES – relies on patient's self-report of clinical events and a normal EEG.

As is done with PMD diagnosis, levels of diagnostic certainty are ranked based on what data are available from history, witnessed event, and diagnostic testing, with levels of Possible, Probable, Clinically Established, and Documented diagnosis.

The roles of the specialists involved in the patient's care, how the information is communicated, and subsequent follow-up needs to be carefully considered in the values trade-offs that occur [72]. The issues of communicating the diagnosis to the patient and making treatment recommendations which should ideally be coordinated using a multidisciplinary team approach, involving the disciplines of neurology, psychiatry, psychology, social work, nursing, and anyone else necessary for this process [65]. The language to be used in this communication requires special attention and dedication, selecting the best descriptor for patients and families that highlights transparency and honesty, with avoidance of stigma and negative emotional response. We argue for providing parents and the patient initial diagnostic feedback separately. We also recommend that after communicating a diagnosis of PNES, neurologist/epileptologist with independent prescriptive authority, in addition to physicians, and families may struggle with the choice of withdrawing AEDs for the treatment of young patients for whom the AEDs have been taken for a long time.

> *Although the* DSM-5 *classification is simple in theory, knowing whether a given patient is faking it is nearly impossible. In some circumstances, intentional faking can be diagnosed only by catching a person in the act of faking (e.g., self-inflicting injuries, ingesting medications or eye drops to cause signs, putting blood in the urine to simulate hematuria)* [49].

When the patient is purposely deceiving the physician (i.e., faking the symptoms), factitious disorder and malingering must to be taken into account. To distinguish factious disorder and malingering from PNES just consider that, in malingering, the reason for the deception is tangible and rationally understandable (albeit possibly reprehensible) such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs. In factitious disorder, the motivation is a pathologic need for the sick role [49].

An important corollary is that malingering is not considered a mental illness, whereas factitious disorder is. As such there are no specific diagnostic criteria for malingering. A generally accepted view is that most patients with PNES have conversion disorder, rather than malingering or factitious disorder [49].

Dacrystic seizures are rare clinical occurrences characterized by sudden lacrimation, grimacing, sobbing, sad facial expression, and yelling, with a special challenging differential diagnosis with PNES. To differentiate dacrystic seizures from PNES can be very difficult from

the point of view of symptomatology of psychiatric symptoms but if vEEG monitoring captures a prolonged seizure compatible with a dacrystic seizure its final diagnosis. The presentation of dacrystic seizures has common elements with PNES, and it is possible that the patient has both types of crisis. Apart from that there are a few medical reports in the literature about this matter [6, 78–80].

> *Laboratory studies are useful in excluding metabolic or toxic causes of seizures (e.g., hyponatremia, hypoglycemia, drugs). Prolactin and creatine kinase (CK) levels rise after generalized tonic-clonic seizures and not after other types of episodes. However, sensitivity is too low to be of any practical value (i.e., lack of elevation does not exclude epileptic seizures)* [49].

2.6.1. Electroencephalogram and provocative techniques, activation or inductions

The "gold standard" for proper diagnosis of PNES is vEEG [77]. During vEEG assessment, behavior and EEG activity are registered at the same time. A spontaneous or elicited event is defined as a PNES, when there is no spike/slow waves EEG activity, during or after the ictus, and semiology is consistent with PNES and not ES.

Jedrzejczak et al. [81] reported a clinical and electrophysiological analysis of type and duration of seizures recorded by means of long-term vEEG monitoring, a method which enables accurate diagnosis of PNES occurring with or without ES. Analysis is based on 1083 patients, hospitalized at their department between 1990 and 1997, with a preliminary diagnosis of epilepsy. A total of 85 patients (7.8%) were diagnosed as PNES. Long-term video-EEG monitoring was performed in 70 patients. In 55 (79%) of these patients, 230 seizures (221 pseudo epilepsy and nine epileptic) were recorded. In 30 patients (32%), the diagnosis was based on clinical observation of the seizures and on the number of EEG recordings, including activating procedures such as sleep deprivation, photo stimulation, hyperventilation, and AED withdrawal. The authors proved the difficulties involved in the diagnosis of psychogenic pseudoepileptic seizures and the negligible value of neuroimaging techniques and interictal EEG recordings in the differential diagnosis of epileptic versus nonepileptic seizures.

We review the influence of gender on psychogenic nonepileptic seizures (PNES) diagnosis and another author did the same.

> *Noe KH et al.* [80] *in 439 subjects undergoing video-EEG (vEEG) for spell classification, of which 142 women and 42 men had confirmed PNES. The epileptologist predicted diagnosis was correct in 72% overall. Confirmed epilepsy was correctly predicted in 94% men and 88% women. In contrast, confirmed PNES was accurately predicted in 86% women versus 61% men (p=0.003). Sex-based differences in likelihood of an indeterminate admission were not observed for predicted epilepsy or physiologic events, but were for predicted PNES (39% men, 12% women, p=0.0002).*

vEEG monitoring refers to continuous EEG recorded for a more or less prolonged period with simultaneous video recording of the clinical manifestations. Having a correlation of the recorded behavior (video) and the EEG cortical activity, the diagnosis of ES or PNES attacks can be made definitely in nearly all cases [81, 82].

Using vEEG of patients, Hubsch et al. [83] *conducted multiple correspondence analysis and hierarchical cluster analysis to construct a practical and useful semiological classification of PNES, which identified five clusters of signs: dystonic attack with primitive gestural activity, pauci-kinetic attack with preserved responsiveness, pseudo syncope, hyperkinetic prolonged attack with hyperventilation and auras, and axial dystonic prolonged attack.*

The ability to diagnose PNES when vEEG is not available may open opportunities to lower and middle income countries, where monitoring is not available.

Provocative procedures, such as saline provocation, hypnosis, simple suggestions, suggestive interview, or a mixture of them, have been used to obtain a typical event; however, the ethics of provocative procedures has been raised.

Activation maneuver, inductions, or provocative techniques can be remarkably useful for the diagnosis of PNES, mainly when the diagnosis is uncertain and no spontaneous episodes occur during assessment. In many epilepsy centers, to use a provocative technique to aid in the diagnosis of PNES is allowed. For example, an intravenous injection of normal saline is traditionally and most commonly used, but other techniques such as hypnosis, among others, can be used. The use of suggestion techniques ranging from simple verbal suggestion to injection of saline may improve rate of seizure capture; at the present moment, an important number of authors are in favor [6, 77, 84–89], while others do not approve these procedures [90, 91]. Some authors support use of simple suggestion techniques, if the patient is clearly informed of what is being done and why (this does not seem to prevent patients from having events during recording) [92].

The recent use of hypnosis in the diagnostic process of PNES includes its use in seizure provocation, which was tested in samples in the recent literature.

2.6.2. Neuroimaging

Excepting lesions with epileptogenic potential (such as mesial temporal sclerosis) neuroimaging findings are of modest differential diagnostic value for ES and PNES at present, but it is diagnostic for patients PLNCC.

All patients presenting epileptic seizures secondary to NCC have abnormalities on CT scan or magnetic resonance imaging (MRI) scan of the brain characterized by calcified edema surrounding or not by perilesional edema and or active cysticerci at different stage [1, 2, 13, 19–40]. However, most patients with idiopathic epilepsy have normal MRI studies [62], and a significant number of patients with lone PNES have abnormalities [61, 77]. More recently, structural and functional imaging studies in patients with PNES have documented changes in cortical and cerebellar regions at group level [92]; in functional connectivity between emotional, cognitive, and motor regions [93–95] and between structural and functional connectivity network coupling [95]. More studies are needed to determine whether there are actual conversion/dissociation networks [93].

Lesions with epileptogenic potential (such as mesial temporal sclerosis) are more commonly found in patients with epilepsy but have also been described in patients with PNES and are clearly not sufficient for a diagnosis of epilepsy.

> *Convergent neuroimaging findings implicate alterations in brain circuits mediating emotional expression, regulation and awareness (anterior cingulate and ventromedial prefrontal cortices, insula, amygdala, vermis), cognitive control and motor inhibition (dorsal anterior cingulate, dorsolateral prefrontal, inferior frontal cortices), self-referential processing and perceptual awareness (posterior parietal cortex, temporoparietal junction), and motor planning and coordination (supplementary motor area, cerebellum). Striatal-thalamic components of prefrontal-parietal networks may also play a role in pathophysiology. Aberrant medial prefrontal and amygdala neuroplastic changes mediated by chronic stress may facilitate the development of functional neurological symptoms in a subset of patients* [94–96].

Neuroimaging studies have demonstrated that PNES are characterized by unstable cognitive-emotional and motor system, which is engaged in hyperactivity of limbic regions and sensorimotor area. The insula, which is a part of the limbic system, includes various sub regions with some distinct connectivity patterns separately, whether these insular sub regions show different connectivity patterns respectively in PNES remains largely unknown according with the investigations done by Rong et al. [97].

> *They investigated the functional connectivity (FC) of insular sub regions in PNES and extend the understanding of the complex pathophysiological mechanisms of this disease. A resting state FC based on the insular sub regions was conducted in 18 patients and 20 healthy controls. They examined the differences in FC values between PNES patients and controls using two sample t tests, and their results showed that patients had significantly stronger FC between insular sub regions and sensorimotor network, lingual gyrus, superior parietal gyrus and putamen, which suggested a hyperlink pattern of insular sub regions involved in abnormal emotion regulation, cognitive processes, and motor function in PNES. Pearson correlation analysis between the mean FC values within abnormal regions and the frequency of PNES further indicated that PNES exhibited abnormal functional organization whose stressful emotion of patients has great direct influence on their motor functions*.

They concluded that *differentially impaired functional connectivity patterns of insular sub regions might provide new insights into the complex neurological mechanism of PNES* [97].

Functional neuroimaging data in various functional neurological disorders increasingly support specific neurobiological dysfunction. However, to date, only one study has been reported on positron emission tomography (PET) in patients presenting with PNES.

> *Arthuis et al.* [98] *reported sixteen patients being evaluated in a specialist epilepsy centre underwent PET with 2-deoxy-2-[fluorine-18] fluoro-d-glucose (18) FDG-PET) because of suspected intractable epileptic seizures. However, in all patients, the diagnosis was subsequently confirmed to be PNES with no coexisting epilepsy. (18) FDG-PET was also performed in 16 healthy controls. A voxel by voxel intergroup analysis was performed to look for significant differences in interictal (resting state) cerebral metabolism. In addition, metabolic connectivity was studied using voxel-wise inter-regional correlation analysis.*

They found that patients with PNES exhibited significant PET hypometabolism within the right inferior parietal and central region and within the bilateral anterior cingulate cortex. A significant

increase in metabolic correlation was found in patients with PNES, in comparison to healthy participants, between the right inferior parietal/central region and the bilateral cerebellum and between the bilateral anterior cingulate cortex and the left parahippocampal gyrus. Although they cannot exclude that their data reflect changes due to comorbidities, they may indicate a dysfunction of neural systems in patients with PNES. Hypometabolism regions might relate to two of the pathophysiological mechanisms that may be involved in PNES, that is, emotional dysregulation (anterior cingulate hypometabolism) and dysfunctional processes underlying the consciousness of the self and the environment (right parietal hypometabolism) [97].

2.7. Treatment

The first treatment phase in PNES is patient engagement. Treatment is complex, requiring multidisciplinary care and patients, and their families must understand the diagnosis to comply with the recommendations of the psychiatric caregiver [49]. The next phase of treatment is acute interventions, and most research studies focus on short-term evidence-based interventions. It seems to be that the cognitive-behavioral therapy is supported by most of randomized controlled pilot trials. However, psychotherapeutic and psychopharmacological interventions have been less well-studied using controlled and uncontrolled trials [98].

Treatment of PNES varies and can include psychotherapy and use of adjunctive medications to treat coexisting anxiety or depression. Psychogenic symptoms are, by definition, a psychiatric disease, and a mental health professional should manage them. The main obstacle to effective treatment is effective delivery of the diagnosis. The physician delivering the diagnosis must be compassionate, remembering that most patients are not faking, but also firm and confident to avoid the use of ambiguous and confusing terms. Patients who accept their diagnosis and follow through with therapy are more likely to experience a successful outcome; therefore, patient education is critical and is the first step in treatment [49].

LaFrance Jr et al. [6] found that a cognitive behavior therapy-informed psychotherapy significantly reduces the seizures in patients with PNES.

> *"Cognitive behavioral therapy has evidence of efficacy, including one pilot randomized, controlled trial where cognitive behavioral therapy was compared with standard medical care. The antidepressant sertraline did not show a significant difference in event frequency change when compared to placebo in a pilot randomized, double-blind, controlled trial, but it did show a significant pre- versus post treatment decrease in the active arm."*
>
> *"Other interventions that have shown efficacy in uncontrolled trials include augmented psychodynamic interpersonal psychotherapy, group psychodynamic psychotherapy, group psycho education, and the antidepressant venlafaxine"* [6].

Some investigations done in 2010 and 2013 suggested serotonin selective reuptake inhibitors (SSRIs) and sertraline may be helpful in reducing seizures in PNES, respectively [49].

> *Carlson and Nicholson Perry* [99] *"evaluated and synthesized the available evidence from the previous 20 years regarding the utility of psychological interventions in the management of*

psychogenic non-epileptic seizures (PNES) and found that 82% of people with PNES who complete psychological treatment experience a reduction in seizures of at least 50%."

Hilmarsdóttir et al. [100] *"addressed the current research on psychotherapeutic treatment for PNES by discussing recent reviews and six randomized controlled trials (RCTs) on the subject and concluded that, larger well-designed randomized controlled trials are needed in order to support the evidence of psychological interventions for their patient group".*

Duncan et al. [101] *"reported that half of their patients informed being free of seizures following intervention. Being employed predicted good outcome, but the best predictor of being seizure free at 6 months was having an internal locus of control. This may be useful practically and requires further study".*

"No good predictors of long-term outcome were found, possibly because of loss to follow up. PNES may manifest themselves in very different ways and usually have complex root causes". Optimal treatment of persons experiencing PNES requires close cooperation between the neurologist and the psychiatrist [102].

The delivery of brief manualized psycho-educational intervention for PNES by health professionals with minimal training in psychological treatment was feasible. The intervention was associated with higher rates of PNES cessation than those observed in previous studies [103].

Some authors investigated whether initial adherence to treatment in PNES differed on the basis of mental health treatment modality and which subject characteristics were predictive of adherence. Initial adherence rates were 54% for combined treatment conducted in the same institution (integrated intervention) and 31% for psychotherapy and psychiatric management offered in different settings (divided intervention). Cognitive complaints and current exposure to antiepileptic drugs (AEDs) were more common among nonadherent patients, and being married (or having a live-in partner) was more common among adherent patients. A predictive model using the mentioned variables (intervention type, marital status, cognitive complaints, and concurrent use of AEDs) showed that this set of variables was predictive of adherence [104].

While PNES is treated by mental health professionals, continued involvement by a neurologist or epileptologist is associated with better outcomes, regardless of the limited direct care provided. Moreover, parents of children with PNES are expected to discuss the diagnosis with the pediatric epileptologist/neurologist, and this expectation should be respected [72].

Plioplys [105] *suggests that "professionals in epilepsy care that lack sufficient knowledge about PNES may be more likely to continue AEDs at a parent's request. These professionals may also be more likely to continue AEDs in order to facilitate acceptance of the diagnosis and/or to prevent a delay in psychological treatment. A clinician may be concerned that refusing a request to continue AED treatment will result in the family seeking out a clinician who would unquestioningly supply them with requested medicines, i.e. "doctor-shopping." This risk may be heightened if parents observe their child's non-epileptic episodes becoming worse. Parents may also wish to continue AEDs as a means to avoid social stigma associated with PNES, particularly at school".*

It is clear-cut defined that clinicians are under obligation to provide medical treatment deemed to be inappropriate or ineffective [106, 107]. Instead of continuing to prescribe AEDs, exploring the underlying reasons for why the parents want to continue AEDs despite the PNES diagnosis allows the physician to directly address parents' concerns regarding discontinuation. PNES patient and their relatives may turn to clinicians for advice regarding disclosure of PNES diagnosis to third-parties, including school nurses, school administrators, teachers, classmate, day care providers, and peers. The clinicians' obligation is to counsel patients and their parents on the conflicting values that are at stake: preserving the patient's and family's privacy, protecting the patient from social stigma and physical harms, and promoting continuity of therapeutic care.

Neurologist and epileptologist should educate the patient and their relatives that these values are not easily reconcilable and deciding whether to disclose the diagnosis involves an inherent trade-off, and the prognosis of these patients is still relatively poor, and a good outcome seems dependent on a young age at diagnosis, early diagnosis, less severe psychological comorbidities, and continued follow-up and management by the diagnosing neurologist, epileptologist, or clinician [8, 49, 105, 108–116].

The arguments for disclosing with both parents and child together would be primarily based on cultivating trust with patient and parents and between patient and parents through maximal transparency [72].

2.8. PNES vs. epileptic seizures

Impairment of consciousness and reduced self-control are key features of most psychogenic nonepileptic seizures (PNESs), although, compared with patients with epilepsy, those with PNESs demonstrate greater conscious awareness during their seizures.

> *Some authors* [117, 118] *"suggest that an understanding of conscious experiences and discrepancies between subjective impairment of consciousness and the lack of objectifiable neurobiological changes in PNESs may benefit from an examination of emotion processing, including understanding sensory, situational, and emotional triggers of PNESs; emotional and physiological changes during the attacks; and styles of emotional reactivity and regulatory capacity* [117] *reported allergies helps distinguish epilepsy from psychogenic nonepileptic seizures"* [118].

Psychopathology levels are elevated in patients with PNES and those with epilepsy. However, patients with PNES report higher rates of trauma and neglect, poorer health-related quality of life (HRQoL), and an increased prevalence of insecure attachment. In this study, patients with PNES reported higher levels of anxiety and depression and lower HRQoL than those with epilepsy. PNES: No significant correlations were found with HRQoL but depression correlated positively with attachment avoidance, attachment anxiety, and relationship conflict. Anxiety correlated positively with attachment avoidance, attachment anxiety, and relationship conflict, and negatively with relationship depth and support. Epilepsy: HRQoL correlated negatively with seizure severity, depression, anxiety, attachment avoidance, and attachment anxiety. Depression correlated positively with attachment avoidance, attachment anxiety, and relationship conflict. Anxiety

correlated positively with seizure severity, attachment avoidance, and attachment anxiety. Correlations between measures of relationship quality and anxiety were stronger in patients with PNES versus those with epilepsy (zs = 2.66 to 2.97, $p < 0.004$). Attachment style and relationship quality explained larger amounts of variance in depression (45%) and anxiety (60%) in the patients with PNES than those with epilepsy (16 and 13%). In conclusion, levels of anxiety and depression were higher in patients with PNES than those with epilepsy. Interpersonal problems were much more closely associated with anxiety and depression in patients with PNES than those with epilepsy. The findings support the use of therapeutic interventions for PNES focusing on attachment and relationship issues [119].

Some investigations have attempted to compare patients affected by PNES to patients affected by functional motor symptoms from a demographic, clinical, and psychological perspective. Nevertheless, results are quite controversial, and significant conclusions have not been reached. Therefore, some authors evaluated the phenomenology of psychology of the two groups assessing levels of dissociation and its subcomponents, alexithymia and interceptive sensitivity in patients with PNES and in patients with FMS, and the investigation showed different psychological mechanisms underlying patients with PNES and patients with FMS [120].

> *Some authors* [121] *"studied eligible patients (n = 51) that were divided into those with PNES + ES (n = 24) and those with PNES alone (n = 27). The follow-up period was 4.8 ± 0.3 and 4.3 ± 0.3 years, respectively. Both groups had similar female predominance and similar age at admission to the vEEG unit. Time from PNES onset to hospitalization was longer in PNES patients compared to those with PNES + ES. The majority of subjects in each group reported a history of at least one major stressful life event. Opisthotonus was significantly more frequently observed in PNES patients, and they had more events during vEEG hospitalization. Psychogenic events ceased during the follow-up period in 22% of the PNES patients and in 58% of the PNES + EPI patients (P > 0.001)".*
>
> *Their results indicate that following vEEG-based diagnosis of PNES, the long-term outcome of PNES cessation may be more favorable for patients with concomitant epilepsy than for patients without epilepsy.*

Neuropsychological tests do not distinguish ES from PNES at the individual level. Clinical features that favor PNES are:

Fluctuating course.

Asynchronous movements (frontal lobe partial seizures excluded).

Pelvic thrusting (frontal lobe partial seizures excluded).

Side to side head or body movement (convulsive events only).

Closed eyes during the episode.

Long duration.

Other signs that can help are gradual onset, no stereotyped events, flailing or thrashing movements, opisthotonus "arc en cercle", tongue biting, urinary incontinence, and "swoon" type events should raise suspicion of PNES if prolonged over a minute, atonic ESs are much

shorter and typically occur in the epilepsies with other seizure types, for example, Lennox–Gastaut syndrome.

Signs that favor ES.

Occurrence from EEG-confirmed sleep.

Postictal confusion.

Stertorous breathing.

Occurrence during sleep only (*EEG-confirmed sleep).*

2.9. Associated minor or major injuries

Ictal injuries in PNES have been reported previously and history of any minor (e.g., tongue biting, bruises, and lacerations) or major (e.g., burns and fractures) physical injuries associated with their seizures, since their disease started is well known. In our region, one of the most common type of reported injury was burning lesions that happened in patients fitting close to the fire used to heat the room apart from tongue biting, lacerations, bruises, limb fractures, and dental injury. Therefore, PNES is also associated with physical injuries. Despite the shibboleth that injuries rarely occur during PNES, mild injuries commonly happen and even severe injuries such as fractures and burns are not uncommonly reported in these patients. *Patients with more dramatic seizure manifestations (e.g., urinary incontinence) were more likely to report ictal injuries* [121].

Tongue biting (TB) may occur both in seizures and in PNES. A systematic review to determine sensitivity, specificity, and likelihood ratios (LR) of TB was done.

> *"Five studies (222 epilepsy patients and 181 subjects with PNES) were included. There was a statistically significant higher prevalence of TB (both without further specifications on site of lesions and lateral TB) in patients with seizures. Pooled accuracy measures of TB (no further specifications) were sensitivity 38%, specificity 75%, pLR 1.479 (95% CI 1.117-1.957), and nLR 0.837 (95% CI 0.736-0.951). Pooled measures of lateral TB were sensitivity 22%, specificity 100%, pLR 21.386 (95% CI 1.325-345.169), and nLR 0.785 (95% CI 0.705-0.875). Only a pooled analysis of data demonstrated a statistically significant pLR for lateral TB. Lateral TB but not 'any' TB has diagnostic significance in distinguishing seizures from PNES, supporting the diagnosis of seizures. Tongue biting without further specifications has, therefore, no value in the differential diagnosis between seizures and PNES"* [122].

3. Ethics

> *Currently, only a very narrow window of ethical dilemmas in PNES has been explored.*
>
> *Numerous distinct ethical dilemmas arise in diagnosing and treating pediatric and adolescent patients with PNES. Important ethical values at stake include trust, transparency, confidentiality, professionalism, autonomy of all stakeholders and justice* [122].

In 2003, we had not video-EEG facilities and then a procedure to provoke and to distinguish PNES from ES in our setting is introduced. At that time, we got IRB number, an approval by the Ethical Advisory Board (A0;012-2000) and written informed consent from selected patients. However, today, we have no doubt that it was a nonethical procedure, and in spite of that we did not afford any problem, we deeply regret about that procedure.

Confirming a PNES diagnosis and disclosure this information to the child, parents and other interested people build up a special challenge related to the values of justice professionalism, human resource utilization, and trust for health care providers in relation to patients, families, and other colleagues. The preservation of an adequate therapeutic relationship plays strongly in the values at stake. Most of neurologists felt confident about discontinuing the medical treatment when diagnosis of PNES is confirmed, but ethical dilemma arises when the prescribing clinician faces is discontinuing AEDs in a timely manner without losing the trust and confidence of the patient and/or the patient's relatives. Sometimes some patients and relatives decide to seek for a second medical opinion and we have to respect that.

Elements often taken into account during ethical dilemmas include the patient and family's treatment preferences, developmental stage, psychosocial background, quality of life, applicable laws, institutional policies, professional duties, and other practical stakeholder obligations and responsibilities. Even the most skilled attending doctor struggles with ethical dilemmas that arise during diagnosis and management of PNES patients. These relationships coupled with the uncertainty and stigma surrounding PNES result in complex dilemmas for treating clinicians. Significant mental health, social, and community resources are frequently necessary to effectively treat this patient population, but these resources are scarce. To ensure a successful management of PNES, all ethical values should be taken in to consideration from the first clinic [122–126].

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2. Cole et al. [123].
3. Benbadis [49].

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Chapter 6

Treatment and Diagnosis of Psychogenic Nonepileptic Seizures

Cicek Hocaoglu

Additional information is available at the end of the chapter

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Abstract

Psychogenic nonepileptic seizure (PNES) is one of the most common clinical conditions in which the diagnostic complexity is experienced. Misdiagnosis leads to many years of wrong treatment regimens, side effects of drugs, additional financial burdens and adverse effects on social life. Differential diagnosis with epileptic seizures (ES) is one of the most common problems in neurology clinics as well as other health centers. A careful history from the patient and his relatives, detailed neurological and psychiatric examination are very important in reaching the correct diagnosis and treatment. Although imaging advances such as video electroencephalography (vEEG) have improved the ability of physicians to accurately identify these disorders, the diagnosis and treatment of PNES is still a challenging issue. Early diagnosis, young age, less psychiatric comorbidity have a positive effect on prognosis. Psychiatric evaluation of patients with PNES may be particularly helpful in elucidating the etiology and detecting comorbid diseases and may be helpful in the long-term treatment of these patients.

Keywords: psychogenic nonepileptic seizures, diagnosis, treatment

1. Introduction

Psychogenic nonepileptic seizures (PNESs) are neuropsychiatric disorders caused by the combination of neurological findings and basic psychological conflicts [1–3]. Over a period of a century, medical community collects data and information about the phenomenology, epidemiology, risks, comorbidities and prognosis of PNES [4–9]. However, information about PNES is insufficient. Video electroencephalography (vEEG) has become a gold standard in diagnostic examination to distinguish neurological seizures from PNES [10–15]. For this reason, video electroencephalography is preferred for diagnosis. In this section, we

systematically reviewed our current knowledge about diagnosis, differential diagnosis and treatment of PNES.

2. What is a psychogenic nonepileptic seizure?

PNESs, also referred to as hysteroepilepsy, pseudoseizure, hysterical seizures, psychogenic seizures, dissociative disorders, are sensory, motor or behavioral episodes similar to epileptic seizures (ES) without accompanying abnormal neuronal discharges [15–18]. PNESs do not have neurological roots, on the contrary, they are concrete manifestations of psychological distress. The prevalence in the society ranges from 1/3000 to 1/5000 [6]. Although the prevalence is lower than the epilepsy, it causes serious workload in the emergency departments and neurology clinics due to the tendency to frequent repetition. About 10–30% of patients admitted to epilepsy centers with the history of treatment-resistant seizure are created by patients with PNES [19, 20]. ES have also been reported in 5–40% of patients with PNES at the same time. In other words, both types of seizures can be seen together in the same patient [5, 6, 9, 20–22]. Although ESs and PNESs are seen in both sexes and ages, PNESs often affect young adult women. Lesser reviewed 21 studies investigating gender differences (734 women and 250 men diagnosed with PNES) [23]. It has been reported that 75–85% of the diagnosed PNES patients are female, it is 10 times more likely to be seen than men, and the majority of patients are 30–40 years old [24–25]. There are also cases of PNES diagnosed in childhood and adolescence [2]. Two studies have reported sexual abuse in female patients and work-related problems in males more frequently [26, 27]. However, traumatic experiences such as warfare and captivity are higher in male patients [28]. About 5–10% of patients followed up with a diagnosis of epilepsy and 20–40% of patients with epileptic patients receiving inpatient treatment experienced PNES [24, 29]. These patients often have accompanying psychiatric illnesses (mostly depression, posttraumatic stress disorder, other dissociative and somatoform disorders and personality pathology), especially borderline personality types [30]. In most cases, it is reported that there is a story of childhood trauma (story of sexual or physical abuse) [31–35]. In one study, it was suggested that childhood traumatic experience may be a predisposing factor for PNES [36]. Patients with PNES followed up with the diagnosis of ES are diagnosed at an average of 7.2 years [2]. This situation led those patients with PNES to be exposed to incorrect treatment regimens for many years with the diagnosis of epilepsy, additional financial burdens, drug side effects and adverse social life [29, 36]. Considering that the cases were exposed to aggressive interventions such as intubation, considering status epilepticus by the emergency department, the importance of early differential diagnosis with epilepsy is once again emerging [37].

3. Diagnosis

3.1. Epileptic seizure? Psychogenic nonepileptic seizure?

The main question to be answered in patients with seizure history is whether there is an epileptic seizure. When the patient is brought to the clinic, the seizure is usually terminated

and the most important information is obtained in order to distinguish from the patient and the relatives who witnessed it during the seizure. Although any other diagnostic methods are available for diagnosis of epilepsy such as electroencephalogram (EEG), vEEG, cerebral magnetic resonance imaging (MRI), cerebral perfusion scintigraphy and, the most important first step in diagnosis is accurate history from patients and their relatives, and careful neurological examination, as well as semiologic recording of the seizure [38]. In cases where anamnesis is not sufficient, the differential diagnosis of the patient becomes difficult. With good history, information can be obtained to suggest whether there is a nonepileptic seizure. For example, many reasons may be useful for differential diagnosis such as the onset and the duration of seizure, the appearance pattern, motor movements and reflex changes, the induction property of seizure [16, 39, 40]. If the seizures happen very often and repeat several times a day, this is a more common finding for PNES. Furthermore, while patients are normal in the period between the seizures due to the absence of postictal confusion in PNES, there may be consciousness disorders during the period between seizures in patients with ES due to prolonged confusion and sleepiness in frequent seizures. While epileptic seizures generally last a few minutes, PNESs tend to last much longer [41, 42]. Patients with epilepsy generally respond to treatment with one antiepileptic drug at around 50%, while patients with PNES do not respond to treatment with antiepileptic drugs [41]. During examination, it is often learned that patients with PNESs received prior antiepileptic treatment and no response obtained to treatment. If the seizures are in a specific place, time and crowded environment, it is favorable for PNES. In ES, such a place and time difference is generally absent. While ES is seen in sleep and awake state, PNESs are seen awake state [17, 18]. A careful history can be used to determine that the patient is not asleep, although the patients report that they are asleep. vEEG can be used as an assistant method in cases where sleep and awake state cannot be distinguished [40]. The type of seizure is generally the same with the reason that the discharge is in the same region in the brain in ES. In PNES, seizure types can be seen in different forms in the same patient [43]. While seizures are usually sudden onset in epileptic patients, it starts gradually in patients with PNES. While there are complaints such as screaming, palpitations, hyperventilation, numbness in the hands and feet before the seizure in PNES, epigastric sen sations, deja vu, swallowing, swallowing and automatisms in the hands may occur in ES [17, 18]. A complete loss of consciousness is observed according to type of seizure in ES, no loss of consciousness is seen in PNES, the patient hears around, and cannot respond. There may be physical injuries in ES due to fall. Even the patients with PNES fall, they usually have controlled falls and injuries are not often experienced [23, 42, 44]. In ES, contractions occurring in the extremities are tonic, clonic or tonic-clonic and rhythmic, whereas PNES is more tonic in contraction and not rhythmic. When the eyelids are attempted to open, patients with PNES show resistance, but this is not observed with ES. At ES, abnormal alignment of the eyes and unilateral clonic contractions in the eyelid can be seen [43]. In patients with epilepsy, pupil dilatation and reflex changes are observed, however, these neurological findings are not seen in patients with PNES. In patients with PNES, pelvic pushing is a frequent finding, while it may be seen much less and lighter in epileptic patients [16]. Urinary incontinence is a more common finding in ES, although it is rarely reported in patients with PNES [42]. In the differential diagnosis, sudden onset of seizures, pupillary dilation during seizure and postictal confusion are semiologic findings in favor of ES, awareness of the environment, influencing the severity of seizures by the presence of people around and blinking of the eyes are

semiologic findings in favor of PNES [45]. At ES, there may be epileptic cries at the onset of the seizure and tonic-clonic contractions continue with wheezing. In patients with PNES, longer moaning during seizures, speech, which can be understood, can be observed with challenging hyperventilation, and generally last longer than ES [43]. While postictal confusion is a frequent finding in ES, postictal confusion is not seen after PNES. EEG is the most important diagnostic method besides clinical information. Because it is a noninvasive and inexpensive method, it still maintains its importance as the most commonly used method in the orientation of diagnosis and treatment today. However, the normal EEG of the patient with seizure does not exclude the diagnosis of epilepsy, and many epileptic patients may have continuous normal EEG findings during the interictal period. Again, especially in cases where seizures with low frequency are difficult to get caught in the ictal period and take EEG recording, it often cannot help the diagnosis. In PNES cases, EEG taken during interictal and ictal period is normal. However, it should not be forgotten that EEG cannot be sufficient for the differential diagnosis of ES and PNES. Comparisons of clinical characteristics of ES and PNES are given in **Table 1**.

3.2. Video EEG imaging in psychogenic nonepileptic seizures

For the differentiation of PNES and epileptic seizures, when the decision cannot be taken with anamnesis, clinical examination and EEG, '*gold standard'* method is video EEG imaging. Despite the use of antiepileptic drug, it is recommended for all patients with no change in seizure frequency [46]. However, its use is limited due to the difficulties in its implementation, not being in every center, extending the length of hospital stay and having a high cost.

Features	PNES	ES
Antiepileptic treatment response	No response	Usually present
Psychiatric changes	Common	Rare
Seizure duration	May be prolonged (10–15 min)	Short (1–2 min)
Onset of the seizure	Gradually	Sudden
Urinary incontinence	Rare	Present
Biting tongue, physical injury	Rare (tongue tip)	Common
Cyanosis	No cyanosis	Common
Pupil dilatation, reflex changes	Absent	Present
Motor movements	Extended, uncoordinated	Automatism, coordinated, short
Postictal confusion	Rare	Common
Seizure type	Variable	Usually the same
Interictal EEG	Normal	Frequently changed
Ictal EEG	Normal	Changed

Table 1. Comparison of clinical characteristics of ES and PNES.

This system works by taking the patient's long-term EEG recording and simultaneous video recording [16]. In this way, it enables the observation of the ictal semiology of the seizures clearly, it is possible to evaluate both the clinical features of the seizure and the EEG records in the ictal period together [16]. The absence of a change in the EEG record during the clinical event and not being compatible with some partial epileptic seizures which is not accompanied by EEG changes are diagnostic in favor of PNES. In addition, some impressions such as gradual starting and ending of the seizure acquired during the monitoring of the video recording, noncontinuous (stopping and starting) irregular and asynchronous activity, head movements to the side, pelvic push movements, opistotonic posture, stuttering, groaning, crying, yelling and abusive speech, conscious self-protection during motor activity and insistently keeping the eyes closed support the diagnosis of PNES. However, it should be noted that none of these behaviors are diagnostic for the PNES alone [46]. Al-Quadah and colleagues have evaluated an average of eight patients with seizure classification with an average of 3.2 h of vEEG in the study and could record episodes in five patients. In this study, it was determined that three epilepsy episodes were nonepileptic [47]. In another study, epileptic seizures were seen in eight patients (22%) and epileptic seizures were not seen in two patients (67%). This means EN/PNES can be distinguished in 32 patients (89%) [48]. McGonical and colleagues have examined cases with seizure story with short-term vEEG and the diagnosis of PNES was detected in 50% of cases [49]. It can be said that the vEEG technique is a successful method for imaging the ictal period in patients and the differential diagnosis of ES/PNES. In this way, the wrong diagnosis, treatment, health expenditure burden will also be reduced by preventing misdiagnosis and wrong treatment. However, it should be known that vEEG cannot be sufficient in differential diagnosis of all patients.

3.3. Is there a biomarker and a test for a psychogenic nonepileptic seizure?

The search for biomarkers for the differentiation of ES and PNES has been a subject of interest to many authors. In the first studies in this area, changes in prolactin level after epileptic seizures and whether these changes were different in ES and PNES were examined. Ohman and colleagues found that plasma levels of prolactin increased after electroconvulsive therapy and it has been emphasized that an increase in prolactin level after epileptic seizures may be an important predictor of PNES differentiation [50]. It has been revealed in eight of these studies that the postictal increase in serum prolactin level had a positive diagnostic value in terms of epilepsy but no increase did not exclude epilepsy and no significant increase was seen in PNES, whereas it has been revealed in the other two studies that there was a statistically significant increase in serum prolactin level in PNES, but this increase was significantly lower than in epilepsy [51]. Shah et al. have indicated that there was an average increase of 17% in serum prolactin levels after PNES, therefore at least a two-fold increase may be considered significant for epilepsy [52]. In one study, 69% sensitivity and 93% specificity were found for the prolactin level at the distinction of epileptic seizure and psychogenic nonepileptic seizure, in another study, 100% positive predictive value was reported for ES [53]. However, the use of postictal prolactin level as a biomarker in EN/PNES differentiation was not supported in two studies [54, 55]. In addition, while a higher increase in prolactin was expected in generalized tonic-clonic seizures affecting the entire or most part of the brain, increase may not be seen

after simple partial and frontal lobe seizures. Postictal serum prolactin level measurement is recommended to distinguish between epileptic and nonepileptic seizures, but it should be remembered that after half an hour following the seizure, it returns to normal level rapidly and is affected by stress, hypoglycemia, exercise, drug intake. Sundararajan et al. have evaluated 49 studies conducted between 1980 and 2015 on use of biomarkers in the diagnosis of psychogenic nonepileptic seizures. It has been indicated in this review study that neuroimaging (BT, fMRI, SPECT, etc.), autonomic nervous system, prolactin, postictal cortisol, creatine kinase, neuron specific enolase, brain-derived neurotropic factor, ghrelin, leptin, leukocytosis, heart rate have been studied as a biomarker to distinguish psychogenic nonepileptic seizures and epileptic seizures. However, it was reported that none of them could obtain sufficient evidence level. In addition, the authors noted that studies have significant limitations due to small sample and methodological differences and subtypes of psychogenic nonepileptic seizures have not been investigated [56].

Although there is no standardized protocol yet, it is thought that psychological tests may also be helpful for the differential diagnosis of ES-PNES in cases where necessary. It is reported that psychiatric disorders such as anxiety and depression are more frequent in patients with psychogenic seizures than epileptic patients, these patients have a higher incidence of suicide attempts and story of psychiatric treatment. In addition, researchers have also observed that patients with psychogenic seizures have a lower quality of life, more frequent long-term health problems and more dysfunctional family relationships than epileptic patients [57]. Personality problems that occur in patients with psychogenic nonepileptic seizures have been the subject of many investigations. The Minnesota Multiphasic Personality Inventory (MMPI) is a very sensitive but nonspecific test in this area. There were statistically significant differences between the patients with epileptic seizures and psychogenic seizures with MMPI especially in hypochondriasis, depression, hysteria and schizophrenia scales, pathologic elevation (T-score ≥ 70) was detected in patients with psychogenic seizures [58]. However, no significant difference was found in cases with ES and PNES in the other two studies [59, 60]. In other words, there are conflicting results about the clinical benefits of MMPI in the differential diagnosis of ES/PNES.

Alexithymia is a Greek term which is used to describe individuals who have difficulty to define and verbalize their emotions or which means “no words for emotions”, emerged in order to explain the symptoms of psychosomatic patients and gained a quick recognition among psychiatrists. It was first observed in psychosomatic patients who were also been seen on several psychiatric disorders such as depression, posttraumatic stress disorder, substance abuse and dependence [61]. Patients exposed to trauma are reported to exhibit alexithymia more frequently than control group without trauma experience [62]. A significant portion of PNES patients have a trauma history, so alexithymia is also common. On the other hand, alexithymia is not a common condition in patients with ES, so alexithymia can be helpful to distinguish ES/PNES.

Despite not being overworked, it is reported that the tendency of hypnosis is relatively increased in patients with PNES. High tendency of hypnosis has been found in a study conducted on 24 patients with ES and PNES by Kuyk et al. with Stanford Hypnotic Clinical Scale measurements in patients with PNES compared to general population and patients with ES [63].

On the other hand, it is necessary to evaluate whether the patients with psychogenic nonepileptic seizures are surely making symptoms consciously. Simulation is easier to notice as it is obviously benefit-oriented. In artificial disorder, the unconscious desire to 'become ill' is the motive that drives the patient. However, secondary gains can also be clearly identified [64].

As noted above, it is very clear that there have been many unanswered questions, even though there have been many studies to distinguish psychogenic nonepileptic seizures from epileptic seizures. It is seen that comparison was made with patients with generalized epileptic seizure, in a significant part of the studies and the heterogeneous structure of psychological nonepileptic seizures, subgroups and the effect of cultural characteristics were not addressed in studies. Moreover, although many studies point out that ictal vEEG is the 'gold standard' in diagnosis, it is still not certain. On the other hand, the place of psychogenic nonepileptic seizures in the classification diagnosis of epileptic seizures is also uncertain. At present, although there is a lot of information in the ES/PNES distinction, the diagnostic criteria of PNES disorders have not yet been established. The heterogeneous clinical appearance of the PNES causes this uncertainty. It is not clear whether it will be evaluated as multiple comorbid mental and personality disorders or neuropsychiatric syndromes in DSM classification system. Because it is not included in the diagnostic classifications, the development of appropriate treatment options and information and studies related to its prognosis are limited.

4. Treatment

Historically, the use apomorphine, saline injection as a placebo, or mouth and nose closure for 20–30 s have been seen for the treatment of PNESs, defined as 'hysterical seizures'. It is also known that Charcot tried different abdominal compressions that failed in PNES treatment [29]. A more acceptable approach is to ensure that the patient speaks about seizures and distress created by seizures in order to provide self-control rather than strengthening their dependence on others [65]. In this way, the patients experiencing seizures alerts generally learn how to control seizures using external focus and abdominal breathing techniques.

The results of treatment trials are contradictory because patients with PNES form a heterogeneous group. It has been reported in some studies that the psychogenic nonepileptic seizures of approximately one-third of the patients stopped after the diagnosis was told to them, better results were obtained for a group of patients who received psychotherapy than those who did not take, in some cases, 34–53% of patients recovered without treatment [66–69]. One of the most important issues in treatment is to report the diagnosis to the patient, because the transmission of the diagnosis can cause some problems. Some patients evaluate the current situation as 'no physical cause' or 'a mental illness'. At the same time, this can be unacceptable for them [70]. On the other hand, seizures may discontinue with a successful communication in 10% patients who were informed about diagnosis [71]. It is reported in a study that the patients were confronted first their diagnosis, then underwent psychotherapeutic approaches and early diagnosis and therapeutic interventions increased the chances of success of treatment [72]. In another study, the health expenditure of the patient, health institution applications and the vEEG costs decreased within 6 months after the diagnosis [10].

The preliminary aim of treatment is to inform and educate the patient and his/her family about the diagnosis. Thus, it will be possible for the patient to be directed to psychiatric care. In addition, unnecessary admission to emergency services, unnecessary treatments and possible adverse effects will be avoided. Antiepileptic drugs may be useful to prevent return in patients with severe abuse or posttraumatic stress disorder, and sometimes it may be appropriate to continue antiepileptic drugs as a mood stabilizer. Although it will continue to be used, the intended use of the antiepileptic drug should be clearly explained to the patient and his/her family in order not to give a double message. It is necessary to cut the antiepileptic drugs gradually when diagnosed except for these conditions [73, 74]. In a prospective study, epileptic seizures were observed in only 3 of 64 patients that antiepileptic medication was discontinued and those informed that seizures were not due to a brain disorder [26]. Especially for patients with dissociative features it is not possible to say that they will certainly not be harmed by seizures. There was no consensus on the recommendation of restrictions on certain activities (such as driving) until these patients had their seizures controlled [64]. PNES treatment has been reviewed by various authors [29, 75, 76]. Most of the studies related to the subject are in the form of small sample case reports and there are few enough powerful or reliable controlled studies. In a study involving psychopharmacological treatment approaches in this area, inpatient group treated with psychological intervention (paradoxical intention) and outpatient group treated with diazepam (5–15 mg/day) were compared. It has been reported that the anxiety is reduced and the symptoms are controlled more effectively in the group treated with paradoxical intention [77]. However, it should be noted that the control group was formed by 15 cases in the study and only 9 cases completed the study. Despite the fact that antidepressants may be effective in other medically unexplained symptoms, there is no adequate data and studies on the use of antidepressant drugs in patients with psychogenic nonepileptic episodes [29, 78, 79]. In all other studies, individual or group-specific psychological treatment methods were discussed [29]. Especially in these studies, cognitive behavioral therapy (CBT), psychodynamic approaches, interpersonal therapy, operant conditioning, eye movement desensitization and reprocessing (EMDR), biofeedback, hypnotherapy, family therapy and multidisciplinary therapies are at the forefront [80–83]. A significant decrease in seizure frequency, anxiety and depression levels, an increase in psychosocial functioning with CBT targeting fear and avoidance behavior have been reported in a 12-session prospective study which is one of the best study done up to this day [84].

Psychoanalytically, psychogenic nonepileptic seizures are an attempt to counteract/defend the traumatic experience of the patient, and at the same time to resolve conflicts related to this experience. At the same time, it is a defense that serves also in the control of the anger, instead of harming someone else, they prefer to hurt themselves. Therefore, it will be appropriate to shape treatment in the direction of these principles, especially in patients who have trauma or unresolved grievances in the past. In other words, patients diagnosed with PNES form a heterogeneous group, and psychodynamic psychotherapy may be a good treatment option for the patients with psychic trauma stories and those who could not mourn. The story of what happened to the patient needs to be formed and the meanings of it should be studied. At the outset of treatment, psychoeducation, prevention of secondary gains, raising awareness of the patient about the relation of psychic processes and seizures and developing a good therapeutic

alliance is a priority. After that the meaning of the symptoms can be focused in depth [64]. However, it should be remembered that psychotherapy may be beneficial for some patients and the same results cannot be achieved in all patients.

5. Conclusion

As a result, epileptic and psychogenic nonepileptic seizures are two pathological conditions that should be evaluated separately in terms of both etiological, formation mechanism and treatment approach. Detailed history of seizures and careful neurological, psychiatric examination, as it provides for the correct diagnosis and treatment for the patients, it will also prevent many negative consequences that the wrong treatment may bring. Since it has been named as hysterical seizure, there has been considerable progress in the diagnosis of PNES with the use of EEG and vEEG in clinical practice. However, focusing on differential diagnosis for the PNES diagnosis by comparing with cases with epileptic seizure only, and the lack of comparison of the clinical appearance of the different subtypes of PNES are the shortcoming of the work done up to this day. Also, the effects of cultural differences on PNES are unknown. For a better understanding of treatment approaches, there is a need for studies with a large sample involving the control group.

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Chapter 7

Subarachnoid Cysticercosis and Ischaemic Stroke in Epileptic Patients

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Additional information is available at the end of the chapter

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Abstract

Whether subarachnoid neurocysticercosis (SNCC) induces ischaemic stroke (IS) in epileptic patients is not yet confirmed because only short-case series and anecdotal case reports have been published, and no observational studies exist in the literature to date. Our main goals are: to estimate the prevalence of ischaemic stroke in epileptic patients presenting with SNCC and stroke frequency among HIV-positive patients in three subgroups; to determine if the odds of ischaemic stroke are elevated in SNCC-epileptic patients compared to epileptic patients with intraparenchymal NCC (INCC); to determine whether the risk for stroke is elevated in HIV-seropositive patients presenting with SNCC or INCC and epilepsy; and to evaluate if and when the potential interaction varies by location of NCC in the brain (intraparenchymal or subarachnoid). Eligible epileptic patients' seropositive status was recorded, and cross-associations for the independent variables (NCC status and HIV status) and outcome variables (ischaemic stroke event) were performed. Compared to the reference group, the odds of IS in PLWNCC were 2.0 and 2.6 times greater in patients with SNCC and INCC, respectively. The frequency of IS was greater in HIV-positive patients in all three groups, but the risk was especially pronounced when seropositive epileptic patients were both NCC groups when compared with the reference group. Subarachnoid NCC increased the risk of IS three time more.

Keywords: neurocysticercosis, stroke, epilepsy, cross-sectional study, subarachnoid neurocysticercosis, HIV, imagenology

1. Introduction

1.1. Background

Neurocysticercosis (NCC) is a preventable and potentially eradicable neurological disease caused by the larva form of tapeworm *Taenia solium* which primarily affects people living in the developing world. Seizures are widely reported to be the most common symptom, occurring in 70–90% of patients [1]. Most patients respond to praziquantel, if cystic lesions are located in the parenchymal tissue, and albendazole when parasites are located in the ventricular system and subarachnoid space, including patients with an associated HIV infection [2]. A well-designed clinical trial about treatment response in subarachnoid neurocysticercosis (SNCC) has not been published; however, some authors have reported the effectiveness of these drugs in SNCC [3–5], while others have found that parasites remain alive at the subarachnoid space even after high dose of albendazole/praziquantel/prednisone was administered [6–10].

In 1977, Gubbay and Matz [11] reported two cases presenting with intracranial hypertension (ICH) and hydrocephalus in association with chronic meningitis; the authors confirmed that repeated CSF analysis may result in diagnostic confirmation of SNCC causing ICH with hemiparesis, partial seizures, and other neurological signs. Currently, it is well known that SNCC in the basal cisterns may cause inflammatory reaction; the leptomeninges become fibrotic at the base of the brain.

According to Takayanagui and Odashima [12], in approximately 60% of the cases, there is an obstruction of the CSF circulation, resulting in hydrocephalus and raised intracranial pressure. When hydrocephalus secondary to cysticercoid meningitis is present, the mortality rate is high (50%) and most patients die within 2 years after CSF shunting; therefore, ventricular and basal cisternal locations are considered to be malignant forms of NCC. In 2001, Bannur and Rajshekhar [13] reported a case as an example of difficulty in confirming diagnosis: this patient had a hypodense non-enhancing mass on CT scan in the regions of quadrigeminal cistern causing obstructive hydrocephalus. He was initially diagnosed with an epidermoid mass but subsequent MRI evaluation and surgery resulted in the diagnosis of a racemose cysticercus cyst. Authors concluded that clinical features of NCC largely depend on the number, type, size, localisation and stage of development of cysticerci, as well as on the host immune response against the parasite [13].

Typical of South Africa, high incidence and prevalence of NCC is found at the former Transkei, currently region C and D of Eastern Cape Province, which is the most disadvantaged region countrywide [14–18].

Many people in the world who suffer a fatal stroke live in developing countries where NCC is endemic. However, prevalence of several tropical diseases, including NCC, is likely to increase in Western, industrialised nations as a result of demographic changes due to migratory flows. It is very well known that stroke is the third most cause of death and the principal cause of adult disability worldwide. Cerebrovascular complications of NCC include transient ischaemic attacks, ischaemic strokes due to infective vasculitis and intraparenchymal haemorrhage [19, 20].

Several case reports about cerebral infarction related to cysticercosis have been published, including angiographic abnormalities [21–27].

In our region, there are other infectious diseases causing infective vasculitis leading to ischaemic stroke such as HIV/AIDS, tuberculosis, INCC and neurosyphilis, but Chagas disease, malaria, haemorrhagic fever, infective endocarditis and mucormycosis are also reported in the medical literature [28, 29].

In 2001, Rocha et al. [30] reported three cases of stroke secondary to NCC. The first one was a 36-year-old man with bilateral middle cerebral artery occlusions presenting an acute right hemiparesis and expressive aphasia. MRI demonstrated several enhancing subarachnoid cysts surrounding the occluded vessels, a right parietal racemose cyst and a left temporal large infarction area. Angiographic study showed total occlusion of left middle cerebral artery and a subtotal occlusion of right middle cerebral artery. The second one was a 42-year-old man with vasculitis of small cortical vessels presenting headache, seizures and focal neurological deficit. CT scan demonstrated several calcifications and a left temporal infarct. Cerebral angiographic study was normal. The third case was a woman, 53 years old, with a past history of six stroke events, behaviour disturbance and seizures. MRI scan demonstrated several cortical and sub-cortical infarcts and cisternal cystic lesions, and angiographic study showed diffuse arteritis of basilar and carotid arterial system. In all three cases, CSF study showed linfomonocitic pleocytosis and positive ELISA for cysticercosis.

Aditya et al. [31] in 2004 reported two autopsied cases of chronic cysticercal basal arachnoiditis causing large arterial territory infarcts and, in the second case, a hypothalamic mass. Both patients were diagnosed and managed, clinically and by neuroimaging, as stroke and neurotuberculosis, respectively. The diagnosis was established only at autopsy, which revealed NCC causing basal arachnoiditis, major vessel vasculitis and infarcts. Histologically, one case showed degenerating racemose cysticercal cyst within the thick basal exudates. In the second case, remnants of the degenerated cysticercal cyst in the form of hooklets and calcareous corpuscles were identified within the giant cell inciting a granulomatous response to form a hypothalamic mass lesion mimicking tuberculoma. They highlighted the importance of considering the non-tuberculous aetiology of chronic basal arachnoiditis like SNCC before initiating therapy, especially in countries where both NCC and tuberculosis are endemic.

Conspicuously absent in the case reports available in the current medical literature are the following research questions: What is the prevalence of SNCC in patients living with neurocysticercosis (PLWNCC)? Is SNCC a risk factor for ischaemic stroke? Does HIV comorbidity increases the stroke frequency in epileptic patients infected with NCC? The main aim of this study is to explore these inquiries and propose new hypotheses for future study.

1.2. Our study

We performed a non-published cross-sectional study of epileptic patients diagnosed with NCC from January 1999 to December 2003 at Umtata General Hospital and from January 2004 to January 2010 at Nelson Mandela Academic Hospital from the rural areas of Mthatha, South Africa. Selected patients for a case–control study under the project: 'Neurocysticercosis' were taken for this research.

All patients were classified into one of the three respective sample groups according to presence and type of NCC or not, collected in groups A, B and C. All patients from Group A met the following selection criteria (inclusion criteria): a positive serology ELISA test for cysticercosis, CT scan of the brain with intravenous contrast enhancement consistent with definitive evidence of cystic lesion (isolate or racemose) in the subarachnoid space without hydrocephalus and suitable to evaluate: (1) focal arachnoiditis when there was contrast enhancement in only one cerebral basal cistern; (2) bilateral cystic lesions with diffuse arachnoiditis, in which contrast enhancement involved several basal cisterns; and (3) ischaemic infarction, in which the number and location of cerebral lesions were analysed and classified as superficial, deep no lacunar (>16 mm), and deep lacunar (<15 mm) at the basal ganglia, without an associated cardiac disease. Demographic and associated stroke were analysed in accordance with the presence of SNCC, and ELISA test for HIV when it was done.

From the large number of epileptic patients with NCC-HIV co-infection in our database, we selected only a few number of epileptic cases for Group B similar to Group A, regarding age and gender to assure a better statistical analysis and under an absolute diagnosis of intraparenchymal NCC (both active and calcified at the same time) with or without ischaemic stroke. The ELISA test for NCC and HIV were both positive. Patients in Group C had no NCC in any presentation and, ELISA test for NCC was negative and HIV test was positive.

Exclusion criteria: All patients with gross modifiable risk factors for stroke such as uncontrolled hypertension and diabetes mellitus, heavy drinkers or smokers, familial hyperlipidaemia, thrombophilia, bleeding disorders and other haematological disorders were excluded. We also excluded patients with heart problems, diagnosis of infective vasculitis apart from those associated with NCC/HIV, suspicion of primary or secondary arterial disease, cognitive or sensory deterioration, patients who have not had check-ups for their NCC/SNCC and stroke for more than 11 months, patients with intraventricular NCC and/or associated hydrocephalus; patients with terminal illnesses, serious psychological illnesses, active addictions to psychoactive substances; patients younger than 13 years old; pregnant patients; patients living with HIV/AIDS in stage IV, patients who have lived more than 6 months outside of our region, the 'first or worst' headache, headaches with increasing frequency or severity, progressive headache, chronic daily headache, headaches always on the same side, headache not responding to treatment, new-onset headaches in patients who have cancer or who were tested positive for HIV infection and new-onset headaches after age 45.

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc., Chicago, Ill). Analyses were performed using an intention to treat bias. A descriptive analysis and an analysis of baseline comparability between the study groups were performed for all study variables. The main variables are INCC, SNCC, IS and headache. All patients were epileptic and HIV reactive. To investigate the potential associations between ischaemic stroke outcomes and the variables of NCC group type and HIV status, prevalence odds ratio and 95% confidence intervals were calculated.

Written consent forms were administered in the first contact with the eligible patients following verbal agreement for participation. For all patients, information on the study's purpose and procedures was provided in addition to ethical considerations, including the participant's

right to intimacy, anonymity, confidentiality, withdrawal and information. Due to the large proportion of low literacy among the patient population, oral consent was observed and confirmed by an impartial witness in many cases where necessary. For patients selected between 1999 and 2002 only oral consent was taken.

All investigators completed CITI training course on the protection of human research. All are sworn to the Hippocratic Oath and committed to respecting the norms of good clinical practice, as well as the requirements of the Helsinki Declaration.

Methods for patient selection and information processing were approved by clinical governance at Umtata General Hospital, and the research protocol was evaluated and approved by Mthatha Umtata General Hospital, University of Transkei and Walter Sisulu University IRB and the respective Ethical Committees (UGH:0001/99, UNITRA:0018/05 and WSU:0068/009).

Out of 459 eligible epileptic patients asked to participate, five initially refused to participate for the baseline evaluation. Four out of the five patients agreed to participate during their follow-up appointment and their data are included here.

The proportion of SNCC without hydrocephalus in PLWNCC (Groups A and B) was 4.77%.

Group A (n = 144) and B (n = 153) showed no remarkable differences between age, gender and HIV status. The control group C (n = 161) consisted of 35.1-year-old-mean age (SD 15.4), 43.5% were males (n = 70) and 56.5% were female (n = 91) and the frequency of HIV positive (stage I–II, 11.2%) almost similar to Groups A and B (**Table 1**).

In total, 243 serial CT scans with at least one scan (range = 1–2) per subject were available in Group A, 201 CT scans in Group B and 162 CT scans in Group C, over the 10-year study period.

Table 2 shows the frequencies of ischaemic stroke events in SNCC and INCC (Groups A and B) and the reference sample (Group C) without considering HIV status.

Table 2 shows the frequency and odds ratio of IS events in each NCC group (as previously discussed) now stratified by HIV seropositive status. HIV-positive patients in Groups A and B had greater odds of IS compared to the HIV-positive patients without NCC co-infection as expected. However, the increased odds were more pronounced in those HIV patients with SNCC (OR: 2.66, 95% CI). The risk of IS in HIV-negative patients followed similar trend with the greatest odds occurring in SNCC group patients comparatively. The risk of developing stroke was 2.82 times more probable in Group A compared with Group B. (**Table 2** and **Figure 1**). This suggests that although co-infection with HIV increases risk of IS, the location of NCC in the brain is a

Groups	Age	Gender (%)		HIV (%)		
	Mean (SD)	Male	Female	+	–	Unknown
A (144)	38.2 (16.9)	52.1	47.9	13.9	31.2	54.9
B (153)	36.9 (15.3)	47.7	52.3	15.7	28.8	55.6
C (161)	35.1 (15.4)	43.5	56.5	11.2	28.0	60.9

Table 1. Patient characteristics by sample group.

Groups	Stroke		Total
	Yes	No	
A	23(15.97%)	121(84.02%)	144
B	14(9.15%)	139(90.84%)	153
C	4(2.48%)	157(97.51%)	161

Table 2. Frequency of stroke by groups.

better predictor of IS risk than comorbidity status. This is also evident in a similar difference in odds ratio for HIV- compared HIV+ were exhibited in Groups A and B. These results also suggest that the interactive effect of co-infection is generalised and do not vary significantly for one type of NCC.

Taking into consideration the HIV status of patients by groups, we found that 40% of patients presented ischaemic stroke (Group A) and the risk to develop an IS among Groups A and B is almost three times more.

After comparing all three groups with similar age, gender and HIV-positive status, the risk of developing an IS increases to more than seven times in patients presenting SNCC over the control group and almost four times in patients presenting intraparenchymal NCC, as shown in **Table 4**.

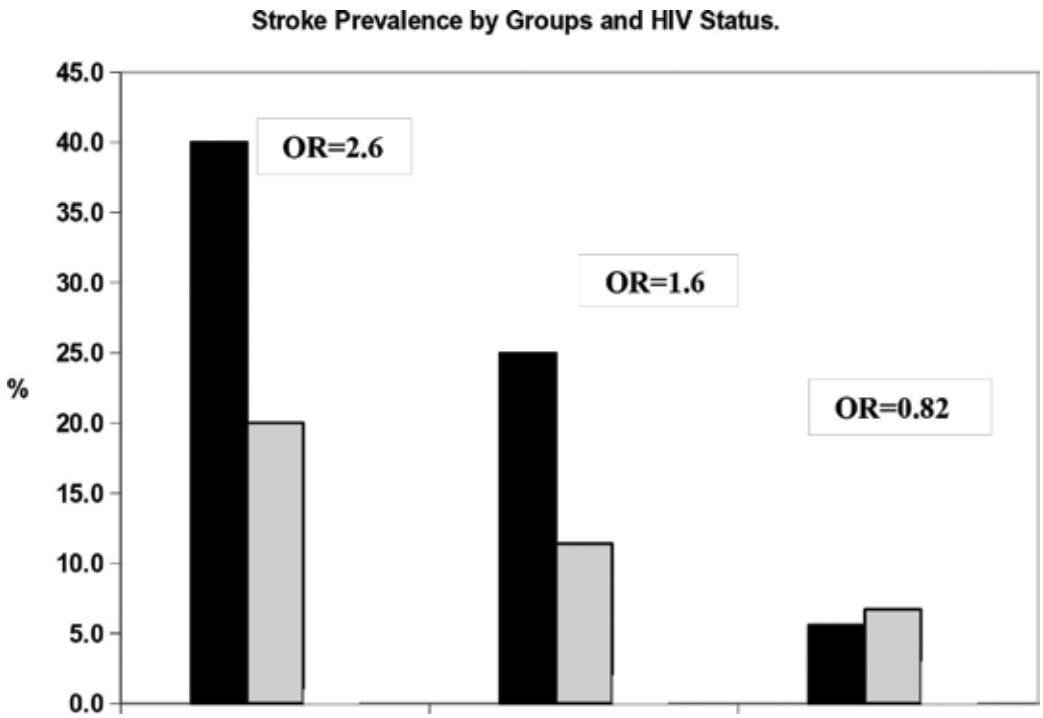

Figure 1. Shows prevalence of stroke by groups and HIV status. *Source*: **Table 3**.

HIV status	Groups	Stroke (%)	OR (95% CI)	A vs. B
+	A	40.0 (n = 20)	2.66 (n = 23)	2.82
	B	25.0 (n = 24)	2.60 (n = 14)	
	C	5.6 (n = 18)	0.82 (n = 4)	
–	A	20.0 (n = 121)		
	B	11.4 (n = 139)		
	C	6.7 (n = 157)		

Table 3. Proportion of patients with IS events by groups and HIV status.

Groups	OR	IC 95%	
A vs. C	7.46	2.51	22.1
A vs. B	1.88	1.33	3.82
B vs. C	3.95	1.27	12.2

Table 4. Odds ratio after comparing different groups.

Concurrent infection with *T. solium* and HIV was expected to occur more frequently because of the increasing frequency of HIV infection in endemic areas of cysticercosis like our region. However, little is known about the influence of HIV infection on the frequency and the clinical course of cysticercosis. Delobel et al. [32] established that giant cysts and racemose forms of neurocysticercosis seem to be more frequent in HIV-infected patients and may be secondary to an uncontrolled parasitic growth because of an impaired cell-mediated immune response.

Prevalence on SNCC in patients LWNCC is not as higher as we expected but can represent the frequency of this problem, while the prevalence of HIV is increasing in countries where NCC is also endemic. Therefore, sooner or later SNCC will be highest, if adequate measures are not taken to eradicate NCC at due time. Other co-infection rates are expected to raise it but unfortunately no systematic reviews of the subject are available in the medical literature.

In spite of the variety of ways used by the parasite to modify host immune response, their mechanism of excretory/secretory product fail and its anti-immune properties are weaker, paradoxically these pathologic changes on the parasite membrane and the surrounding tissue (without remarkable oedema) can be seen in HIV patients with CD4 count around 350 cells/mm^3 and viral load around 55,000 copies/ml or even in window period. Therefore, we have had hypothesised that at the colloid stage, there is an increased microglial activation, associated oligodendrocyte, astroglial changes and subsequent damage of the axonal functions and blood–brain barrier, which can explain the well-known mechanism of *pathological concentration of macrophage histocompatibility complex, interleukin-1 and -6 and tumour necrosis factor-alpha*

among other neurotoxins causing neurovascular lesions, accompanied by increased concentration of pro-inflammatory molecules from meningeal macrophages, choroids plexus macrophages, perivascular macrophages, multinucleated giant cells, according to the number and location of the cysticercus as previously described [33]. *At the present moment, we believe that toxins released by the T. solium cysticercus cause inflammatory changes on the perforating arteries (toxic vasculitis?) at the subarachnoid space rather than a direct effect on the cluster of parasites (mechanical compression). However, the differential of infective vasculitis should be preserved because pathological source is the presence of intracranial cysticercosis.*

In our series, we did not identify any case presenting immune reconstitution inflammatory syndrome, probably because we selected patients from stage I to III of AIDS not on HAART. It is interesting to know that in the brain of patients with ischaemic stroke-associated deaths, there are abundant CD3+, CD8+ and CD68+ cells in the postmortem autopsy [34]. In our study, only one patient died from Group A. We believe that low mortality rate may be related to the exclusion of patients with subarachnoid cysticercosis growing to giant size causing mass effect and obstructive hydrocephalus with mechanical compression, as already discussed [33]. The disease course in SNCC is often long in duration and cysticerci continue to grow and proliferate through tissue. This increase in volume and mechanical resistance from the brain parenchymal may cause osmotic exchange with the CSF and this one factor that may lead to a poor prognosis [35]. Obviously, selecting patients before this stage can help to investigate the effect of the SNCC on the blood vessels without an effect of associated mechanical compression.

Evidence of carotid occlusion in cysticercosis [23, 36, 37], transient ischaemic attack of the vertebrobasilar territory [38] even in children [39] has been reported as anecdotic cases.

The most common affected vascular territory in our series was middle cerebral artery followed by posterior cerebral artery. We did not confirm any patients with SNCC and ischaemic infarct on the anterior cerebral artery territory and only one case has been reported in the medical literature [40].

Haemorrhagic stroke (intracerebral or subarachnoid) associated with NCC and HIV was not selected in our series and some cases reported in the medical literature are not certain [41, 42]. We will investigate the association of haemorrhagic stroke and SNCC in a forthcoming research. Strengths of our study include the large sample size, geographically distinct locations of the participating clinics from the former Transkei in rural South Africa, and potential feasibility of its replication in similar regions worldwide.

Weaknesses of this study include the exclusion of a number of variables that may have contributed to the analysis, such as patient's response to anti-parasitic treatment and the degree of immune compromise. Better reporting of HIV status is also necessary, as over half of the patients selected were HIV-status unknown. In our study, the prevalence of SNCC without hydrocephalus in patients living with NCC is 4.77%.

Risk for ischaemic stroke in patients with subarachnoid NCC is almost three times more for patients with intraparenchymal NCC. Comorbidity of subarachnoid NCC in HIV-positive patients increases up to 7.6-fold.

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2. Racemose neurocysticercosis

Racemose neurocysticercosis (RC) also known as SNCC refers to a very uncommon form of NCC, with the cyst localised mainly in the subarachnoid space and basal cisterns. Usually, the scolex is absent and multiple complex small cysts may form (cluster of grapes), filling the basal cisterns, determining mass effect and distortion of adjacent structures, namely sulci, brainstem and cranial nerves [43–45], these authors consider that in racemose NCC, there is a presence of abnormally large growths of many cystic membranes without a scolex, normally without enhancement, in subarachnoid space and basal cisterns and they found on imagenology that the cysts have a thin wall without a scolex; their signal is isointense or slightly different from CSF, hypointense on T1-weighted images (T1-WIs) and fluid-attenuated inversion recovery (FLAIR), hyperintense on T2-WI, without diffusion restriction, and after contrast there is no wall enhancement. A three-dimensional balanced steady-state free precession sequence (constructive interference in steady state (CISS)), driven equilibrium (DRIVE) or contrast-enhanced MR cisternography helps to detect the underlying cysts [46]. Pamplona et al. [46] reported a case of a *43-year-old woman from Cabo Verde, with an eight-month history of right frontotemporal headaches (without releasing or aggravating factors), ataxia and loss of vision, without significant past medical history of note and no history of head trauma. Home hospital computed tomography (CT) disclosed a large intraventricular cyst, without enhancement after ionic contrast administration, distorting lateral and third ventricles, with obliterations of Monro foramina, determining non-communicating hydrocephalus, with enlargement of occipital and temporal horns of lateral ventricles and ependimary transudation.* They established that *racemose neurocysticercosis (INCC) refers to cysts in the subarachnoid space and is characterised by proliferative lobulated cysts without a scolex.* We also agree with such definition if the presence of scolex is not excluded from the definition, as discussed later. These cysts may vary in size, from 2 to 3 mm in subarachnoid space and basal cisterns, to a few centimetres when intraventricular. Intracranial hypertension and hydrocephalus are two complications that happen when there is a flow obstruction due to intraventricular cysts, arachnoiditis, ependymitis secondary to inflammatory response or mass effect in cases of very large cysts [44, 45].

It is known that in the next several months to years, there is degeneration of the cyst, with associated inflammatory response and peripheral oedema, leading to clinical symptoms and manifestations that may vary according to localisation and mass effect [43–45]. The final stage (calcified) with or without associated oedema is seen in the intraparenchymal presentation and is the main cause of epilepsy in this series; obviously, associated oedema never happens at the subarachnoid space.

The differential diagnosis depends on where the cysts are localised; if in the subarachnoid space and basal cysterns, the differential diagnoses are arachnoid cysts, neuroglial cysts, gliomas, cavernous malformations and echinococcal cysts.

Detection of cysticercal antigens by monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA) in the CSF of clinically suspected patients supports the diagnosis of active SNCC.

3. Stroke

Almost all clinical presentations of stroke can be seen in epileptic patients having SNCC [27, 41, 46–65]. Despite the increasing number of reports on haemorrhagic stroke to the medical literature [19, 20, 23, 24, 26, 27, 29–31, 37–41, 47–62], the prevalence of stroke secondary to NCC remains higher in IS secondary to infectious vasculitis. The most common clinical manifestations of NCC are seizure and headaches. In addition, cysticerci may cause mass effect, obstructive hydrocephalus, intracranial hypertension, cerebral infarction, vasculitis and meningitis [66, 67]. Seizures are more common in intraparenchymal NCC, resulting from cystic perilesional inflammation, new infarcts and vasculitis. Acute encephalitis-like presentation is rare, but can be the first symptom in the paediatric population [66]. Cerebrovascular complications of NCC include lacunar infarction, large-vessel disease, transient ischaemic attacks, progressive midbrain syndrome and brain haemorrhage, resulting from a multiplicity of mechanisms, including luminal narrowing due to sub-intimal cushions, vasospasm due to arteritis in midsized and small perforating vessels of the brain, and fresh thrombi [44, 45].

In our region, the incidence and prevalence of ischaemic stroke due to infectious vasculitis is higher in HIV patients compared with other causes of infectious vasculitis because HIV/AIDS is more common than other mentioned infectious diseases, at the present moment. Tuberculosis (TB) of the CNS and neurosyphilis are not uncommon problems. Unfortunately, the worse prognosis is reserved for HIV/AIDS followed by TB, neurosyphilis and others.

Stroke as a complication of NCC occurs in a very small percentage of cases, mostly involving small perforating vessels while major intracranial vessel involvement is extremely rare. Coleman et al. [47] also reported two autopsied cases of chronic cysticercal basal arachnoiditis causing large arterial territory infarcts and, in the second case, a hypothalamic mass. In their patient, *the diagnosis was established only at autopsy, which revealed SNCC causing basal arachnoiditis, major vessel vasculitis and infarcts. Histologically, case 1 showed degenerating racemose cysticercal cyst within the thick basal exudate. In the second case, remnants of the degenerated cysticercal cyst in the form of hooklets and calcareous corpuscles were identified within the giant cell inciting a granulomatous response to form a hypothalamic mass lesion mimicking tuberculoma*. These authors highlighted the importance of considering the non-tuberculous aetiologies of chronic basal arachnoiditis like SNCC before initiating therapy especially in countries endemic to both NCC and tuberculosis.

> Other authors [48, 49] reported stroke *as a recognised complication of NCC, occurring in 2–12% of cases, mostly in the form of small lacunar infarcts and informed about a 51-year-old Hispanic woman, which was secondary to complete occlusion of the left internal carotid and bilateral anterior cerebral arteries. Their report represents the third reported case of internal carotid artery occlusion and the first reported case of anterior cerebral artery occlusion secondary to neurocysticercosis at that time*. Another author [50] considered that ischaemic stroke *is a relatively common but underrecognised complication of NCC and it is usually caused by inflammatory occlusion of the arteries at the base of the brain secondary to cysticercotic arachnoiditis. In most cases, the involved vessels are of small diameter and the neurological picture is limited to a lacunar syndrome secondary to a small cerebral infarct. However, large infarcts related to the occlusion of the middle cerebral artery or even the internal carotid artery have also been reported* [50]. Viola et al. [57] reported a patient

who *presented with relapsed subarachnoid haemorrhage possibly linked to NCC*. In addition, they performed a *literature review of all of the reported cases of aneurysmal and non-aneurysmal haemorrhagic cerebrovascular events associated with NCC until year 2011 and identified 11 such cases. The majority of the individuals were young males (mean: 38 years; 70% males). Four cases (36%) had aneurysms. Four (36%) others had negative cerebral angiograms and therefore classified as non-aneurysmal, while the remaining three (28%) did not report sufficient information to classify them. All cases with aneurysmal haemorrhage underwent successful surgical repair of the aneurysms. Seven patients received albendazole (including three who have had surgery). Three patients died; all three presented in the pre-albendazole era.* In summary, NCC should be considered in the differential diagnosis of haemorrhagic cerebrovascular events in young patients without classical vascular risk factors who have lived or visited NCC endemic areas [57].

In 1998, using cerebral arteriography Barinagarrementeria and Cantú [27] studied 28 patients (mean age, 37 years) with subarachnoid cysticercosis admitted to their hospital from July 1993 to February 1996 and found that *15 patients had angiographic evidence of cerebral arteritis (53%); 12 of the 15 had a stroke syndrome (P = .02). Eight of the 15 patients (53%) with cerebral arteritis had evidence of cerebral infarction on MRI*. In that series, *the most commonly involved vessels were the middle cerebral artery and the posterior cerebral artery*, as we already discussed [33]. They concluded that *the frequency of cerebral arteritis in subarachnoid cysticercosis was higher than previously reported, and middle size vessel involvement is a common finding, even in those patients without clinical evidence of cerebral ischaemia.*

Some authors [58, 62] consider that NCC *is a disease with protean manifestations, which depends upon the number of parasites, their location and the degree of host inflammatory response. Most common clinical manifestations include late onset epilepsy or symptoms of intracranial hypertension and cerebrovascular complications have been reported to occur in 4–12% of patients* [58, 62]. In the majority of their cases, the diagnoses were ischaemic cerebrovascular events associated with vasculitis and/or thrombosis from surrounding cysts in both small- and large-diameter vessels. *Subarachnoid haemorrhages have been noted in SNCC and have been associated with cerebral aneurysms in some, but not all, cases* [58, 61]. Inflammatory aneurysms are usually located at distal intracranial arteries, not at bifurcations like congenital aneurysms, and are more commonly fusiform in shape. The wall of inflammatory aneurysms and parent vessels are extremely friable, and the possibility of intraoperative rupture is higher; in addition, inflammatory aneurysms are fusiform in shape so clipping of the aneurysm neck while preserving the parent artery is technically challenging [61]. As a result, *they are generally secured by wrapping* [59], *clipping of the proximal artery* [64] *or trapping* [61]. Obviously, SNCC should be considered in the differential diagnosis of aneurysmal and non-aneurysmal haemorrhagic stroke events in all patients living in regions where NCC is endemic.

4. Imagenology

Based on our experience, imagenology is the investigation of choice for confirmation of SNCC. MRI scan is better than CT scan to identify intraventricular NCC and CT is better to confirm calcified intraparenchymal NCC, and both can be used for confirmation of SNCC but

CT scan costs less; for establishing the stage of NCC, one of them are mandatory, and both are necessary before and after the treatment [65–69].

Recently Xiao et al. [70], investigated the imaging features of NCC to provide clinicians with valuable information in the diagnosis and treatment and then investigate the imagenological features of 71 consecutive cases of NCC diagnosed by CT and MRI in 5 years time; finding parenchymal cysticerci in 53 cases (92.9%), subarachnoid cysticerci in 39 cases (68.4%), ventricular cysticerci in 13 cases (22.8%) and spinal cysticerci in 1 case; 35 cases were associated with leptomeningitis, 10 cases were with hydrocephalus and they concluded that the imaging findings of the cysticerci, including their location, numbers, cystic sizes, capsular thickness, densities and signals of the scolices, as well as the peripheral oedema, have distinct value in timely making possible diagnosis of neurocysticercosis for clinicians. Similar characteristics are found in our series [1, 7, 14–18, 33, 71–89]. Combination of SNCC and INCC in the same patient as described by Hauptman [69] was also found in our series.

Apart from CT/MRI, angiographic studies sometimes are necessary to determine the imagenological features of vascular malformations, vasculitis and occlusion of blood vessels of the brain associated with NCC. In a previous study, 15 (53%) out of 28 patients with subarachnoid cysticercosis who underwent cerebral angiography had evidence of cerebral arteritis in middle size arteries (middle cerebral artery and posterior cerebral artery) [27].

> In one of the patient reported by Rocha et al. [48], MRI *demonstrated several enhancing subarachnoid cysts surrounding the occluded vessels, a right parietal racemose cyst and a left temporal large infarction area. Angiographic study showed total occlusion of left middle cerebral artery and a sub-total occlusion of right middle cerebral artery.* In the second case, CT scan *demonstrated several calcifications and a left temporal infarction area. Angiographic study showed diffuse arteritis of basilar and carotid arterial system.* In the patient reported by Levy et al. [49], the MRI demonstrated the presence of enhancing subarachnoid material surrounding these occluded cerebral arteries, providing antemortem, non-invasive documentation of the inflammatory meningeal cysticercoid reaction that was presumably responsible for the occlusive arteritis causing the cerebral infarction. In this setting, CT scan and CSF examination usually support the cause-and-effect relationship between neurocysticercosis and the cerebral infarct by showing abnormalities compatible with cysticercotic arachnoiditis. Pamplona et al. [46] *reported a case of a 43-year-old woman with an eight-month history of headaches, ataxia and loss of vision. CT and MRI showed an intraventricular cyst, causing entrapment of Monro foramina and hydrocephalus, smaller cysts at subarachnoid space in temporal lobes, Sylvian fissures, suprasellar and peri-mesencephalic cisterns, and an intra-orbital cyst. Additionally, there were acute ischaemic vascular lesions on the left thalamus and corpus callosum splenium and sub-acute ischaemic lesions of both occipital lobes.* Gilman et al. [90] reported a patient who presented with a relapsed non-aneurysmal subarachnoid haemorrhage possibly associated with subarachnoid cysticercosis and the *MRI of her brain revealed a new left subarachnoid haemorrhage involving the left suprasellar cistern, inter-peduncular cistern, left ambient cistern, and again the left Sylvian fissure. Additionally, the images showed dilatation of the lateral and third ventricles, and the aqueduct of Sylvius, with obstruction caused by cysts associated with leptomeningeal enhancement of the supracerebellar cistern.* Other authors also reported similar findings [43, 44].

Without doubt, MRI is an ideal test for investigating SNCC. However, imagenological diagnosis of SNCC is usually difficult when classical MRI sequences are used [91]. Therefore, Carrillo et al. [91] evaluated the advantages of 3D MRI sequences [fast imaging employing steady-state acquisition (FIESTA) and spoiled gradient recalled echo (SPGR)] with respect to classical sequences [fluid attenuation inversion recovery (FLAIR) and T1] in visualising *T. solium* cyst in

these locations and they found that 47 *T. solium cysts located in the basal cisterns of the subarachnoid space were diagnosed in 18 Mexican patients. A pre-treatment MRI was performed on all patients, and all four sequences (FIESTA, FLAIR, T1 SPGR, and T2) were evaluated independently by two neuroradiologists*. The mentioned authors found *FIESTA sequences allowed the visualisation of cyst membrane in 87.2% of the parasites evaluated, FLAIR in 38.3%, SPGR in 23.4% and T2 in 17.0%. Therefore, the superiority of FIESTA sequences over the other three imaging methods was statistically significant ($P < 0.001$). Scolices were detected by FIESTA twice as much as the other sequences did, although this difference was not significant ($P > 0.05$). Differences in signal intensity between CSF and parasite cysts were significant in FIESTA ($P < 0.0001$), SPGR ($P < 0.0001$) and FLAIR ($P = 0.005$) sequences*, and they [91] concluded that, *for the first time, the usefulness of 3D MRI sequences to diagnose T. solium cysts located in the basal cisterns of the subarachnoid space was demonstrated. The routine use of these sequences could favour an earlier diagnosis and greatly improve the prognosis of patients affected by this severe form of the disease.* An accurate diagnosis of this condition is important since early treatment with steroids is advised to ameliorate the subarachnoid inflammatory reaction which may cause recurrent cerebral infarcts [50].

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This book contains selected peer-reviewed articles that cover novel information on epileptic seizure and psychogenic non-epileptic seizures written by international researchers. In this book, we discuss self-reporting technologies for supporting epilepsy treatment. We also discuss about the diagnostic testing in epilepsy genetic clinical practice. Clinical aspects related to diagnosis in patients presenting psychogenic non-epileptic seizures vs. epileptic seizures and neurocysticercosis are discussed as well. We delivered novel aspects about the treatment for pseudoseizures. In another chapter, the authors estimated the prevalence of ischemic stroke in epileptic patients presenting subarachnoid neurocysticercosis and ischemic stroke frequency among HIV-positive patients, and finally other authors discuss autoimmune epilepsy, its new development, and its future directions.

We are looking forward with confidence and pride to the remarkable role that this book will play for a new vision and mission.

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