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Ischemic Stroke of Brain

Edited by Pratap Sanchetee

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http://dx.doi.org/10.5772/intechopen.72965
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Contributors

Jolanta Dorszewska, Marta Kowalska, Katarzyna Wize, Iga Wieczorek, Wojciech Kozubski, Wen-Long Hu, Yu-Chiang Hung, Chun-Ting Lee, Dragos Catalin Jianu, Silviana Nina Jianu, Claudia Barsan, Traian Flavius Dan, Georgiana Munteanu, Alvaro Soto, John Cole, Christopher Stack

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First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

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

Ischemic Stroke of Brain
Edited by Pratap Sanchetee

p. cm.

Print ISBN 978-1-78984-219-7

Online ISBN 978-1-78984-220-3

eBook (PDF) ISBN 978-1-83881-709-1

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Meet the editor

Pratap Sanchetee is a Consultant Neurologist at Sanchetee Hospital & MediPulse Hospital, Jodhpur, India. He graduated (MBBS) in 1970 and acquired postgraduate qualification (MD Medicine & Therapeutics) in 1974. He achieved super-specialization (DM Neurology) in 1985 from the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. He served in the Armed Forces India as a Physician & Neurologist for 24 years (1974-1998). He has worked as an Associate Professor at the Armed Forces Medical College (1994-1998), Pune, India. He has published 98 original papers, chapters, review articles in national and international journals and served as the editor of two books and two journals. His area of interest are stroke, epilepsy, headache and delivery of neurology care at peripheral centers. He is currently the Chairperson of the Tropical Neurology Subsection of Indian Academy of Neurology. Currently, he is also the Director (Research) at the International Ahinsa Research & Training Institute of Spiritual Technology (I-ARTIST), Mumbai and guiding research on meditation and the brain.

Contents

Preface

The stroke is the third leading cause of death and disability across the globe. The viability and functions of the brain critically depend on time-dependent blood flow. Today, management of a suspected case of stroke is done by a specialist team of medical and paramedical personnel who are trained and tuned to act swiftly without wasting any time. Contrast to about 5 decades ago, we had a sense of frustration while handling a stroke victim with hardly anything positive to offer. Credit for this goes to advances in imaging, newer therapeutic agents, endovascular management and a strong rehabilitation concept. Multimodal imaging permits the treating team to identify salvageable brain tissue.

The ischemic stroke is commonly thought to be the result of enhanced atherosclerosis of brain vessels with common risk factors being hypertension, diabetes mellitus and smoking. Better understanding and robust epidemiological studies have permitted us to identify many more etiologies and risk factors. The migraine is one such recognized factor that predisposes an individual and this has been highlighted in the first chapter of the book. Traditionally, a stroke was considered to be of primarily arterial origin. With newer imaging and hematological investigations, we are identifying a large number of strokes that are of venous origin. Clinical presentation, investigations and management differs in such cases with that of commonly encountered arterial strokes. The next two chapters are devoted to venous strokes, highlighting clinical presentation and approach to cerebral venous and dural sinus thrombosis.

The modern management of ischemic strokes involves intravenous thrombolysis within a window period of four and half hours. Several new drugs are being tried with an aim of better efficacy and an enlarged therapeutic window. Endovascular management with newer stent retrievers, though highly expertise oriented, has a higher rate of recanalization with an extended therapeutic window. An experience with intravenous thrombolytic in Chile is the topic in the next chapter and it discusses development and benefits with thrombolysis in stroke. Traditional Chinese medicine for neonatal hypoxic ischemic encephalopathy is discussed in the next chapter.

A new era has emerged in the management of ischemic stroke treatment. This book, written by experts, aims to improve the understanding of stroke medicine for postgraduate medical students in medicine and neurology who have an interest in stroke care.

Dr Pratap Sanchetee, MD, DM (Neurology)
Consultant Neurologist
Sanchetee Neurology Research Institute
Jodhpur, Rajasthan, India

Chapter 1

Migraine and Risk Factors of Vascular Diseases

Marta Kowalska, Katarzyna Wize, Iga Wieczorek, Wojciech Kozubski and Jolanta Dorszewska

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72570

Abstract

Migraine is a common neurological disease that affects both women and men in a different age. It is believed that migraine is a multifactorial disease with strong genetic and environmental factors. Current molecular studies in migraine are focused on biochemical (homocysteine, asymmetric dimethylarginine) and genetic (*ACE*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *eNOS*, *NOTCH3*) risk factors associated with vascular diseases. Polymorphisms and mutations in mentioned genes predispose to migraine as well as cardiovascular diseases and stroke. According to the literature data, 13–15% of migraine with aura patients suffer from vascular diseases, too. The strict relation between migraine with aura and stroke is observed in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lifestyle plays an important role both in the pathomechanism of migraine and vascular diseases. Hypertension, obesity, dyslipidemia, and diabetes mellitus are the important risk factors for those pathological conditions. Therefore, early diagnosis of migraine and the implementing effective pharmacotherapy can lead to the prevention of cardiovascular and cerebrovascular diseases.

Keywords: genetic variants, CADASIL, risk factors, cardiovascular diseases, stroke, migraine

1. Introduction

Migraine is a primary headache disorder and one of the most common neurological diseases because it affects 11% of the adult population worldwide. Due to clinical manifestation, the disease is divided into two main subtypes: migraine with aura (MA), the classic form, and migraine without aura (MO), the common form [1]. The exact pathomechanism of migraine remains unclear, but the new explanation underlines the neurovascular background with an

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important role of trigeminovascular system and cortical spreading depression (CSD). CSD is a wave of electrophysiological hyperactivity followed by depression spreading across the cortex. This process leads to decrease in blood flow and is manifested in the aura. Migraine is a polygenetic disease with the contribution of environmental factors [2].

The most significant risk factor of migraine is gender, as migraine is more prevalent in females than in males, but a female: male ratio ranging from 2:1 to 4:1 in several populations [3, 4]. The ratio is not consistent across the age because there is no difference in the percentage of boys and girls among children aged 7–9 affected by migraine. After that age, the migraine is more common in females. The prevalence of migraine is the highest in girls after puberty and among women aged 30–50, and declines in post-menopausal period. However, the similar trend in prevalence of migraine is observed in adult men, but the absolute values are lower (**Figure 1**) [5].

Moreover, female patients with migraine are more prone to vascular diseases as compare to males. The correlation between migraine and vascular diseases, especially cerebrovascular, has been studied from ages due to similar features, such as neurovascular component, a decrease in blood flow and platelet aggregation. MA is often associated with stroke symptoms and ischemic, or rarely hemorrhagic stroke events. No such strong relation was found in MO or other headaches [6, 7]. Numerous meta-analyses underline that MA doubles the risk of ischemic stroke [8–10]. This association is stronger in younger adults, especially women <45 years of age. In the young woman with MA, the combination of smoking and oral contraceptive use has a prominent role in stroke developing [8, 9]. The high frequency of migraine attacks and longstanding history of migraine are also the risk factors for stroke [6, 11]. It may be explained by subclinical ischemic brain lesions observed in magnetic resonance imaging (MRI) of those patients [6].

The risk of ischemic stroke in migraine patients may also be increased by cardiovascular risk factors, e.g., diabetes, hypertension, obesity and dyslipidemia [12], hyperhomocysteinemia, as well as genetic factors, e.g., C677T polymorphism in *MTHFR*, insertion/deletion polymorphism in *ACE* or mutations in *NOTCH3* [13].

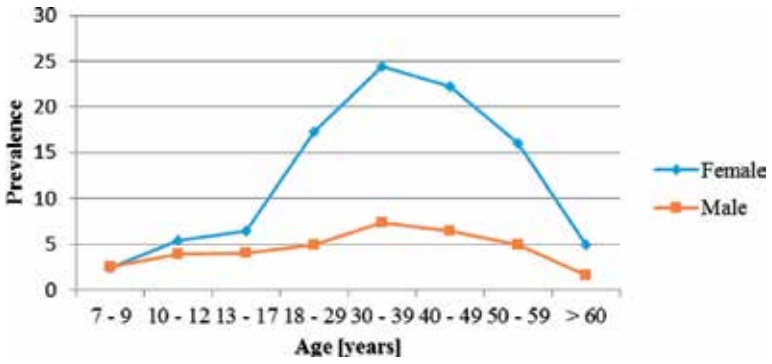

Figure 1. Migraine prevalence by age and sex, based on [5].

http://dx.doi.org/10.5772/intechopen.72570

2. Cardiovascular risk factors

The cardiovascular diseases (CVD) and MA often coexist. The CSD involved in MA pathophysiology, migraine attacks frequency, prothrombotic effects, and impaired vascular reactivity in migraine patients or even migraine-specific treatments may increase the risk of CVD [14]. The risk factors for vascular diseases include changes in female sex hormones, hypertension, obesity, dyslipidemia and diabetes mellitus or elevated concentration of homocysteine (Hcy) and asymmetric dimethylarginine (ADMA).

2.1. Sex hormones

Gender differences in migraine prevalence can be explained by the influence of female hormones. Fluctuation in female sex hormones levels correlates with migraine, as attacks frequency is higher during menstruation [15, 16]. The peak estradiol level in women with menstrual related migraine is lower than in healthy group [17]. Another sex hormone, estrogen is also indirectly involved in pain transmission and pathophysiology of migraine. Additionally, estrogen, which is involved in thrombotic propensity and vasodilatory response, play the protective role against CVD risk. The CVD prevalence surges during menopause, when hormone balance is changed. This relation can explain the higher risk of CVD among younger women suffering from migraine [16].

The prospective cohort study of Kurth et al. [18] shows a consistent link between migraine and CVD events and cardiovascular mortality in women with more than 20 years of follow-up. The authors found that an approximately 50% increased risk of major CVD like myocardial infarction, stroke, coronary artery procedures, and angina pectoris. The previous study in women indicates that only MA is associated with elevated risk of CVD [14, 19]. However, in the men group, migraine is correlated with increased risk of subsequent major CVD, which was driven by the increased risk of myocardial infarction [20].

2.2. Hypertension

The major CVD risk is hypertension, which high appearance was found in individuals with migraine [21]. Hypertension occurs in migraine patients, both females and males, in younger age than in the non-migraine population. The 5-year prospective cohort study in Finland demonstrated that migraine is associated with an increased risk of hypertension among working-age population [22]. Among patients suffered from hypertension-migraine comorbidity the onset of both disorders occur at about 45 years of age, with the migraine starting significantly later than in only migraine patients and hypertension significantly earlier than in the hypertension-only group. Moreover, comorbidity group has a higher occurrence of the history of cerebrovascular events [23]. It is important to control hypertension in migraine and apply the proper treatment, because uncontrolled may lead to worsening of a headache and therapeutic failure. It is also crucial for the control of cerebrovascular risk, which is already increased in patients with MA [24].

2.3. Obesity

Modifiable risk factor for both CVD and migraine is obesity. Migraine and obesity are associated in several ways [25]. Obesity is related to higher migraine prevalence, higher attacks frequency, and also with elevated risk for developing chronic daily headache with migrainous features or transformation from an episodic migraine to chronic form [26, 27]. According to Bigal et al. [28], only 4.4% of migraneous with normal weight had 10–15 headache days per month, but percentage increases with bigger weight, in the overweight group it was 5.8%, in the obese 13.6%, and the morbidly obese 20.7%. The age and sex are also important covariates in associations between obesity and migraine [25].

The literature indicates that MA and obesity seem to be connected with CVD. It is known that such inflammatory mediators, like cytokines (interleukin 6—IL-6 and tumor necrosis factor-α—TNF-α), and calcitonin gene-related peptide (CGRP), which levels are increased in obese individuals, play important role in migraine pathophysiology. They may enlarge the number and duration of migraine attacks, which in turn cause central sensitization. Repeated central sensitization may be associated with neuronal damage and with poor modulation to pain. Plasma CGRP level is mostly elevated in women and its secretion can be increased by fat intake. Other peptides, the hypocretins (hypocretin-1 and -2) may also link the metabolism and pain. They control nociception and release of CGRP from trigeminal neurons. Hypocretins regulates appetite and energy metabolism: their activity is decreased in obesity. It is postulated that the dysmodulation in the hypocretinergic pathways is associated with increased susceptibility to neurogenic inflammation and migraine attacks [27, 28].

2.4. Dyslipidemia

Obesity is directly connected with dyslipidemia. Several studies explored the relationship between dyslipidemia and migraine in a cardiovascular context. The population-based study of men and women aged 20–65 year in the Netherlands s found that adult MA patients have "riskier" profile for CVD than MO [29]. The authors indicated that increased total cholesterol (≥240 mg/dL) and the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio (>5) had been associated with MA. The study of Gruber et al. [30] showed that in normal weight MA patients, not only total cholesterol level is elevated, but also low density lipoprotein cholesterol (LDL-C) and oxidized LDL-C levels as compared to normal weight controls. It was demonstrated that elevated oxidized LDL-C increases the risk of migraine almost eight times. In the cross-sectional study from France, elevated levels of total cholesterol and triglycerides were associated with MA, but not with other headaches in the elderly [31]. There is also a correlation between cholesterol levels (total and LDL-C) and degree of migraine severity, with higher cholesterol values for more frequent and intense migraine attacks [32]. Moreover, the positive associations among MO, and VLDL cholesterol (VLDL-C) and remnant VLDL particles (VLDL3) were observed in women and men, respectively. VLDL is fractioned into IDL and VLDL3, which has been previously connected with higher CVD risk [33].

2.5. Diabetes mellitus

It is postulated that diabetes mellitus (DM) is associated with migraine, but there are conflicting results that relationship is interesting because DM affects vascular reactivity, induces neuropathy, and can be important in the pathophysiology of migraine [34]. The prospective cohort study from Finland observed that women with a headache are more often diabetic [35]. Haghighi et al. [36] showed no significant differences in the prevalence of migraine between diabetic and non-diabetic patients, these results confirmed previous study [37]. However, the authors indicated that migraine prevalence is related to the family history of migraine in the first-degree relatives, the history of hypoglycemia and durations of DM type 2. Other results demonstrated that migraine is significantly less prevalent in patients with DM than without DM [34, 38]. The study of Aamondt et al. [34] also showed that migraine prevalence is lower among patients with duration of DM ≥ 13 years or HbA1c levels >6.6%.

2.6. Hcy and ADMA

Hcy is an endogenous sulfur amino acid, which is formed as the intermediate product during metabolism of methionine in kidney, liver, small intestine, pancreas, blood vessels, and skin [39]. In its transformation, some enzymes and co-factors are involved, e.g., methylenetetrahydrofolate reductase (MTHFR), cystathionine beta synthase (CBS), methionine synthase (MS), also known as 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), folic acid, and vitamins B6 and B12 [40]. Increased level of Hcy (which can lead to hyperhomocysteinemia) is an important risk factor for ischemic heart disease, venous thromboembolism, ischemic stroke, and other CVD [41]. The elevated Hcy level has also been reported in patients suffering from MA [42], which may indicate an increased risk of CVD in this group. Mechanisms of adverse effects of Hcy on blood vessels are seen in the intensification of oxidative stress, reduced amount of nitric oxide (NO), the cytotoxic effect on endothelial cells, inflammation in the vascular walls, and abnormalities of the coagulation process [43]. The level of Hcy may be regulated by polymorphisms in genes encoding enzymes necessary for its metabolism, e.g., *MTHFR*, *MTR*.

ADMA is a naturally occurring amino acid, an analog of L-arginine that competitively inhibits endothelial nitric oxide synthase (eNOS) activity, causing vasoconstriction and endothelial dysfunction leading to CVD [44]. eNOS catalyzes arginine oxidation to NO, which is one of the strongest vasodilators in the human body. Studies have confirmed that NO, changing cerebral blood flow, is responsible for migraine headaches [45]. Elevated levels of ADMA have been reported in patients with migraine compared to the control group, without any difference between MA and MO. It is interesting that the same studies also showed higher NO level in migraineurs than in control. The possible reason for increase in both ADMA and NO concentrations may be an attempt to compensate for elevated NO level and excessive vasodilatation [46]. However, there are also reports that ADMA and NO levels in migraine patients do not differ from the control group [47]. Higher concentration of ADMA may be caused by abnormalities in the function of dimethylarginine dimethylaminohydrolase (DDAH) whose role is to degrade ADMA to dimethylamine and citruline [48]. There are two forms of this enzyme: DDAH1 and DDAH2, encoded by different genes: *DDAH1* and *DDAH2*,

respectively. It was found that polymorphisms (rs233109, rs6669293, and rs12140935) in the *DDAH1* gene may influence the ADMA level [49]. The interaction among Hcy, DDAH, and ADMA was also investigated. Studies conducted on neuronal cell cultures show that DDAH inhibition by Hcy results in higher ADMA accumulation and a decrease in NO production [50]. Overexpression of DDAH protects from adverse effects for cerebral blood vessels, that results from elevated levels of Hcy [51].

3. Genetic risk factors

Migraine is a polygenetic disease. According to population-based family studies, MA is four-times more common in individuals with first-degree relatives suffering from MA, while the risk for MO increases two-times in terms of having first-degree relatives with MO [52]. Therefore, numerous studies investigated the association between genetic polymorphisms or mutations and MA, MO. Polymorphisms in gene coding angiotensin I—converting enzyme (ACE) and in genes related to Hcy metabolism, may increase risk both for migraine and vascular diseases. Moreover, the strict relation between migraine, especially MA and stroke, is presented in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

3.1. Angiotensin I-converting enzyme (ACE)

ACE, which is a part of the renin-angiotensin system (RAS), converts the inactive angiotensin I to angiotensin II. Angiotensin II is an active peptide responsible for vasoconstriction, regulation of blood pressure and blood volume [53]. The ACE inhibitors are used in migraine prophylaxis, and for hypertension and coronary artery disease treatment [54]. The activity of ACE may be controlled by insertion/deletion (I/D) polymorphism (rs1799752) in *the ACE* gene. The DD genotype of *ACE* I/D polymorphism is associated with the higher ACE activity, which increases angiotensin II level and in result leads to the imbalance in RAS [55]. The I/D polymorphism was linked to numerous diseases, e.g., hypertension, ischemic stroke, and migraine (MA, MO or an overall migraine, depending on the study) [56]. Thus, there is a possible association between this polymorphism, migraine, and CVD. According to Schurks et al. [57], the MA patients carrying D allele have the two-fold increased risk of CVD. The data about DD genotype and migraine attack frequency are inconsistent. Schürks et al. [58] showed that *ACE* D allele does not influence the MA or MO attack frequency while Paterna et al. [56] found that carrying the D allele determines more frequent MO attacks. The protective effect of II genotype may contribute to the reduction of the dose of ACE inhibitors in migraine prophylaxis [59].

Both polymorphisms in *MTHFR* and *ACE* genes promote oxidative stress, endothelial dysfunction and in consequence, may predispose to stroke. It was suggested that *MTHFR* C667T TT and *ACE* DD genotypes in combination might increase the migraine susceptibility, especially MA [60]; while the other study did not confirm this conclusion [61]. The meta-analysis indicated that *MTHFR* C667T TT genotype increases the MA risk, while the *ACE* II genotype protects against both MA and MO, but only in non-Caucasian populations [62].

3.2. MTHFR, MTR, MTRR, CBS, and eNOS

MTHFR is responsible for the conversion of 5,10-methylenetetrahydrofolate (CH2THF) to 5-methyltetrahydrofolate (CH3THF), which is a donor of the methyl group in remethylation of Hcy to methionine. Polymorphisms in *MTHFR* gene may be the reason of higher level of Hcy in blood. Fourteen rare mutations of *MTHFR* gene and one common C677T polymorphism in *MTHFR* gene were associated with severe enzymatic deficiency [63]. The *MTHFR* C677T polymorphism (Ala222Val) is associated with the decreased enzymatic activity to 30% in TT homozygous subject and 60% in individuals with CT genotype as compared to wild type genotype CC [64]. Several studies analyzed the association between *MTHFR* gene polymorphisms and migraine and obtained different results. Studies carried out in Japanese and Turkish population showed the higher frequency of TT genotype in migraine patients than in the controls [65, 66]. Moreover, Kowa et al. [65] found the particularly high frequency of *MTHFR* C677T TT genotype in MA, what correlates with results of Caucasian population studies [67, 68] reporting that TT genotype may be a risk factor for MA, but not for MO. On the other hand, studies conducted on the group of Finns excluded the association between *MTHFR* C667T polymorphism and migraine [69]. Recent meta-analyzes confirmed that the TT genotype of *MTHFR* C677T polymorphism is significantly associated with the risk of MA both in Caucasian [70] and non-Caucasian group [71] and total migraine in the non-Caucasian group [70, 71].

Another, less common *MTHFR* gene polymorphism that may be associated with migraine is A1298C (Glu429Ala). Studies by Kara et al. [66] showed that CC genotype is more common in migraine patients than in control subjects. The *MTHFR* A1296C polymorphism also reduces the activity of MTHFR without the increase in Hcy level and decrease in folate level in individuals with CC genotype. However, heterozygous patients with both *MTHFR* C677T and A1298C polymorphisms had higher levels of Hcy as compared to those who carried only C677T *MTHFR* polymorphism [72, 73].

The level of Hcy and folate may also be altered by the polymorphism in *MTR* gene encoding MTR enzyme responsible for remethylation of Hcy to methionine with the participation of vitamin B12 and 5-methyltetrahydrofolate [74]. So far, one common polymorphism A2756G (Asp919Gly), has been described in the *MTR* gene [75]. However, the effect of this polymorphism on Hcy and folate levels is not entirely clear. Li et al. [76] showed an association of *MTR* A2756G with increased Hcy and decreased folate level. On the other hand, Klerk et al. [77] denied that G allele of *MTR* A2756G affects Hcy level. Also, there was no association between *MTR* A2756G and migraine [42, 78], even in the coexistence of *MTHFR* 677CT TT genotype [79].

Another enzyme involved in Hcy metabolism is 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR), encoded by *MTRR* gene. The *MTRR* A66G (Ile22Met) polymorphism may lead to elevated Hcy level [80, 81], with greater effects observed in individuals with GG genotype than GA [80]. Furthermore, the coexistence of *MTRR* A66G AG or GG genotypes with the *MTHFR* A677T TT genotype increases the adverse effect of the MTHFR variant [82].

MTHFD1 is a trifunctional enzyme composed of methylenetetrahydrofolate dehydrogenase, methyltetrahydrofolate cyclohydrolase, and formyltetrahydrofolate synthetase, encoded by *MTHFD1* gene. The most commonly analyzed polymorphisms of the *MTHFD* gene are G1958A

(R653Q) and C401T (R134K). The G1958A or C401T polymorphism individually does not increase the risk of migraine [79, 83]. However, the risk of migraine, especially MO, increases when the A allele of *MTHFD* G1958A polymorphism occurs together with the T allele of *MTHFR* C677T polymorphism. On the other hand, the group of Australian scientists found no association of *MTHFD* C401T and G1958A with the increased risk of suffering migraine [79].

CBS is an enzyme responsible for the conversion of Hcy to cystathionine, a cysteine precursor, and is encoded by *CBS* gene. Numerous genetic variants in this gene have been described, including silent polymorphisms (C699T, C1080T) [84], sense change mutations (T833C, G919A) and insertions (844ins68) [85, 86]. The most common polymorphism of the *CBS* gene, the T833C, results in the elevated level of Hcy [87] and predisposes to stroke [88]. The 844ins68 polymorphism alone does not affect Hcy plasma levels [89], whereas T833C/844ins68 induces mild hyperhomocysteinemia [90]. The occurrence of this insertion together with T allele of *MTHFR* C677T polymorphism results in lower Hcy levels as compared to the subject carrying only insertion [91]. The silent polymorphism in *CBS* gene seems to have a protective effect against CVD. Subjects with C699T TT genotype had lower Hcy level than subjects with the CC genotype [92] and consequently lower risk of CVD [93]. Also, *CBS* C1080T polymorphism leads to decrease in Hcy level, but this effect is endured by of 844ins68 mutation carriers [92]. On the other hand, the study conducted by Lievers et al. [94] showed no association between the occurrence of the silent polymorphisms and the change in plasma Hcy levels [94].

eNOS gene encoded endothelial NO synthase. Several polymorphisms in the *eNOS* gene were described, including T786C and G894T (Glu298Asp), but their relevance to migraine pathomechanism remains ambiguous. According to Eröz et al. [95], presentence of T alleles of *eNOS* T786C and *eNOS* G894T polymorphisms are more common in migraine patients than in controls. Other studies indicated that the TT genotype of *eNOS* G894T is associated only with a higher risk of MA [96] or there is no association [97].

3.3. CADASIL

The strict relation between MA and stroke was observed in CADASIL syndrome. It belongs to the group of leukodystrophies and is caused by mutations in *NOTCH3* gene [98].

CADASIL is the most frequent inherited ischemic disease of a small vessel of the brain [98]. The key features of CADASIL are MA, recurrent subcortical ischemic events and vascular dementia. The subcortical ischemic stroke is presented in 85% CADASIL patients in mean age 46 without atherosclerosis risk factors. Two of three cases are the lacunar stroke, while one of three is ishemispheric stroke. 20–40% of individuals suffer from psychiatric disorders, mostly depression or apathy. Dementia is presented in 31–60% of CADASIL patients, aged between 50 and 60, as a result of stroke history, leading to severe disability and premature death [99, 100].

Often (20–40% of cases) the inaugural symptom of CADASIL is MA started in the second–third decade of life (females: 25; males: 30–35 year of life). Interestingly, MA is five-times more frequent in CADASIL patients than in general population and may remain as the isolated symptom [100]. CADASIL patients may experience aura without a headache or atypical aura (e.g., hemiplegic, basilar, or prolonged) or even acute confusional migraine. Thus it is suggested that

atypical aura should indicate the diagnosis of CADASIL [101–104]. The frequency of MA attacks decreases after the disease progression (stroke event). Unfortunately, migraine as a common neurological disease is not a specific symptom of CADASIL, which often is misdiagnosed [100].

As mentioned before, CADASIL is a result of the mutation in the *NOTCH3* gene (19p13.12), encoding receptor protein NOTCH3. NOTCH receptors are made up of the functional extracellular domain (ECD)—containing multiple epidermal growth factor-like (EGF-like) repeats, the transmembrane domain and intracellular domain (ICD). The variants of NOTCH (NOTCH1–4) differ in the number of EGF repeats [105]. The NOTCH3 is essential for the development of vascular smooth muscle cells (VSMC) and maintenance of their function. Moreover, it protects against apoptosis and regulates the response of smooth muscle cells to external factors. NOTCH3 occurs mostly in the arteries and capillaries.

At least 200 mutations have been identified in *NOTCH3* and are located in N3-ECD. Those missense mutations create or destroy cysteine residues. As the name of disease indicates, they are inherited in the autosomal dominant pattern. *NOTCH3* consists of 33 exons, but 73% of mutations are localized in exon 4, 8% in exon 3, 6% in exons 5 and 6 [99, 106, 107]. The first step of genetic screening is analyze of exon 4, if there are no mutations the analysis is extended to exons 2, 3, 5, 6, and 11. The last step may be the screening of all exons using next generation sequencing (NGS). Different *NOTCH3* mutations were revealed among Asian of Caucasian populations [108, 109].

The CADASIL scale proposed by Pescini et al. [110] for selecting patients for genetic analysis is summarized in **Table 1**. A total score of ≥15 is an indication for genetic testing. The clinical course of CADASIL may vary between individuals with the same mutation in *NOTCH3* gene. The heterogenic manifestation of clinical symptoms makes the CADASIL underdiagnosed

CADASIL scale	Points
Migraine	1
Migraine with aura	3
Stroke	1
Stroke onset ≤50 years	2
Psychiatric disturbances	1
Cognitive decline/dementia	3
Leukoencephalopathy	3
Leukoencephalopathy extended to temporal pole	1
Leukoencephalopathy extended to external capsule	5
Subcortical infarcts	2
Family history in at least one generation	1
Family history in at least two generations	2

Table 1. Scale used to select CADASIL patients for genetic screening of *NOTCH3* mutations [110].

due to difficulties in distinguishing with, e.g., MA, familial hemiplegic migraine, or progressive ataxia [107]. The *NOTCH3* mutation analysis should be performed in cases with clinical features of CADASIL, even with the negative disease history.

There are two hypothesis explaining the role of *NOTCH3* mutations in CADASIL pathomechanism. According to the first of them, the mutated NOTCH3 receptor gains new functions leading to the development of degenerative changes in blood vessels. The signaling pathway is unchanged, but the cerebral blood flow autoregulation is disturbed due to the decline of VSMC functions. The persistent stress conditions lead to VSMC remodeling, reduction of cerebral vasoreactivity, the decrease in blood flow in white matter, and in consequence to chronic ischemia. The second hypothesis assumes proteinopathy as a result of N3-ECD and granular osmiophilic material (GOM) deposition in walls of blood vessels. The GOM is also presented in skin biopsy. Abnormal folded NOTCH3 protein tends to create aggregates and is not removed because of dysfunction of the ubiquitin-proteasome system. The deposition begins in 20-year-old CADASIL patients, while the changes in MRI are visible in 30-year-old patients. Interestingly, almost all CADASIL patients aged 35 with *NOTCH3* mutations have changes in MRI, e.g., white matter hyperintensities (WMH), lacunar infarcts or microbleeds. WMH lesions in T2 and FLAIR sequences may be presented even 15 years before stroke [111–113]. Four case-studies indicated that the brain MRI may be unremarkable [114].

4. Summary

Migraine is a multifactorial disease with both genetic and environmental background. Polymorphisms and mutations in numerous genes, e.g., *ACE, NOTCH3, MTHFR, MTR, MTRR, MTHFD1, CBS,* and *eNOS* are the genetic factors involved in its pathomechanism. Changes in biochemical parameters, such as Hcy and ADMA leading to CVD, stroke and

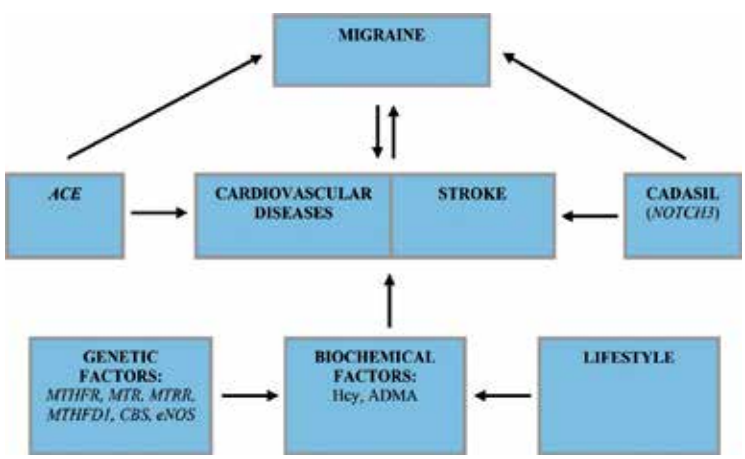

Figure 2. Association between migraine and cardiovascular diseases, stroke and genetic, or biochemical risk factors. ACE: angiotensin I-converting enzyme; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MTHFR: methylenetetrahydrofolate reductase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase; MTRR-5: methyltetrahydrofolate-homocysteine methyltransferase reductase; CBS: cystathionine β-synthase; eNOS: endothelial NO synthase; Hcy: homocysteine; ADMA: asymmetric dimethylarginine.

migraine may be a result of lifestyle. Migraine alone can also lead to CVD and stroke. It seems that better knowledge of the migraine pathomechanism may lead to early diagnosis of migraine and the introduction of more effective pharmacotherapy and, in consequence, to the prevention of common vascular disease (**Figure 2**).

Author details

Marta Kowalska[1], Katarzyna Wize[1], Iga Wieczorek[1], Wojciech Kozubski[2] and Jolanta Dorszewska[1]*

*Address all correspondence to: dorszewskaj@yahoo.com

1 Laboratory of Neurobiology, Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

2 Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

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Chapter 2

Cerebral Venous Thrombosis: A Clinical Overview

Christopher A. Stack and John W. Cole

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79049

Abstract

Cerebral venous thrombosis (CVT) is a less common cause of stroke that is an often under recognized entity in clinical practice. The goal of this chapter will be to provide clinicians with the knowledge to succinctly recognize the various presentations of CVT, emphasizing rapid diagnosis and the potential treatments necessary to produce optimal clinical outcomes. Detailed descriptions of the relevant anatomy and associated clinical syndromes will be discussed. Detailed sections regarding CVT epidemiology, pathophysiology, etiology, diagnosis and treatment will be provided. Prognosis and long-term follow-up will also be discussed. Relevant literature will be cited and clinical trials across the spectrum of CVT will be highlighted.

Keywords: cerebral venous thrombosis (CVT), etiology, diagnosis, treatment

1. Introduction

Cerebral venous thrombosis (CVT) is a less common cause of stroke that is often under recognized in clinical practice. CVT accounts for 0.5–1% of strokes that has a preponderance to occur in women [1, 2]. The goal of this chapter is to provide clinicians with the knowledge and ability to recognize and treat CVT early in its time course leading to the best clinical outcomes.

2. Anatomy and associated clinical syndromes

The cerebral venous system is a network of superficial sinuses and deeper cortical veins that drain the superficial surfaces of both cerebral hemispheres and the deeper brain structures ultimately returning blood back to the heart via the internal jugular veins. The cerebral venous

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system is divided into a superficial system (superior sagittal sinus, inferior sagittal sinus, cortical veins) and a deep system (transverse sinus, straight sinus, sigmoid sinus, deeper cortical veins). The flow patterns and anatomy can be seen in in **Figures 1** and **2**.

The superficial cortical veins adhering to the arachnoid layer are thin walled and have no valves [3]. Typical cerebral venous flow starts with the superficial cortical veins draining into the superior/inferior sagittal sinus or straight sinus draining into the confluence of sinuses (also known as torcula or torcular herophili) to the transverse sinuses, sigmoid sinuses, and then internal jugular veins. The superior sagittal sinus drains the superior-lateral cerebral hemispheric surfaces bilaterally. The diploic, meningeal and emissary veins drain into the superior sagittal sinus. This is of clinical importance in scalp and CSF infections as prothrombotic venous drainage into the superior sagittal sinus can induce thrombus formation within that structure. The inferior sagittal sinus drains the bilateral medial cerebral hemispheres as well as the falx cerebri. The inferior sagittal sinus joins with the great vein of Galen to form the straight sinus. The great vein of Galen is formed by the internal cerebral vein (formed by thalamostriate vein, septal vein and choroid vein) and basal vein of Rosenthal (anterior/middle cerebral vein and striate vein) which drain the basal ganglia and deep white matter bilaterally. The lateral sinuses (transverse and sigmoid sinuses) receive drainage directly from the posterior cerebral hemisphere, brainstem and cerebellum bilaterally. Of clinical importance, the anatomical positioning of these lateral sinuses near the mastoid air cells increases their susceptibility to thrombosis formation in the setting of ear infections such as chronic otitis media and mastoiditis [4].

Two unique parts of the venous sinus drainage system are the anastomotic veins and the bilateral cavernous sinus. The superior anastomotic vein of Trolard connects the superior sagittal sinus and the superficial vein of Sylvius. The inferior anastomotic vein of Labbe connects the superficial middle cerebral vein and transverse sinus. The cavernous sinus receives drainage

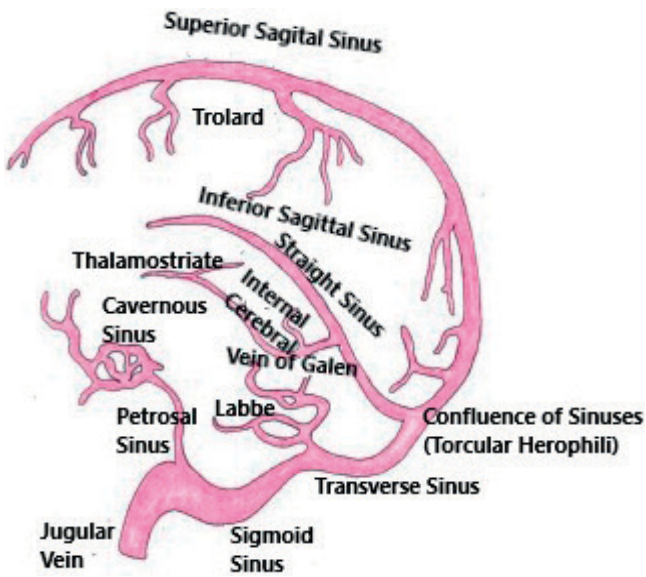

Figure 1. Cerebral venous anatomy.

http://dx.doi.org/10.5772/intechopen.79049

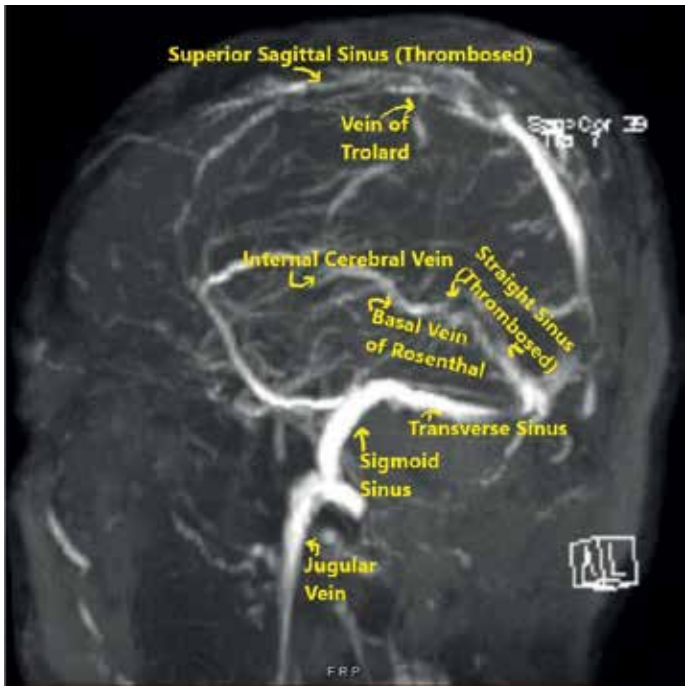

Figure 2. Cerebral venous anatomy on magnetic resonance venogram (MRV).

from the orbits, inferior frontal lobe, inferior parietal lobe and the face in the nasal region. Given that cranial nerves CNIII, CN IV, CN V-1, CN V-2 and CN VI pass through the cavernous sinus this becomes an important clinical localization point in the setting of facial and nasal infections.

Much of neurology involves pattern recognition in the setting of clinical findings and syndromes. Clinical syndromes of the venous system are less well stereotyped than the more commonly seen and appreciated arterial stroke syndromes. Cerebral cortical veins often have a common presentation of focal seizure activity correlating with the specific region of the cortex involved. Thrombosis involving the deep venous system leads to mental status changes and can progress to coma when the bilateral thalami are involved. Notably, thrombosis involving the deeper venous system generally results in a more rapid deterioration compared to the superficial system. Clinically, thrombosis in the superior sagittal sinus syndrome can present quite variably, but the classic syndrome includes bilateral motor deficits, neurobehavioral issues related to frontal lobe injury, and seizure activity related to hemispheric cortical involvement. Other findings can include scalp and/or face edema, and dilated scalp veins based on the lack of venous flow into the sagittal sinus [5]. Thrombosis in the transverse venous sinus typically results in parietal lobe deficits with patients presenting with either aphasia or neglect depending on hemispheric dominance. Accompanying symptoms often include headaches, ear and/or mastoid pain. The visual pathways can also be affected in a lateral sinus thrombosis syndrome thus resulting in hemianopia secondary to occipital lobe involvement. Cavernous sinus thrombosis typically presents with diplopia, proptosis, headache and orbital pain, or some combination of these, with the examiner eliciting cranial nerve palsies involving CN-III, CN-IV, CN-V1, CN-V2, CN VI.

3. Epidemiology

CVT, in absolute terms, is an uncommon diagnosis occurring in 5 per 1 million adults every year [1]. In all, CVT accounts for 0.5–1% of all strokes [6]. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) trial, which evaluated 624 patients in 24 countries, subjects had a median age of 37 years old (78% cases <50 years old) with 74% of enrollees being female, illustrating that CVT is generally a disease of young women [3]. The overall incidence of CVT is 1.32 per 100,000 person-years [7]. CVT occurs in women at a higher rate than men, with the women aged 31–50 years harboring the greatest risk with an incidence of 2.78 per 100,000 person-years [7, 8]. Among the young stroke population, CVT accounts for approximately 5% of cases [9].

The incidence of CVT in the Canadian Pediatric Ischemic Stroke Registry (CRISR) was 6.7 per 1 million [10]. A majority (54%) of the children were younger than 1 year old with 45% below the age of 1 month. This patient population will be further discussed in the following section.

4. Pathophysiology

The potential causes for CVT are numerous, but the underlying reason is the coagulation balance is tipped towards a pro-thrombotic state. There are numerous predisposing factors that contribute to the formation of CVT. Examples include medical problems such as thrombophilias, infections and inflammatory states (e.g., autoimmune diseases), transient physiological states including dehydration and pregnancy, medications especially oral contraceptives (OCPs), smoking, and head trauma [11, 12].

The main data on epidemiology of CVT comes from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). An ISCVT study demonstrated that more than 44% of the subjects were identified to have more than one cause to their CVT [13]. In that study the most common contributing factor was OCP use (54%) followed by thrombophilia (34.1%), puerperium (14%), infection (12%), malignancy (7.4%) and pregnancy (6%). These contributing factors give credence to the predilection for women in child bearing years. Specifically, OCP use, pregnancy and puerperium risks are exclusive to that subset of patients. An estimated 2% of strokes during pregnancy can be attributed to CVT [14]. The puerperium period is the first 6–8 weeks after childbirth, and it is in that period where the risk of all venous thromboembolic events is increased, with an overall frequency of CVT estimated to be 12 per 100,000 delivers [15, 16]. Although there is limited evidence, factors that have been associated with puerperium CVT include hyperhomocysteinemia, advanced maternal age, cesarean delivery, maternal hypertension, infections and excessive vomiting during pregnancy [17, 18]. In developing and underdeveloped countries, postpartum strokes are relatively common with contributing risk factors including poor antenatal and postpartum care, home deliveries, anemia, and dehydration. During pregnancy itself, the highest incidence worldwide is during the 3rd trimester [19].

The proposed mechanism for the observed young female preponderance is that hormonal factors create a prothrombotic state. The reason many authors cite this to be true is that the incidence of CVT among elderly and children is sex-independent [10, 20]. More evidence supporting hormonal contribution to the pathophysiology is the association between CVT and ovarian hyperstimulation syndrome [21]. The relative risk of CVT among OCP users was as high as 15.9 in one study [22]. A meta-analysis that examined 17 CVT studies calculated an OR 5.59 increased risk of CVT with OCP use [23]. The effect is synergistic when OCP use is combined with a hereditary prothrombotic factors including factor V Leiden or prothrombin G20210A mutation, with the latter demonstrating an OR of 149.3 in one study [24, 25]. Pregnancy and OCP use, absent genetic conditions, are thought to be transient and thus generally not thought to carry a higher risk of recurrence.

Numerous studies have been dedicated to exploring the association between genetic hypercoagulability and CVT risk. A meta-analysis that reviewed 26 case–control studies including 1183 CVT cases and 5189 controls, demonstrated the two gene mutations that most clearly associated with CVT risk were Factor V Leiden/G1691A (OR 2.40 [1.75–3.30; *p-value* 0.00001) and prothrombin gene mutation (OR 5.48 [3.88–7.74]; *p-value* 0.00001) [26]. In the same study, they performed an iterative analysis which showed a statistically significant association with methylene tetrahydrofolate reductase/C677T (OR 2.30 [1.20–4.42; *p-value* 0.02). Similar associations were described in systematic reviews that showed statistically significant increases in odds ratio (OR) for prothrombin gene mutation (9.27 [5.85–1467]), Factor V Leiden (3.38 [2.27–5.05]) and hyperhomocysteinemia (4.07 [2.54–6.52]) [27]. In ISCVT 22% of the patients had a genetic hypercoagulable state [13]. In decreasing order of frequency, the identified genes were G20210A prothrombin mutation, Factor V Leiden, anticardiolipin/antiphospholipid antibodies, protein C deficiency, protein S deficiency and antithrombin III deficiency [3, 15, 18, 24, 27–31].

Another acquired hypercoagulable state that is common in the setting of CVT is malignancy. The mechanism by which malignancy causes hypercoagulability is varied. Authors have suggested that potential mechanisms may include tumor invasion of venous sinuses, compression of dural venous sinuses, an imbalance in systemic inflammatory mediators, chemotherapy, and targeted hormone therapy (i.e., tamoxifen for breast cancer treatment) [32–35]. The associated malignancies represented were primary CNS tumors (2.2%), metastases of solid tumors (3.2%) and hematologic malignancies (2.9%) [3].

Infections are another well-established cause of CVTs. Developed countries have shown a decline in infection related CVTs, but in developing countries at ~18% it remains a prevalent cause [36]. In ISCVT infection accounted for 8.2% of adults [37]. Locations of the parameningeal infections were in the ear, sinus, mouth, face and neck. Cavernous sinus thrombosis specifically is overwhelming caused by skin infections of the face and/or nasal sinuses, where the venous drainage flows directly into the cavernous sinus. Another syndrome, called Lemierre's syndrome, results from oropharyngeal infection leading to thrombosis of the internal jugular vein which may back propagate causing extensive CVT. Further, the localized inflammation may also invade the internal carotid arteries (ICA) as they pass through the oropharynx, thereby leading to arterial strokes.

In children, infection was the most common cause of CVT. Among neonates, infection occurred in 84% of all patients [10]. In patients older than 1 month, the majority of case etiologies shifted towards chronic medical conditions, including connective tissue disorders (23%), hematologic diseases (20%) and cancers (13%) [10].

5. Clinical presentation

CVT is a diagnosis that is often delayed given its variable presentation. ISCVT patients were diagnosed a median of 7 days after symptom-onset, most of whom diagnosed were diagnosed between 48 hours and 30 days from symptom-onset (56%,). This time-period was followed by: acute <48 hours (37%), and chronically >30 days (7%). Across all time-periods, the median delay from symptom-onset until admission was 4 days [3, 38, 39]. Interestingly, delay in diagnosis was associated with increased risk of visual deficits [39]. Men and patients with isolated elevated ICP were diagnosed later. It is helpful to consider the two primary mechanisms that cause neurologic dysfunction: (1) increased intracranial pressure (ICP) and (2) hypoperfusion.

The increased intracranial pressure is due to poor venous outflow effectively leading to increased cerebral venous resistance and decreased CSF drainage, thus increasing ICP [40]. The increased ICP generally results in three manifestations: headache, diplopia and papilledema. In ISCVT, almost 90% of patients examined had headache as a presenting symptom. The headaches were generally described as diffuse progressing over days to weeks, with thunderclap headache being the rare presentation [3, 41]. The authors recommended a higher index of suspicion for high risk patients (women of childbearing age especially on OCPs in isolation or in combination with smoking) who have a new and/or atypical headache not responsive to over the counter analgesics [41]. Patients presenting with isolated headaches had a favorable prognosis in one study [42]. Patients not presenting with headache in the ISCVT cohort were older men and were more likely to have cancer [43]. The mortality was higher in that group, but there was no statistically significant difference when adjusting for confounders in the data [42].

In addition, the increased ICP may also lead to papilledema. The clinical symptoms can be transient visual obscurations, transient vision loss, peripheral vision loss and pulsatile tinnitus. Nausea and vomiting are also common. The diplopia is often caused by compression of one or both abducens nerves leading to horizontal diplopia. More directly, cavernous sinus thrombosis may lead to diplopia via localized involvement with the oculomotor and abducens nerves as they pass through the cavernous sinus. Class I, level C evidence in guidelines suggests cerebral venous imaging in patients with clinical symptoms of increased intracranial pressure [38].

The other primary mechanism is venous infarction as related to a combination of hypoperfusion, ischemia and/or hemorrhagic injury. In such instances, focal neurologic syndromes are encountered in the patterns previously described in the previous “Anatomy and Associated Clinical Syndromes” section. Should hemorrhagic and/or ischemic strokes develop, focal neurologic deficits such as aphasia or hemiparesis can be seen. Patients can present with acute

psychosis, typically in combination with other signs and symptoms, but rarely as the sole manifestation. Seizures are also very common, as there is often a disturbed blood–brain barrier with edema development in the setting of viable cortical neurons and supporting cells. Seizures can be focal, unilateral or bilateral, and can also secondarily generalize. In ISCVT seizures were present in 40% of subjects [3].

6. Diagnostic evaluation

After a thorough history and physical examination, the most useful diagnostic tool is imaging. As with most patients, the initial scan will be a non-contrast computed tomography (CT) of the head. The purpose of these initial screening images is to evaluate for signs of ischemia, hemorrhage, a "filled" or hyperdense delta sign and/or other evidence of hyperdense venous sinuses. These are the radiographically important CT imaging findings seen in the setting of CVT. The non-contrast CT is estimated to be abnormal in 30% of individuals with CVT [1, 23, 44–48]. ICH is the initial presentation in 30–40% of CVT patients [49, 50]. The filled delta sign is a triangular hyperdensity in the posterior portion of the superior sagittal sinus in the area of the confluence of the sinuses. A hyperdense dural sign, indicating CVT in a dural vein, is appreciated on approximately 1/3 CVT cases undergoing CT head [44, 45, 47]. Furthermore, the index of suspicion is raised higher if there is hemorrhage that is atypical in appearance, meaning that it is close to venous sinuses and/or crosses typical arterial vascular borders.

When patients present with focal neurologic deficits within an acute intervention window (up to 24 hours since last known well in certain circumstances), the recommendation of the authors is to perform an emergent CT angiogram (CTA) with delayed phase CT venogram (CTV) as part of the initial evaluation. These studies evaluate patients for large-vessel arterial occlusion, with the CTV performed primarily to evaluate for collateral flow in the setting of potential mechanical thrombectomy. However, an added benefit of the delayed phase CTV is that one is also able to evaluate for venous thrombus. Anecdotally, the authors have discovered CVT in the initial CT/CTA/CTV approach in patients with hemorrhagic strokes presenting acutely. A dedicated CTV evaluates the venous sinuses themselves, which would demonstrate thrombosis if present. Some suggest that CTV is more valuable in the subacute and chronic phases because it shows varying density of the thrombosis within the sinuses [38].

MRI is also helpful in the evaluation of CVT. In addition to ruling in or out other diagnoses on the differential, including brain tumors for example, it can provide helpful information for confirming CVT. Consistent with the non-contrast CT brain, the pattern and location of injury can be helpful if hemorrhage or ischemia is present. Parenchymal damage can manifest as ischemia (restricted diffusion), edema and hemorrhage. Edema without hemorrhage is more easily detected on MRI versus CT brain (25% versus 8%) respectively [10, 44, 46, 51–57]. Hemorrhage-specific MRI sequences are positive in up to 40% of CVT patients [44, 51, 53, 57–60]. The pattern of parenchymal injury often provides clues to the venous structures involved. For example, simultaneous injury involving the frontal, parietal and occipital cortices would correspond to a superior sagittal sinus thrombosis. Transverse and sigmoid sinuses result in temporal lobe injury. Deep structures are injured in thrombosis of the straight sinus

and/or vein of Galen. MRI T2 weighted sequences can provide insight into the venous sinuses themselves, with absent flow voids manifesting as T2 hypointensities. Such findings, can be suggestive of CVT especially with accompanying parenchymal changes discussed above. Although uncommon, hyperintense cortical veins on T2 sequences can be used to identify isolated cortical vein thrombosis [51, 61–68].

If CVT is clinically suspected, dedicated venous imaging is required, even if the initial plain brain CT brain or brain MRI were negative. As discussed, CTV can be used, however MRV is another option. MRV reveals loss of flow signal in the venous sinuses [69]. This can be especially helpful when combined with above modalities. In our practice, we use susceptibility weighted imaging on MRI to help augment diagnostic accuracy in combination with MRV.

DSA is indicated in patients with parenchymal changes (edema and/or hemorrhage) without conclusive venography on CTV or MRV. A 4-vessel DSA will help evaluate for possible arterial etiologies to the observed parenchymal damage, however the late-phase contrast runoff can be used to examine the venous system. As another option, some authors suggest direct venography via micro-catherization of the internal jugular vein [70, 71]. Such a technique might be useful if an intervention is being considering.

From a serology standpoint, D-dimer has an excellent negative predictive value (99.6%), which is helpful in identifying patients with low probability of having CVT [72, 73]. In one prospective multicenter trial, D-dimer had a specificity of 91.2% and sensitivity of 97.1% [72]. There was a smaller study that found that the false negative rate was 10% in patients presenting with isolated headache [73]. Interestingly, there was a positive correlation with D-dimer level and extent of CVT, and negative correlation with duration of symptoms [72–77].

After the diagnosis is established it is important to identify the etiology. Recommended lab tests as per evidence-based guidelines in the acute setting include: complete blood count (CBC), complete metabolic panel (CMP), prothrombin time (PT) and activated partial thromboplastin time (aPTT). Hypercoagulable testing for protein C, protein S, antithrombin, anticardiolipin and antiphospholipid antibodies, prothrombin G20210A mutation and factor V Leiden [38, 78–82] are also valuable and should be considered early. In the setting of anticoagulation use, only antibody and genetic tests are possible. If infection is considered, blood cultures should be attained. In certain populations, it is not unreasonable to perform a malignancy screen with CT chest, abdomen and pelvis ±testicular ultrasound.

7. Treatment

Patients who are suspected of having CVT benefit from evaluation by a vascular neurologist and being admitted to a stroke unit [83, 84]. Once a CVT is confirmed, the goal of therapy is to initiate anticoagulation quickly with the goal of preventing thrombus propagation. The data for CVT is certainly not as robust as many other areas of stroke therapy with a total of 12 published studies to date [3, 40, 49, 55, 85–94], with only 2 randomized-prospective-controlled trials [40, 85].

The first study evaluating CVT treatment was published in Lancet [85]. This double-blind placebo-controlled trial aimed to shed light on the ongoing treatment controversies at that time in clinical practice [85]. The prevailing thought that anticoagulation frequently caused ICH. The study included 20 patients with aseptic CVT randomized to anticoagulation versus placebo. The anticoagulation arm consisted of a heparin bolus of 3000 international units (IU) followed by continuous infusion adjusted to goal PTT 2× the pretreatment value. The primary outcome measure was a CVT severity scale which considered headache, focal signs, seizures and level of consciousness. The secondary outcome was ICH. The study was powered to evaluated 60 patients; however, enrollment was stopped at 20 given the clear benefit of treatment with anticoagulation at the interval analysis. The heparin group showed statistically significant benefit (Mann-Whitney U test $p < 0.05$) comparing the primary outcome at day 3 and day 8 ($p < 0.01$). At 3 months 8 patients in the treatment arm had complete recovery and 2 had slight neurologic deficits. In the placebo group 1 patient had complete recovery, 6 with neurologic deficits, and 3 patients were deceased. Notably, none of the treatment group patients developed ICH.

The larger of the two RCTs enrolled patients in the United Kingdom and Netherlands between 7/1992 and 11/1996 [40]. The entire population included 59 patients who were confirmed to have CVT using MRI, MRV and/or angiography. These were adult patients (≥18 years old) with the major exclusion criteria including pregnancy, contraindications for heparin use, poor baseline prognosis, increased ICP requiring lumbar puncture (LP) or shunt. The two arms evaluated nadroparin (190 units/kg/24 hours) versus placebo. After 21 days the blinding was broken and patients in the treatment arm got 10 weeks of warfarin with an international normalized ration (INR) goal 2.5–3.5. The placebo group did not receive anticoagulation or have sham bloodwork. The primary outcome was the Barthel index (BI) at 21 days expressed as a percentage, with a poor outcome defined as BI >15. Notable baseline characteristics for enrolled patients included: a mean age of 36.9 years old (range 18–80), 85% female, delay to randomization 10.6 days, 95% with recent headache, 47% with seizures, 96.6% with a focal neurologic deficit and 49% with cerebral hemorrhage. After 3 weeks, the anticoagulation arm was shown to have poor outcome in 20% of patients versus 24% for placebo, which was *not* statistically significant. At 12 weeks a secondary evaluation of poor outcome was performed, defined as death or Oxford Handicap Score ≥ 3. Poor outcomes were shown in 13% of anticoagulation group versus 21% of placebo group (risk difference 27% [−26–12%]) which was also *not* statistically significant. The primary take home point per the study investigators was that there was no new hemorrhage, this, even in the treatment group. As such, anticoagulation was deemed safe despite the presence of cerebral hemorrhage at the time of CVT presentation. Although, the presence of cerebral hemorrhage at presentation was associated with mortality in the study. Notably, the lack of increased frequency of new ICH while receiving anticoagulation therapy is in agreement with other studies that demonstrating low hemorrhage rates after initiation of anticoagulation in the setting of CVT [85, 88].

In the setting of CVT, a non-randomized prospective cohort study compared the efficacy of unfractionated heparin (UFH) versus low molecular weight heparin (LMWH); 302 patients received UFH versus 119 patients received LMWH [95]. The primary endpoint was functional

independence at 6 months defined as modified Rankin score < 3. More patients in the LMWH arm were functionally independent after 6 months (92% versus 84%). This was statistically significant in univariate (OR 2.1 [1.0–4.2], p 0.04) and multivariate adjusted analysis (OR 2.4 [1.0–5.7], p 0.04). There was no statistically significant difference in the main secondary endpoints, which included: complete recovery—measured as a modified Rankin Scale (mRS) 0–1, mortality, and new intracranial hemorrhage. Another study, performed in India, further substantiated the claim that LMWH has a benefit in hospital mortality as compared to UFH [96].

The most recent guideline recommendations are that patients with confirmed CVT should be given anticoagulation initially with either UFH or LMWH followed by warfarin offered as class IIa and level of evidence B [40, 85, 88, 92, 97, 98]. There are no large studies evaluating the efficacy of direct acting oral anticoagulants (DOACs) in CVT, as such, warfarin is generally preferred. However, there are occasions when the authors consider and do initiate DOACs/NOACs, including patient preference and in the setting of warfarin interactions with other medications [99, 100].

7.1. Rescue therapies: endovascular intervention

Endovascular intervention is considered when there is clinical deterioration despite anticoagulation [101–110]. These patients often have clot propagation leading to further infarction or hemorrhagic injury, worsening ICP elevated due to poor venous outflow, or a combination of these factors. One of the approaches for so-called rescue therapy in CVT is delivery of intrasinus thrombolytics. At present, there are no randomized, double-blinded, placebo-controlled trials evaluating the efficacy of intrasinus thrombolysis. This procedure is rarely performed and would be best referred to a large academic center with robust interventional neuroradiologic experience [103].

A systematic review evaluated at total of 26 patients undergoing intrasinus thrombolysis including 80.8% with superior sagittal sinus thrombosis and 19.2% with deep sinus involvement [104]. Urokinases were used in 73.1% of the cases, followed by streptokinase (7.7%), with the remainder utilizing recombinant tissue plasminogen activator (rTPA). Radiographic success of recanalization was attained in 61.5% patients, with 88% attaining a mRS 0–2 at last available follow up. Complications included ICH in 11.5% of cases, extracranial hemorrhages in 19.2%, and 2 deaths (7.7%).

Another 29 patients were evaluated in a series conducted from 4/2013 to 4/2016 all of whom were treated with in-situ tPA with the tPA delivered directly into the venous sinus via microcatheter [105]. The radiographic success of recanalization was 100% in this series, of which 82.8% had favorable outcome (mRS 0–1), 10.3% mRS of 2, and 3.4% (1 patient) died.

Another prospective case series evaluated patients with CVT who underwent intrasinus thrombolysis among patients with altered mental status, coma, straight sinus thrombosis, or large space occupying lesions [106]. The population included 20 patients (80% women, mean age 32 years old) who received infused urokinase via internal jugular catheter. Clinically 60% of patients were comatose and 70% had hemorrhage prior to treatment. In 75% of patients the thrombolysis was coupled with mechanical thrombus disruption or removal. Post intervention

the mortality rate was 30% (6 patients), 5 of whom had large hemispheric infarcts and edema prior to intervention. Ultimately an mRS of 0–2 was achieved in 60% of cases.

Another study evaluated 37 CVT patients between 1/2007 and 12/2009 who underwent intrasinus urokinase infusion thrombolysis using a microcatheter [107]. At 6-month follow up, radiographic canalization was obtained in 97% of patients, with functional outcome rates of mRS 0–1 (75.8%), mRS 2 (18.2%), mRS 4 (3.0%), and a 3.0% mortality rate (mRS 6).

Another rescue therapy utilized is mechanical thrombectomy. One systematic review evaluated patients from 42 studies treated between 1/1995 and 2/2014 undergoing mechanical thrombectomy with or without intrasinus thrombolysis [108]. The review included a total of 185 patients with CVT, 62% of whom had ICH prior to intervention. Clinically 47% were either stuporous or comatose. The most commonly used interventional device for mechanical thrombectomy was an AngioJet, used in 40% of the cases, although it was associated with a lower complete recanalization rate (OR 0.2 [0.09–0.4]) and lower chance of mRS 0–2 (OR 0.5 [0.2–1.0]) as compared with other therapies. A total 71% of these patients also underwent intrasinus thrombolysis. A mRS 0–2 was observed in 84% of patients and the mortality rate was 12%. At least partial recanalization was obtained in 95% of cases. The major complications included new or increased ICH in approximately 10% of the cases.

Another systematic review in BMJ evaluated 17 studies totaling 235 patients [109]. Intrasinus thrombolysis was used in 87.6% of patients. Radiographically complete revascularization was achieved in 69% of patients, with a mortality rate of 14.3%, 1.2% recurrent CVT rate, and a new or worsening ICH rate of 8.7%.

Another review evaluated CVT patients undergoing mechanical thrombectomy between 1990 and 2012 [110]. A total of 64 patients underwent mechanical thrombectomy with different techniques including AngioJet (46.9%), Penumbra (4.7%), Fogarty catheter (1.6%), microsnare (3.1%), balloon venoplasty without stenting (18.7%), balloon venoplasty with stenting (4.7%), and a combination approach (18.7%). The mortality rate in this review was 16.1%. The morbidity data showed mRS 0–2 (62.5%), mRS 3–5 (10.9%) and 12.5% were unreported.

7.2. Decompressive surgery

Patients with CVT are at risk of herniation syndromes due to multiple factors as related to mass effect. Herniation is a major cause of death in CVT, thus decompressive surgery is an important option in the treatment armamentarium. Herniation is generally due to large ischemic regions and/or large hematomas. One study evaluated the safety and efficacy of decompressive surgery in a retrospective fashion by evaluating a registry of acute CVT patients [111]. A total of 69 patients were included in the study, 45 underwent decompressive craniectomy, 7 underwent hematoma evacuation, and 17 received both therapies. The primary outcome was mRS at last follow-up analyzed in dichotomously (favorable mRS 0–2 versus unfavorable mRS 5–6). In median 12-month follow-up 17.4% had an unfavorable outcome. This also resulted in favorable functional outcomes in the secondary analysis demonstrating 37.7% with near complete recovery (mRS 0–1), 56.5% (mRS 0–2), 5.8% (mRS 4–5), and a 15.9% mortality rate. As consistent with decompressive surgery in arterial ischemic stroke, it

is important to treat early, ***before*** patients decline into a comatose state. As demonstrated in the just described study, patients who were comatose were less likely to be independent mRS <2 than non-comatose patients (45% versus 84%, *p-value* 0.003).

7.3. Seizures

Seizures are very common at presentation among patients with CVT. One prospective observational study found seizures in 39.3% of CVT patients and 6.9% of patients had early seizures (within 2 weeks) [112]. Factors associated with seizures at presentation were supratentorial lesions, cortical vein thrombosis, sagittal sinus thrombosis, and puerperal CVT. Beyond seizures at presentation, supratentorial lesions were also a predicator of early seizures. Patients who suffer a seizure at presentation, or in the early phase of CVT, should be treated with antiepileptics for prevention of further seizures, this, whether a parenchymal lesion is seen on imaging or not. Currently, it is not recommended to treat prophylactically in the absence of a seizure. However, patients with acute and florid CVT are quite prone to seizures, with the occurrence of even a single seizure potentially negatively impacting outcome. Hence, in such situations, initiating a short course of antiepileptic drugs is highly reasonable and should be considered. As a general guideline, the authors treat for 14 days when there is one isolated seizure at presentation or early in the course. If there is more than one seizure the authors will treat for 3–6 months and discontinue therapy if no additional seizures occurred outside the acute phase. One observational study provides some evidence supporting prophylactic AED treatment in the setting of supratentorial lesions in the absence of seizures reporting 1 seizures in 148 patients treated with AEDs versus 25 in 47 patients without AEDs (OR 0.006 [0.001–0.05]) [112].

7.4. Increased intracranial pressure

Obstruction of the venous sinuses will increase the intracranial pressure (ICP). Common symptoms include headache and papilledema. Patients who experience papilledema and visual disturbances need to be monitored closely for further decompensation of visual fields. In the event symptoms, acetazolamide can be initiated with similar dosing to idiopathic intracranial hypertension (IIH). The authors generally initiate therapy at 500 mg twice a day and up-titrate as needed for therapeutic efficacy. If additional supplementation is needed, or for prophylaxis, the authors generally use topiramate titrated to efficacy with maximum daily dose being 200 mg total in 2 equally-divided doses. Abortive headache management approaches start conservatively with acetaminophen followed by ibuprofen or other NSAIDs (i.e., ketorolac), then tramadol, opioids and lastly migraine cocktails.

The treatment of emergency vision loss requires rapid, but careful consideration. Possible etiologies include elevated ICP or retinal ischemia. Treatment options for elevated ICP in a correlated disease, idiopathic intracranial hypertension (IIH), include optic nerve sheath fenestration and ventriculoperitoneal shunt procedures. The issue unique to CVT is the fact that the underlying visual loss etiology is due to venous obstruction and/or congestion. Thus, there are circumstances where it would be beneficial to evaluate if the venous outflow is completely obstructed, thereby leading to retinal flow stasis and subsequent retinal ischemia.

In that case, the authors would advocate serious consideration of interventional clot extraction to restore venous flow and thus decrease ICP. This is based on opinion. Guidelines do cite LP, optic nerve decompression, and shunts as possible treatment options but do not delineate timing of these procedures in relation to rescue revascularization therapy. Deep venous system or cavernous sinus thromboses progressing to occlude retinal outflow tracts are particularly worrisome. These etiologies can cause permanent blindness and should be considered in the setting of acute vision loss. An urgent ophthalmological evaluation in such situations is highly warranted.

Lumbar punctures (LP) are not required in the diagnostic evaluation of CVT. However, if ICP measurement is necessary, it is safe to do an LP even in the acute phase [113]. The expected CSF chemistry profile is a pleocytosis (50%) and an elevated protein (35%) [3], but these CSF abnormalities are not specific to a CVT diagnosis. LP is generally used to measure ICP and/or to evaluate for other underlying etiologies (e.g., infection).

7.5. Special considerations

7.5.1. Pregnancy

The ISCVT cohort evaluated 119 women for a median follow up time of 14 months with a total of 82 pregnancies occurring among 47 women [114]. Recurrent venous thrombotic event (VTE) occurred only in 3 of the 82 pregnancies (1 of which was recurrent CVT). A majority, 83%, of the total cohort received prophylactic DVT treatment during at least one trimester, including 2 of the 3 patients that had a VTE event. The outcomes of the pregnancies were as follows: 51 full-term newborns, 9 preterm births, 2 stillbirths, and 20 abortions (14 spontaneous). CVT patients who are pregnant or become pregnant are recommended to continue anticoagulation. Warfarin is ***not*** recommended because of its teratogenic effects. In these cases, the authors recommend using enoxaparin throughout the duration of pregnancy. LMWH is preferred over UFH. Guidelines also suggest continuation with either LMWH or warfarin 6 weeks postpartum [38]. If this becomes problematic, then the authors would consider the use of DOACs with the preference being apixaban in patients with normal renal function.

In women of childbearing age, especially those who had a CVT due to OCP use, it is recommended that the women use contraceptive methods without hormonal components. Generally, this is intrauterine device (IUD) therapy. Sometimes emergency contraception is indicated [115]. CVT does not preclude one from getting pregnant in the future but should be monitored closely in a high-risk pregnancy clinic as dictated by an obstetrician. Collaboration between the neurologist and obstetrician is recommended. The decision for prophylactic therapy during subsequent pregnancies should be done on an individual patient basis. However, the authors generally recommend daily prophylaxis with enoxaparin especially in the third trimester.

7.5.2. Infections

Analysis of the ISCVT cohort revealed that new ICH was more frequent in patients with infection as the etiology of their CVT [116]. The study compared infected versus noninfected

patients, with infected patients representing 9.4% of the cohort. New ICH occurred in 12.3% versus 5.3% (*p-value* 0.04) within similar rates of heparin use in each group. Notably, there was no difference in death or dependency between the two groups.

7.5.3. Steroids

A subset (24%) of patients in ISCVT received steroids in the acute CVT phase. Steroid use in the acute phase is not clinically beneficial. Hence, steroids are not used in the setting of CVT.

7.5.4. Pediatrics

The approach to children with CVT is similar to adults. However, because children often have an infectious component to their CVT, much of the diagnostic evaluation should also include evaluations for infection [117–119]. Patients beyond 28 days old are recommended for acute therapy with LMWH and they should continue anticoagulation for 3–6 months (warfarin) [38]. Neonates should be considered for anticoagulation on a case by case basis. In pediatric patients, one should have a lower threshold to evaluate with EEG.

8. Prognosis and long-term follow-up

Many studies demonstrate a CVT recurrence rate between 2 and 5% [3, 7, 120–122]. Other VTE was demonstrated in 4.3–8% of patients in those studies. The ISCVT recurrence rate for CVT was 1.5 per 100 person-years, or 2.2% [123]. In the ISCVT study, mortality was 8.3% at 16 months [3]. A majority of patients (79%) had complete recovery defined as mRS 0–1, 10.4% with mRS 2–3, 2.2% with mRS 4–5. Bilateral lesions were associated with unfavorable outcomes (50% versus 11%, p 0.004) and death (42% versus 11%, p 0.025) [111]. A previous VTE was a predictor of recurrence but not secondary or unprovoked CVTs [122]. Recurrence tended to occur within a year of the first CVT [3]. CVT has lower mortality and morbidity in comparison to other stroke types [1, 2]. Factors associated with poor outcome were older age, malignancy, CNS infection, and ICH [1]. Gender was not associated with poor outcomes after adjustment [8]. Independent predictors of death in the ISCVT were reported to include coma, mentational disturbances, deep CVT, right hemispheric ICH, and posterior fossa lesions. Causes of death were either transtentorial herniation or diffuse edema [13]. In a national database from 2000 to 2007 the mortality rate was 4.39%. The mortality predictors in this study were older age, ICH, hematologic disorders, systemic malignancy and CNS infection [124].

Prognostic information was evaluated in the ISCVT patient cohort. With a median follow-up of 16 months, 57.1% had a mRS of 0, signifying no symptoms, while 8.3% died. The multivariate analysis identified statistically significant predictors of death and disability to include age > 37 years (hazard ratio (HR) 2.0), male sex (HR 1.6), coma (HR 2.7), GCS <9 (HR 2.65) hemorrhage on admission CT scan (HR 1.9), thrombosis of the deep cerebral venous system (HR 2.9), central nervous system infection (HR 3.3), and cancer (HR 2.9) [125]. Another study looked at the predictors of CVT outcome in patients with ICH, this in the ISCVT cohort [49].

Early ICH was defined as ICH present at time of CVT diagnosis. A logistic regression analysis was performed using mRS 3–6 as dependent variable. The patients with early CVT represented 39% of the CVT population at month 6. The independent predictors of death or dependency at 6 months with early ICH in CVT included: older age (adjusted OR for 1-year increase in age, 1.05 [1.02–1.08], male gender (adjusted OR 3.25 [1.29–8.16]), deep CVT (adjusted OR 5.43 [1.67–17.61], right lateral sinus CVT (adjusted OR 2.56 [1.03–6.40] and motor deficit (adjusted OR 2.94 [1.21–7.10] [49].

9. Conclusions

CVT is a less common, but highly treatable, cause of stroke accounting for 0.5–1% of all strokes with a preponderance to occur in women. Our goal was to provide clinicians with the knowledge to rapidly diagnose CVT with an emphasis on etiologies and treatments in an effort to produce optimal clinical outcomes. Clinicians must possess a working knowledge of the relevant anatomy and associated clinical syndromes, and be aware of the relevant clinical trials as described herein. Clinicians must consider CVT when evaluating patients suffering with acute neurological changes, particularly those with predisposing risk factors such as OCP use, smoking, and a postpartum state, among others.

Author details

Christopher A. Stack and John W. Cole*

*Address all correspondence to: jcole@som.umaryland.edu

Department of Neurology, Maryland Stroke Center, Baltimore VA Medical Center and University of Maryland School of Medicine, Maryland, USA

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Chapter 3

Cerebral Vein and Dural Sinus Thrombosis

Dragoș Cătălin Jianu, Silviana Nina Jianu, Georgiana Munteanu, Flavius Traian Dan and Claudia Bârsan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76918

Abstract

Cerebral venous thrombosis (CVT) is an uncommon disorder in the general population. At least 1 risk factor can be identified in 85% of patients with CVT. Because of the high frequency of thrombophilia among patients with CVT, screening for hypercoagulable conditions should be performed. Two pathophysiological mechanisms contribute to their highly variable clinical presentation. Four major syndromes have been described: isolated intracranial hypertension, focal neurological abnormalities, seizures, and encephalopathy. Cavernous sinus thrombosis represents the single CVT which produces a characteristic clinical syndrome. Head Computed Tomography is the most frequently performed imaging study, but Magnetic Resonance Imaging of the head combined with Magnetic Resonance venography are the most sensitive studies. Acute phase therapy for CVT focuses on anticoagulation, management of seizures, increased intracranial pressure, and prevention of cerebral herniation. The majority of patients have a complete or partial recovery, however they have an increased incidence of venous thromboembolism. Clinical and imaging follow-ups 3–6 months after diagnosis are recommended to assess for recanalization.

Keywords: cerebral venous thrombosis, thrombophilia, isolated intracranial hypertension, magnetic resonance imaging of the head, magnetic resonance venography, anticoagulation

1. Introduction

Rare (0.5–1% of all strokes), but alarming disease, cerebral venous thrombosis (CVT) has a higher frequency among young adults (<40 years of age), patients with thrombophilia, and women who are pregnant or using oral contraceptives [1–4]. The most frequent symptoms are headache,

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papilledema, seizures, motor, sensory or language deficits, altered mental status and decreased consciousness. CVT can be caused by multiple predisposing conditions and precipitants. At least one risk factor can be identified in more than 85% cases, multiple risk factors, in about ½ of patients, while in less than 15% no underlying cause can be found [1, 2, 5]. Contemporary brain imaging techniques [angiography, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA)] allow the diagnosis of benign forms of CVT with minimal, nonspecific symptoms and spontaneous recovery [1, 3]. The CVT treatment is based on a combination of etiologic and symptomatic medications. Currently, the main treatment of choice for CVT is heparin (intravenous heparin or subcutaneous low-molecular-weight heparin) in therapeutic dosages [1, 5]. The CVT prognosis depends on the early detection, but it should be mentioned that mortality trends have diminished over the last decades [6]. Because of its frequently misleading presentation, its wide spectrum of causes, its unpredictable course, and its occasional treatment problems, CVT remains a challenge for the clinician [1, 6]. We also want to emphasize that, due to its features, CVT should remain a disease of interest not only for neurologists, but also for other specialists – neurosurgeons, ear, nose and throat (ENT) specialists, ophthalmologists, hematologists, obstetricians, internists, and oncologists [5].

2. Dural sinuses and encephalic veins anatomy

2.1. Encephalic veins

The veins within the cranium contain approximately 70% of the cerebral blood volume (**Figure 1**) [7]. Blood of the brain is drained by the cerebral venous system which consists of the cerebral veins and dural venous sinuses. The cerebral veins don't follow the same path as the arteries. Emerging as fine branches from the substances of the brain, the cerebral venous blood vessels form a pial plexus from which arise the larger venous channels (cerebral veins) which empty into the sinuses of the dura mater. Cerebral veins have thin walls and no valves; they are linked by multiple anastomoses, which allows the development of a collateral circulation and the reversal of blood flow toward the head and brain if there is an occlusion [1, 5, 8, 9].

Cerebral veins comprise three groups: (a) *the superficial venous system,* (b) *deep venous system,* and (c) *posterior fossa veins*: [5].

a. Due to its high proportion of number, course, and anastomoses, *the superficial cerebral (cortical) venous system* is difficult to diagnose in cases of occlusion. The superficial veins are divided into superior, middle (sylvian), and inferior cerebral groups. They drain the major part of the cerebral cortex. The superficial cerebral veins are linked by Trolard's great anastomotic vein, which connects the superior sagittal sinus (SSS) to the middle cerebral veins, which are themselves connected to lateral sinus (LS) by Labbé's vein. The frontal, parietal and occipital superior cerebral veins drain into the SSS. The middle cerebral veins consist of a superficial and a deep vein. The superficial middle vein empty into the cavernous sinus, while the deep one, drain into the basal veins of Rosenthal [1, 5–7, 9].

b. Deep white matter, the corpus callosum, the basal ganglia, and the upper brainstem are drained *by internal cerebral and basal (Rosenthal) veins* which join to form *the great vein of*

Galen and empty, together with the inferior sagittal sinus (ISS), into the straight sinus (SS). In contrast to the superficial veins, the deep system is consistent and is always visualized at angiography, thus any thrombosis in this system is easily recognized [1, 3, 5, 6].

The two cerebral venous systems are connected through many anastomoses [6].

c. *Veins of the posterior fossa* may be divided into three groups: superior veins (draining into the galenic system), anterior veins (draining into the petrosal sinuses), and posterior veins (draining into the troncular and neighboring SS and LS). They are variable in course, and number making the angiographic diagnosis of their occlusion, extremely difficult [1, 5].

2.2. Dural sinuses

The dural sinuses represent a system of intercommunicating trabeculated endothelium-lined channels located between the meningeal and periostal layers of the dura (**Figure 1**). The walls of the sinuses are formed by the inner and outer fibrous layers of the dura mater. Inside of dural sinuses are found the Pacchioni's or arachnoid granulations, which play an essential role in the cerebrospinal fluid (CSF) resorption, especially in SSS and SL [6, 9].

The major dural sinuses are: SSS, ISS, LS, cavernous sinus and SS; they empty into the two internal jugular veins (IJV) to drain into the superior vena cava. Dural sinuses are divided into posterior-superior (P-S) and antero-inferior groups (A-I). P-S comprises the SSS, ISS, LS, SS, and occipital sinus. The A-I group includes the superior and inferior petrosal sinuses and the cavernous sinus. The confluence of the sinuses (torcular herophili) is formed by the junction of SSS, straight, occipital and transverse sinuses [1, 5–7].

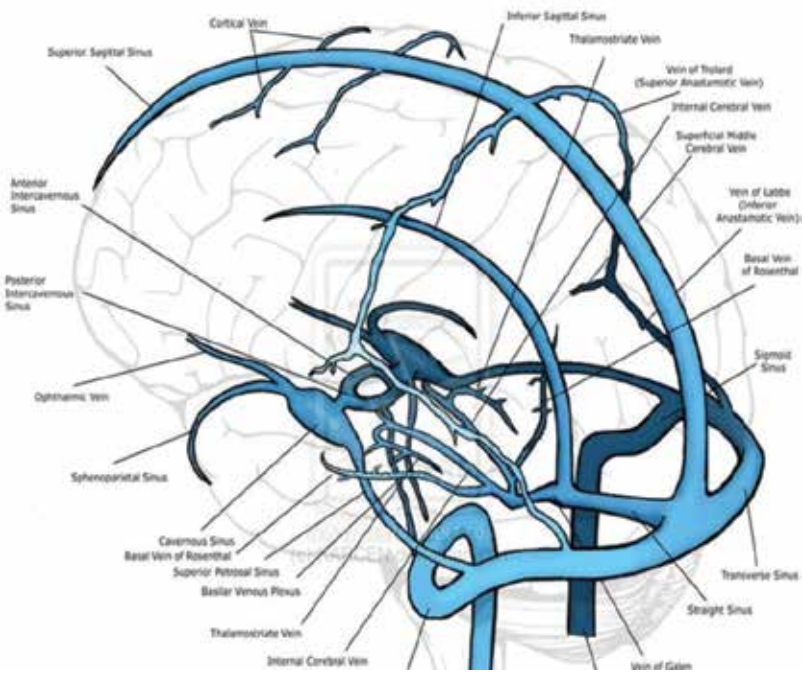

Figure 1. Dural sinuses and encephalic veins anatomy [70].

The superior sagittal sinus (SSS) is located in the attached margin of falx cerebri, receives superficial cerebral veins and drains the major part of the cerebral hemispheres. It also receives the diploe, dura mater, the scalp, and the pericranial veins which explains some cases of SSS thrombosis after cutaneous infections or head trauma. The SSS along with LS sinuses play an important role in CSF circulation, considering that CSF pressure depends directly on the intracranial venous pressure [1, 6, 7, 9].

Each lateral sinus (LS) consists of two sections: the transverse portion and the sigmoid portion which drain blood from cerebellum, brainstem, and posterior portions of the cerebral hemispheres. They also receive some of the diploic veins and some small veins from the middle ear thus becoming vulnerable to infections thrombosis in patients with mastoiditis or otitis media. Asymmetry of the LS is frequent (50–80% of the cases) [1, 3, 6]. The right LS which is often a direct continuation of the SSS, is usually larger than the left so an isolated lack of filling of the left transverse sinus is thus suggestive more of hypoplasia than of thrombosis [1, 7].

Cavernous sinuses are complex, multiseptated extradural venous spaces located on each side of the sella turcica. They drain the blood from the orbits and from the anterior part of the base of the brain receiving superficial cortical veins, the ophthalmic (superior and inferior) and facial veins. Each cavernous sinus has important anatomical relations with other structures. Thus, the oculomotor and trochlear-cranial nerves, along with the ophthalmic and maxillary branches of the trigeminal nerves, traverse along the lateral wall of the cavernous sinuses, whereas the abducens nerve and the cavernous portion of the internal carotid artery (ICA) lie within the sinus itself. Infection is still the leading cause of cavernous sinuses thrombosis as a consequence to infections of the face or sphenoid sinusitis. The cavernous sinuses communicate with each other via *intercavernous sinuses and basilar venous plexus*, and drain into the *petrosal sinuses (superior and inferior)* which empty into the sigmoid sinuses and the IJVs [1, 3, 6, 7].

The inferior sagittal sinus (ISS) receives blood from the corpus callosum and the cerebellum (through the deep cerebral veins) and it becomes continuous with SS [9].

The straight sinus (SS) is formed by the junction of ISS with the vein of Galen. It has a triangular lumen and is situated at the junction of the tentorium cerebelli with the falx cerebri. SS runs postero-inferiorly and ultimately joins torcular Herophili at the internal occipital protuberance [9].

The occipital sinus is the smallest dural venous sinus, receiving tributaries from the margins of the foramen magnum. It runs along the inner surface of the occipital bone and may anastomosis with the sigmoid sinuses and *posterior internal vertebral plexus* that drain into the torcular Herophili [10].

The internal jugular veins (IJV) are the continuation of the sigmoid sinus. They drain blood from the brain and the superficial parts of the face and neck. In contrast to the cerebral veins, they have valves in order to prevent blood going upwards in cases of increased intra-thoracic pressure [9].

The major cerebral venous outflow pathways are represented in adults by the IJV, for supine position, and the vertebral venous system for the upright position [11].

http://dx.doi.org/10.5772/intechopen.76918

3. Epidemiology

The prevalence of CVT is higher than previously reported probably because this rare type of stroke is now more frequently diagnosed due to an increased awareness and improved imaging techniques [12, 13]. CVT represent 0.5–1% of all strokes and may affect all age groups – from neonate to the very old [14]. CVT is more common in children than in adults, and among children, is more frequently diagnosed in neonates than in older children. The peak incidence in adults is in their third decade: the median age in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort was 37 years, with only 8% of the patients older than 65 [5, 15–16]. CVT has a prominent differential sex prevalence, with a female-to-male ratio of approximately 3:1, with an even more marked difference in the age range of 31–50 years. The female predominance of CVT has been attributed to hormonal factors considering that the incidence is sex-independent in children and in the elderly [5, 16–18].

4. Risk factors

Several disorders can cause or predispose patients to CVT and often, this condition proves to be multifactorial, meaning that the identification of a risk factor or a cause should not deter from a search for other causes, in particular inherited or acquired thrombophilia [1, 3, 16, 19]. Supporting this affirmation, the ISCVT results showed that at least one risk factor can be identified in more than 85% of patients with CVT and multiple risk factors, in about half of them. The most frequent risk factors are prothrombotic conditions, oral contraceptive (OC) use, puerperium or pregnancy states, infection and malignancy. Among the CVT risk factors, thrombophilic disorders are the most frequent; only for the cavernous sinus, the main cause of thrombosis remains the skin infections of the face [5].

In the pre-antibiotic era, *localized or systemic infections were the most common cause of dural sinus occlusions.* Septic CVT is usually caused by pyogenic infections of the mastoid air cells, the paranasal sinuses, face, ears, scalp, or throat. It may also result as a complication of meningitis, secondary to brain or epidural abscesses or after an open traumatic injury. However, since the introduction of antibiotics, septic thrombosis, has become a relatively rare, although severe condition [20].

In the 624 patients included in ISCVT, 34% had a form of *thrombophilia* and an inherited thrombophilic defect was detected in 22% of them. It is important to mention that usually an additional precipitating factor is present in patients with thrombophilia who develop CVT [4, 5, 16, 19].

Inherited thrombophilias are the main genetic disorders associated with CVT. Three highly prevalent mutations have been linked to thrombosis: factor V Leiden, factor II-the prothrombin variant (PT 20210A), and the homozygosity for MTHFR C677T. Among them, the factor V Leiden and the prothrombin gene mutation are the most frequent [3, 21–23]. The Q506 mutation in the gene coding for factor V (factor V Leiden) causes inherited resistance to activated protein C. Factor

V Leiden is the most prevalent inherited coagulation disorder and an important cause of CVT, being associated with a 9-fold higher risk, especially if females with this mutation take OC or become pregnant [12, 14, 20]. The prothrombin G20210A mutation (PT20210A) is considered the most important genetic thrombophilic risk factor associated with CVT. This mutation is present in about 2% of Caucasians causing an elevation of the plasmatic factor II level [14, 22]. According to Martinelli, PT20210A determines a 10-fold increase in the cerebral thrombosis risk, especially in OC users [12, 24]. Other genetic coagulation disorders reported to be involved in CVT include: plasminogen deficiency, decreased release of plasminogen activator, sickle cell disease (homozygous sickle cell anemia), and elevated levels of factor VIII [20, 22].

Acquired thrombophilias. Antiphospholipid antibodies are directed against phospholipid-binding plasma proteins and include anticardiolipin antibody and antibodies directed against β 2-glycoprotein. They were described in patients with lupus erythematosis, other connective tissue diseases and as isolated abnormalities, being strongly associated with arterial and venous thrombosis [21].

Antithrombin III and proteins C and S are natural inhibitors of coagulation. They can be deficient on a hereditary basis or be reduced by disease. Congenital deficiency of antithrombin III may be quantitative or qualitative and is usually an autosomal-dominant condition. Inherited deficiencies of proteins C and S (both vitamin K dependent anticoagulants) can also contribute or cause hypercoagulability. Acquired deficiencies of antithrombin III may be associated with liver diseases or renal loss (nephrotic syndrome) [20].

Hyperhomocysteinemia (HHcy) is a disorder that is defined by an elevated plasma homocysteine (Hy) concentrations. HHcy may have a toxic effect on the vascular endothelium affecting the clotting cascade. Increased plasma Hcy levels can be caused from several different genetic mutations in enzymes involved in Hcy metabolism (hereditary forms). Within these, the mutation of the MTHFR C677 → T gene is the most prevalent. There were also described acquired forms of HHcy which are determinated by low levels of folic acid, vitamin B6 or vitamin B12. HHcy is known to be associated with an increased risk for deep venous thrombosis (DVT) and arterial occlusive disease [12, 14, 19]. According to different studies, HHcy could be considered an independent and strong risk factor for CVT [19, 25, 26].

The gender-specific risk factors – pregnancy, postpartum state, oral contraceptive (OC) use and the hormone replacement therapy – are the most frequent risk factors in women with CVT, they being responsible for the marked feminine preference of this condition [4, 6, 18].

Pregnancy and puerperium In high-income countries, 5–20% of all CVT are related to pregnancy or puerperium, according to ISCVT, the peripartum etiologies being responsible for 15% of CVT cases [16, 27–29] However, the incidence is much higher in low-income countries where puerperium is the most common risk factor for CVT accounting for 31% of cases [27, 30, 31]. Explanations for the frequency of intracranial venous thrombosis in pregnancy and the puerperium include poverty, absence of antenatal care, home delivery, vegetarian diet, depletion of vitamin and protein stores and dehydration associated with primipara and anemia [32]. Most pregnancy-related CVT occur in the third trimester or, more frequently,

in the first 3 week post-partum. In these cases, CVT could be accompanied by venous thromboses outside the nervous system (pelvic or lower extremity phlebothrombosis and pulmonary embolism), probably, as a consequence of the hypercoagulable state and the venous stasis that occurs during pregnancy [3, 17, 20]. The prothrombotic changes induced by pregnancy include increasing of fibrinogen and several coagulation factors and decreasing of antithrombin III and plasminogen. These alterations in the coagulation system persist at least during early puerperium when the hypercoagulability worsens as a result of volume depletion, trauma and additional risk factors as infection, unhygienic environments, certain rituals, higher birth rates, instrumental delivery or cesarean section [3, 14, 28, 33, 34]. On the other hand, *pelvic phlebothrombosis may determine CVT via the venous plexuses of the vertebral canal, and the basilar venous plexus.*

Estrogens, whether administrated for contraception or therapeutic purposes (replacement therapy, suppression of lactation), are associated with a significant risk for venous and arterial thrombosis. Particularly, the administration of OC (especially the third-generation agents) is considered to be an independent risk factor for CVT, the great majority of younger no pregnant women with this condition being OC users [3–5, 14]. It is also important to mention that the risk of thrombosis, whether intra- or extracerebral in women taking OC is almost 6 times higher than that of non-users if this contraception method is combined with an underlying hereditary prothrombotic abnormality like those listed above [5, 14, 17, 35]. In most of the cases, the use of OC is found together with other conditions such as systemic lupus erythematosus, Behçet's disease or inherited thrombophilia. However, in about 10% of the CVT cases, the prothrombotic effect of OC remains the only identifiable etiologic factor [1]. Pregnancy and OC use represent transient risk factors for thrombosis and they are not necessarily associated with a higher risk for recurrence [17].

Hormonal abnormalities may also interfere with normal coagulation mechanisms in males. Supporting these statement, we mention the reported case of a young healthy man who develop extensive dural sinuses thrombosis after taking intramuscular injections of androgens for body building [20, 36].

In the ISCVT, *cancers* account for 7.4% of all CVTs [16]. Mechanisms associated with CVT in cancer patients include: direct tumor compression, tumor invasion of cerebral sinuses, leukostasis, the hypercoagulable state caused by increase in acute-phase reactants or altered coagulation factors from therapy (chemotherapeutic and hormonal agents).The most frequent cancers linked with CVT are the hematologic malignancies, breast tumors, nephroblastoma, Ewing's tumor, gallbladder carcinoma, medulloblastoma and medullary carcinoma of the thyroid [14, 20].

Hematologic disorders. Philadelphia-negative myeloproliferative disorders (MPDs), especially polycythemia vera (PV) and essential thrombocythemia, are associated with a high risk of venous thrombosis, CVT being reported as a complication of these conditions in 2.8% of the ISCVT cases. The acquired Janus kinase 2 V617F mutation (JAK2 V617F) has been found in more than 90% of patients with PV and in about 50% of those with essential thrombocythemia. The presence of JAK2 V617F is associated with an increased incidence of major thrombosis and a poor prognosis. This mutation has been also identified in patients with venous

thrombosis occurring in up to 15 years before diagnosis of overt MPD [37]. Other hematological conditions can determine or predispose to venous occlusion and among them we mention: myelofibrosis, myeloid metaplasia, gammopathies, paroxysmal nocturnal hemoglobinuria, iron deficiency anemia, heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura [14].

Vasculitides. Numerous systemic autoimmune disorders has been associated with CVT: inflammatory bowel disease, systemic lupus erythematosus (SLE), with or without nephrotic syndrome, Behçet's disease, Sjögren's syndrome, Wegener's granulomatosis, sarcoidosis, Hughes-Stovin syndrome, malignant atrophic papulosis [1, 4, 14].

Local causes such as head trauma, brain tumors, porencephaly, arachnoid cysts or arteriovenous malformations, and *mechanical factors* including cranial and systemic surgery, epidural blood patch, spontaneous intracranial hypotension, jugular venous cannulation and lumbar puncture can also determine dural sinus and cerebral venous occlusions [1, 4, 14, 20].

Other conditions have been associated with CVT in case reports or small series including severe dehydration (mostly in children and elderly), malnutrition, cardiac failure, and chronic obstructive pulmonary disease [5, 16, 20].

There is still a significant number of *idiopathic CVT* cases. According to ISCVT results, in almost 13% of adult CVT patients extensive search reveals no underlying cause. We also want to emphasize that among these patients, in 37% of those over 65 years no risk factors could be identified [16].

5. Pathophysiology

The venous system of the brain is a complex three-dimensional structure that is often asymmetric, having a significantly more variable pattern than the arterial anatomy (**Figure 2**). The cerebral vasculature plays a major role in maintaining the local physiological hemodynamic course in order to meet the metabolic needs of the brain. Based on principles of physics applied to intracranial contents, within the closed skull, the sum of brain volume plus cerebral spine flow (CSF), plus cerebral blood volume always remains constant and, consequently, an increase in one of these parameters should cause a reduction in one or both of the remaining two. Therefore, the permeability of the vascular bed is essential in order to preserve the cerebral compliance [38, 39].

The cerebral blood drainage depends on the gradient between venous pressure and intracranial pressure. Also for tissue perfusion to occur, the blood pressure in the feeding artery must exceed the pressure in the tissue and draining veins. Another pressure difference, the one between CSF and SSS, maintains the CSF absorption across the arachnoid villi into the SSS [6, 20, 39].

CVT is a multistep process that usually begins when thrombus partially occludes a dural sinus. In situ thrombus formation occurs due to the usual pathogenic factors – activation of the coagulation system and blood hypercoagulability [1, 3, 20]. The vessel wall is usually normal. The thrombosis may progresses, obstructing first the sinus and then the smaller

http://dx.doi.org/10.5772/intechopen.76918

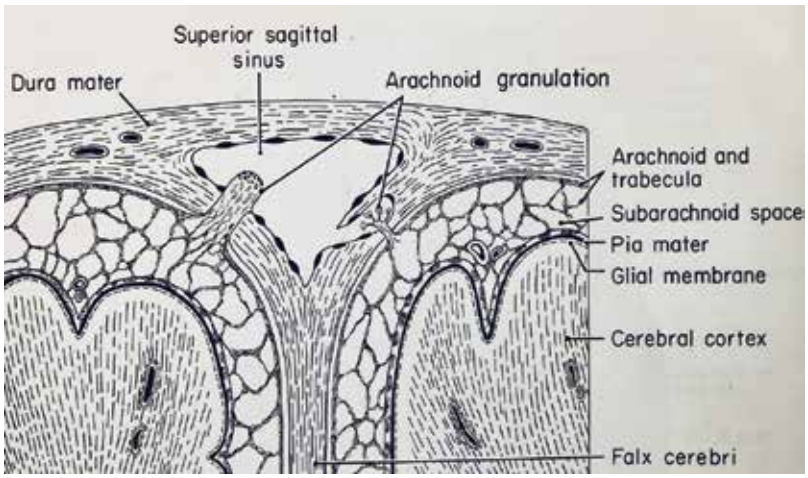

Figure 2. Diagram of meningeal-cortical relationships [8].

venous tributaries. The distribution of the possible consecutive lesions depends on a variable balance between prothrombotic and thrombolytic processes and compensation of occlusions by collateral circulation. Symptoms usually appear when this compensatory mechanism is no longer effective [3, 9, 39].

The two major pathophysiological mechanisms responsible for the clinical manifestations of CVT are: (1) *increasing of venular and capillary pressure,* and (2) *decreasing of CSF absorption* [4].

1. Thrombosis of cerebral veins or sinuses causes a progressive increase of venular and capillary pressure.

In the early stages of venous obstruction, the extensive collateral circulation within the cerebral venous system provides a significant degree of compensation. Therefore, an adequate perfusion of the affected brain tissue might still be possible at lower flow rates, if the blood is effectively drained through collateral pathways and the pathological pressure changes are thus, neutralized. As a result, large areas of the brain can be functionally and metabolically impaired, but not irreversibly damaged [6, 39].

However, prolonged intravenous hypertension corroborated with a poor collateral flow will result in extension of the thrombosis within cortical venous tributaries, lowering even more the cerebral perfusion pressure [39], which will lead to:

a. local ischemic injury and cytotoxic edema,

b. disruption of the blood–brain barrier leading to vasogenic edema, and.

c. venous and capillary rupture culminating in parenchymal hemorrhage and, less frequent, subarachnoid hemorrhages [4].

In milder cases, dural sinuses thrombosis may cause only an increase in intracranial venous or CSF pressure with minimal symptoms like headache or papilledema, or can remain

completely latent. Usually, the occlusion of cerebral veins is the one that leads to so-called venous infarct. The most common anatomic presentation is that of extensive bilateral hemorrhagic infarcts, located in the superior and internal parts of both hemispheres, due to thrombosis of the SSS and its tributary cortical veins [1, 6]. The limited drainage that occurs due to CVT and resulting increased venous pressure, often causes fluid to back up into the brain, causing vasogenic edema. This type of edema accumulates within the extracellular space of the cerebral and cerebellar white matter under the influence of hydrostatic pressure (increased blood pressure and blood flow) and osmotic gradients. Vasogenic edema does not necessarily imply neuronal injury, considering that the fluid in the extracellular compartment can potentially be removed. On the other hand, cytotoxic edema is caused by energy failure with movement of ions and water across the cell membranes into cells. The intracellular edema, as a consequence of ischemia, is associated with the presence of a large volume of dead or dying brain cells and implies a bad outcome [20]. In venous infarcts, the vasogenic edema is much more prominent that the cytotoxic type as has been also proven by diffusion-weighted imaging which sustains the fact that the venous infarcts are different from arterial ones and explains, at least partly, the much better recovery reported in those with CVT [1, 19]. Brain edema and increased intracranial pressure cause headache, decreased consciousness and vomiting, but the most important concerns related to these pathological processes are the pressure shifts and the risk for brain herniation which can be life-threatening due to possible pressure-related damage to adjacent tissues [20]. The raised venous and capillary pressure also determines the occurrence of vessel damages and erythrocytes diapedesis through the blood–brain barrier disruptions, both resulting in brain hemorrhage. However, the neuronal damage associated with CVT-induced hemorrhage is often less severe than the lesions caused by arterial ischemia [20, 39].

2. Cerebrospinal fluid is normally absorbed through arachnoids granulations especially into the SSS and LS. Another effect of cerebral sinuses occlusion, especially of the SSS and LS is the decreasing of CSF absorption which, ultimately raises the intracranial pressure. Consequently, increased intracranial pressure worsens venular and capillary hypertension and contributes further to parenchymal hemorrhage and edema [4, 6].

Histological analysis in CVT patients reveals dilated and congestionated veins, brain edema with flattened gyri, obliterated sulci and compressed ventricles, ischemic neuronal damage. The thrombus is like other venous thrombi (rich in red blood cells and fibrin and poor in platelets-when it is fresh; and replaced by fibrous tissue, sometimes with recanalization-when it is old) [1, 6, 9, 20].

6. Clinical presentation

CVT present with a wide spectrum of symptoms, signs and modes of onset. Usually, these conditions are characterized by a gradual or stepwise development of symptoms. Thus, in 50–80% of cases the onset is subacute (over 48 h, but under 30 days); in a third of the patients the onset is acute (under 48 h), and in 7%, chronic (over 30 days). Besides

puerperal and infectious cases which tend to present acutely, the progressive increase in symptoms and fluctuating course are the rule in patients with other causes of venous occlusion. The gradual onset of CVT' symptoms can be explain by the slow evolution and propagation of thrombosis and the potentially broad collateralization which may be able to maintain for a while an adequate drainage of cerebral blood [1, 5, 16, 20].

In patients with altered mental status associated with focal neurological deficits, seizures and headaches, CVT always must be considered a possible diagnosis. On the other hand, there were reported cases with atypical presentation and occasionally, isolated symptoms such are headache, a single seizure or nonspecific behavioral symptoms. In young children and especially neonates, CVT have a mostly nonspecific clinical presentation with seizures, respiratory distress syndrome, hypertonia, lethargy or coma [5, 9].

The clinical features of CVT depend on the following factors: gender and age of the patient, interval from onset to admission to hospital, site and number of thrombosed sinuses and veins and presence of parenchymal lesions [5, 9, 19].

The most common syndromes of CVT are: isolated intracranial hypertension, focal neurological deficits, seizures, and subacute encephalopathy. Depending on the extent and location of cerebral venous occlusion, these syndromes may be found in combination or as isolated groups of symptoms.

1. *Isolated intracranial hypertension* is the most homogeneous clinical pattern found in CVT (40%). It is characterized by headache with or without vomiting, papilledema and sixth nerve palsy [1, 4, 5, 20].

Headache is an extremely common symptom in patients with CVT, being present in almost 90% of patients in the ISCVT [14–16, 20]. It is the earliest symptom in 2/3 of cases. It is also important to mention that headache is much more common in patients with venous thromboses than in patients with cerebrovascular ischemic arterial disease [6, 20]. The presence of this symptom in CVT cases can be explained by the increased intracranial pressure and the local inflammatory reaction which activates pain-sensitive fibers existing in the walls of the occluded sinuses, dura and overlying skull [14, 19, 20]. The headache associated with CVT is mostly gradual in onset, diffuse, severe in intensity, progressive and permanent; it may worsen with Valsalva maneuvers or position change [1, 9, 40]. Its features can be misleading, mimicking migraine or the typical thunderclap headache of subarachnoid hemorrhage; in puerperal cases, it can be misdiagnosed as post-dural puncture headaches. Nevertheless, it is almost every time accompanied by other neurologic signs [1, 14, 34]. However, isolated headache without focal neurological findings or papilledema occurs in up to 25% of patients with CVT, being typically associated with LS thrombosis [6, 14, 19].

Papilledema occurs in about 25–40% of patients with CVT; it can cause transient visual impairment, and if prolonged, optic atrophy and blindness. Visual loss is usually insidious, with progressive constriction of the visual fields and relative sparing of central visual acuity. Delayed diagnosis may expose the patient to an increased risk of later visual deficit [6, 14]. Transient loss of vision can occur in association with spells of intense headache and papilledema [5].

2. *Focal neurological deficits* are inaugural in 15% of cases and are present in about half of patients with dural sinus and cerebral veins occlusions during the course of the disease [1]. Focal cerebral signs include central motor and sensory deficits, aphasia or hemianopia and are consequences of focal parenchymal abnormalities [9, 15, 20]. Unilateral or, less frequently, bilateral motor deficits are the most common focal findings and may be present in up to 40% of patients. Among this signs, hemiparesis is probably the most common. Sensory deficits are less frequent. Other possible symptoms associated with CVT are aphasia (usually in left LS thrombosis), hemianopia and ataxia (found in posterior dural sinuses occlusion) [4, 5, 20].

3. *Seizures* (focal, generalized or even status epilepticus) are the inaugural symptom of CVT in about 12–15% of cases and are present at some point during the disease in about 40% of patients with an even higher incidence in peripartum (76%) and neonates (71%). Particular attention should be paid to pre-eclamptic patients with CVT that develop seizures, considering that in these cases the diagnosis can be delayed until the empirical treatment for eclampsia fails to resolve the seizures [1, 4, 20, 34] Seizures are about equally divided between focal and generalized types, and the association of both types is common [1]. It is important to know that seizures are more frequently seen in CVT than in other stroke types [4, 5, 15]. According to numerous studies, a higher risk for inaugural and early seizures was found in patients with supratentorial parenchymal lesions (especially anterior to the central sulcus), intracranial hemorrhage, SSS and cortical veins thrombosis (which drain venous blood from the motor and sensory cortices), and in those who have motor or sensory deficits [4, 19, 41–44]. Also, the patients with presenting seizures are considered to have a higher risk of early seizures. On the other hand, the risk of early seizures in patients without supratentorial parenchymal lesions or presenting seizures was very low. Also, the antiepileptic drug (AED) prophylaxis significantly decreased the risk of early seizures in CVT patients presenting the predisposing factors listed above [41].

4. *Subacute encephalopathy*-manifested mostly as a depressed level of consciousness (varying from drowsiness to deep coma) is present in about half of cerebral venous disease cases and is found in patients which are often either very old or very young [1, 4]. Alteration of consciousness is usually a late one, but it can be found in about 15% of patients with CVT at hospital admission [1, 15]. It may occur when CVT is a terminal event during another severe condition, or as a result of extensive acute CVT with large venous infarcts and bilateral thalamic involvement, cerebral edema, or parenchymal hemorrhages that cause brain herniation. In CVT the alteration in level of consciousness is mostly reversible, however, coma at admission remains the strongest predictor of a poor outcome [20, 15]. The differential diagnosis of CVT encephalopathy includes encephalitis, disseminated intravascular coagulation and cerebral vasculitis [1]. Psychiatric disturbances (irritability, anxiety, depression, delirium) in association with CVT are relatively infrequent (6%) and may be confused to postpartum psychosis [1, 9].

The clinical pictures of CVT differ according to the location of the occluded sinus or vein, however, in approximately two thirds of patients thrombosis affects multiple veins or sinuses [1, 5, 20, 45]. The two most frequent sites of thrombosis are the SSS (62–80%) and the LS (38–86%). The isolated involvement of one sinus occurs in a minority of cases: less than 30%

for SSS and 10% for LS [1, 16, 45]. Cerebral veins are often involved but almost never in isolation. Thrombosis of the galenic system is rare. It is important to know that the management of CVT it is not influenced by the topographic diagnosis [1, 20].

Superior sagittal sinus (SSS) thrombosis is the most commonly affected and is the favorite location for thrombosis during the puerperium. The usual presentation of the isolated SSS occlusion is that of an isolated intracranial hypertension. Symptoms and signs depend on the involvement of cerebral veins and other dural sinuses, especially LSs. Extension to cortical veins is followed by the onset of a focal motor or sensory deficit (more marked in the leg), focal or generalized seizures. Bilateral motor signs may also occur as a consequence of the bihemispheric injuries caused by the SSS thrombosis [1, 14, 20].

Lateral sinus (LS) thrombosis has variable presentation. Patients with isolated thrombosis of LS usually present a pseudo tumor syndrome (isolated intracranial hypertension) [1, 19, 20]. The infectious etiology is much more common in LS thrombosis than in SSS occlusion. Isolated LS thrombosis has mostly been reported in otologic patients as a consequence of ear and mastoid infections, hence the term "otitic hydrocephalus" [20, 45]. The symptoms related to an underlying otic infections in patients with LS thrombosis are relatively characteristic. Fever, headache, neck pain and neck tenderness, vertigo, nausea and vomiting, diplopia caused by sixth nerve palsy and signs of fifth nerve irritation manifested as temporal and retro-orbital pain are often present. The mastoid region may be sensitive to finger percussion. Decreased alertness may occur [14, 20]. Intracranial hypertension is more common after right-sided LS thrombosis because the left LS is often hypoplasic; in these patients right LS occlusion will cause a bilateral drainage impairment, affecting structures on either side of the tentorium, especially the inferior portions of the temporal lobe and cerebellum. Therefore, combined temporal lobe and cerebellar signs on one side suggest LS thrombosis [20]. Fluent aphasia, is common in left transverse sinus thrombosis (40%) and can be accompanied by right hemianopia or superior quadrantanopia. Right temporal lobe involvement causes an agitated state and left visual field defect. Nystagmus and gait ataxia are the typical signs of cerebellar involvement [4, 5, 20]. The thrombotic process spreads, in most of the cases, to other sinuses and veins, especially to the SSS. Focal signs are present when thrombosis extends to superior or inferior petrosal sinuses (5th and 6th cranial nerves involvement), SS and deep venous system, adjacent cortical veins and the jugular bulb (9th, 10th and 11th cranial nerves involvement) [1, 5]. In rare cases, a patient with thrombosis limited to the left LS (without involvement of tributary veins), presents an atypical clinical picture (migraine-like acute isolated headache), and the thrombosis is not due to an ear infection, but to a thrombophilia [4, 46]. In consequence, we have to systematically look for LS thrombosis (and other CVT) in patients with recent headache even in the absence of associated symptoms and signs, and ear infections.

Cavernous sinus thrombosis usually has an infectious cause. The most common germs implicated in septic cavernous sinus thromboses are staphylococcus, streptococcus and pneumococcus [20, 47]. Cavernous sinus thrombosis represents the single CVT which produces a characteristic clinical syndrome which includes: chemosis, conjunctival edema, proptosis and painful complete or partial ophthalmoplegia [1, 5, 9, 20]. Papilledema is common and may be associated with hemorrhages of the retina. Symptoms generally start in one eye, but within a

couple of days the other eye is usually affected via intercavernous sinuses. Headache, facial pain and fever can precede the typical syndrome described [9, 20]. The direct relationship between the cavernous sinus and the dura results in symptoms of meningeal irritation. When the occlusion extends to other sinuses and cortical veins, seizures and motor weakness may occur [9, 47]. Head trauma, surgery on intracranial or facial structures, prothrombotic states and thrombosis of dural arteriovenous fistulas can result in aseptic cavernous sinus thrombosis. The signs and symptoms of this disease take a more indolent form with an isolated abducens nerve palsy and mild chemosis and proptosis [1, 20, 47].

Thrombosis of the superior and inferior petrosal sinuses is usually a sequela of cavernous or LS thrombosis. The occlusion of the superior sinus presents as a trigeminal palsy, while the thrombosis of the inferior one is characterized by an abducens palsy [1].

Cortical veins thrombosis. Isolated thrombosis of cortical veins without associated dural sinus occlusion is infrequent (2%) [1, 20]. The most often involved are the superior cerebral veins (rolandic, parieto-occipital and posterior temporal) which empty into the SSS. This condition presents as focal deficits or seizures of sudden or progressive onset. However, if the collateral circulation is efficient there will be only an area of localized edema (that can be asymptomatic) or no parenchymal lesion at all. The neuronal lesions that may appear are mostly reversible, thus the clinical recovery is complete in some cases. Usually, thrombosis spreads to the SSS and to cortical veins on the opposite side, leading to signs of intracranial pressure and bilateral parasagittal infarct [1].

Thrombosis of the deep venous system is more frequent in children; it is much less common than dural sinus thrombosis. This condition can cause extensive thalamic and basal ganglia hemorrhagic infarcts and edema, sometimes with bilateral brain involvement [14, 20]. The clinical picture is usually severe. Most patients present with rapid neurological deterioration, manifested as stupor or coma, decerebration, decortication, signs of raised intracranial pressure, papillary changes, vertical gaze palsy, mental troubles, and motor deficits [1, 14, 19, 20]. The most common symptoms in adults are headache, nausea and vomiting, gait ataxia, neuropsychological symptoms, disturbances of consciousness, hemiparesis (that may be bilateral or alternating) and seizures. When patients survive, they often show residual signs such as abulia or memory impairment. It was reported the possibility of benign forms of galenic thrombosis [1, 20].

Venous infarctions in the posterior fossa result from thrombosis of LS, SS and the superior petrosal vein. The isolated form is extremely rare due to the abundant collateral venous drainage of the posterior structures. However, it is an important differential diagnosis in patients who has risk factors for CVT and presents with cerebellovestibular symptoms, headache, intracranial hypertension syndrome, and atypical findings on brain CT such as pan-cerebellar and vermian infarcts, cerebellar hemorrhages of irregular shapes, or with extension to the subarachnoid space and cerebellar peduncles [48]. Cerebellar veins thrombosis causing cerebellar infarction has only rarely been described. This condition is usually associated with LS thrombosis. The clinical pictures of venous and arterial cerebellar infarcts are similar, the most common signs being headache, vomiting, ataxia and unilateral dysmetria; these symptoms can be associated with a decrease in conscious level and papilledema suggesting obstructive hydrocephalus. If the thrombotic process spreads to IJV, the patients may develop cranial nerve palsies (9th and 10th cranial nerves involvement) [1, 20].

Internal jugular vein (IJV) thrombosis is, in most of the cases, a consequence of LS thrombosis extension, presenting with unilateral pulsating tinnitus or multiple cranial nerve palsies. IJV thrombosis can be rarely, accompanied by pulmonary embolism. The thrombophlebitis of the jugular vein may occur as a complication of the syndrome of tonsillopharyngitis (Lemierre's syndrome) [1, 9, 20].

The emissary veins (EV) (e.g. petrosquamosal sinus (PSS)), are residual valveless veins which connect the intracranial dural venous sinuses and the extracranial venous system. Posterior fossa EVs go through cranial apertures and participate in extracranial venous drainage of the posterior fossa venous system, in addition to IJV. EVs are usually small and have no clinical significance in healthy people; however they may become enlarged in patients with high-flow vascular malformations, IJV aplasia or thrombosis. In such cases, the clinical picture may include various craniofacial syndromes and tinnitus [49, 50].

7. Diagnosis

The diagnosis of CVT is typically based on clinical suspicion and imaging confirmation – demonstration of an occluded sinus/vein and of the thrombus [2, 14]. Patients with CVT are younger, usually female and have low frequencies of vascular risk factors (hypertension, coronary artery disease, diabetes and smoking) when compared with patients with arterial occlusive disease [20]. The clinical evolution in CVT patients is slower than in those with arterial occlusion and is characterized by headache and other signs of intracranial hypertension associated with focal neurological deficits and new seizures. The presence of hemorrhagic infarcts, especially if multiple or in no arterial vascular territories also indicates CVT [4, 20]. The highly variable clinical picture of cerebral venous disease often cause important delays in diagnosis [4].

8. Laboratory testing: thrombophilia testing

In order to establish the underlying cause of cerebral venous disease, there may be necessary several laboratory investigations [1].

Blood assay. A complete blood count, chemistry panel, sedimentation rate, measures of the prothrombin time and activated partial thromboplastin time are indicated for patients with suspected CVT. These tests may demonstrate abnormalities suggestive of a hypercoagulable state, infective, inflammatory or malignant disorders. (Class I; Level of Evidence C). A urinalysis may reveal proteinuria indicating a nephrotic syndrome. Considering that in elderly CVT patients, the proportion of cases with malignancies and hematological disorders is higher and that, sometimes, the cause of CVT is revealed only weeks or months after the acute phase, searching for an occult neoplasm is always recommended in elderly patients and idiopathic cases [1, 2, 14].

D-dimer concentrations are increased in most patients so a low level of D-dimer (<500 ng/mL) may help identify patients with low probability of CVT (Class IIb; Level of Evidence B). It is important to mention that normal D-dimer level does not exclude the diagnosis, particularly

in patients who present with isolated headache and in case of prolonged duration of symptoms (i.e. >1 week) before the test [4, 14, 20, 51].

Lumbar Puncture is indicated only if there is a clinical suspicion of meningitis. Elevated opening pressure is a frequent finding in CVT and is present in about 80% of patients. Also, there may be observed a mild lymphocytic pleocytosis, increased protein and red blood cells. The CSF is rarely (10%) entirely normal in CVT, but there are no specific CSF abnormalities associated with this condition [1, 9, 14].

Thrombophilia screening is recommended in all CVT patients, especially in those with high probability of carrying severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at CVT, CVT without a transient or permanent risk factor) [4, 14]; these tests should be performed even when another associated condition is already found because they imply a systematic family study and modify the long term management of the patients. Testing for prothrombotic conditions should include evaluation for prothrombin G20210A mutation, factor V Leiden mutation, protein C, protein S, antithrombin deficiency, antiphospholipid syndrome (lupus anticoagulant, anticardiolipin antibodies), and hyperhomocysteinemia. Testing for protein C, protein S, and antithrombin deficiency must be performed at least 6 weeks after a thrombotic event and 2–4 weeks after stopping warfarin. (IIa/ B) [2, 4, 14]. Protein C, S, and antithrombin levels may be also influenced by oral contraceptives, pregnancy, severe liver disease, L-asparaginase chemotherapy and nephrotic syndrome. The screening results should be confirmed with repeat testing and family studies [2, 4]. Other tests may include a functional plasminogen assay and qualitative testing of platelet functioning.

A diagnosis of antiphospholipid syndrome requires abnormal laboratory testing on 2 or more occasions at least 12 weeks apart because abnormal results may occur transiently due to the disease process, infection, some medications or other causes. However, if a normal result is obtain at the time of clinical presentation, the antiphospholipid antibody syndrome is ruled out [14].

9. Imaging

The diagnosis of CVT is based on neuroimaging. The goal of this tests is to determine vascular and parenchymal changes associated with this condition (**Figure 3**) [14, 19].

Computed tomography is usually the first investigation performed in patients who present with new-onset neurological symptoms such as headache, seizure, mental alteration, or focal neurological signs [5, 14]. It is useful especially in the emergency setting because is fast and widely available [2, 52]. The place of CT scanning in the diagnostic strategy of CVT is mainly the rule out other acute cerebral disorders that CVT can imitate including arterial stroke, abscess, tumors and subarachnoid hemorrhage. Sometimes, CT identifies lesions that can themselves cause CVT such as meningioma, abscesses, sinusitis or mastoiditis [1, 4, 5].

There have been described various direct and indirect CT signs associated with CVT.

a. *Direct signs of CVT* can be founded in about 1/3 of CVT cases; they correspond to the visualization of thrombus itself and include: the "cord sign, the "dense triangle sign," and the "empty delta sign." [5, 6, 14]

http://dx.doi.org/10.5772/intechopen.76918

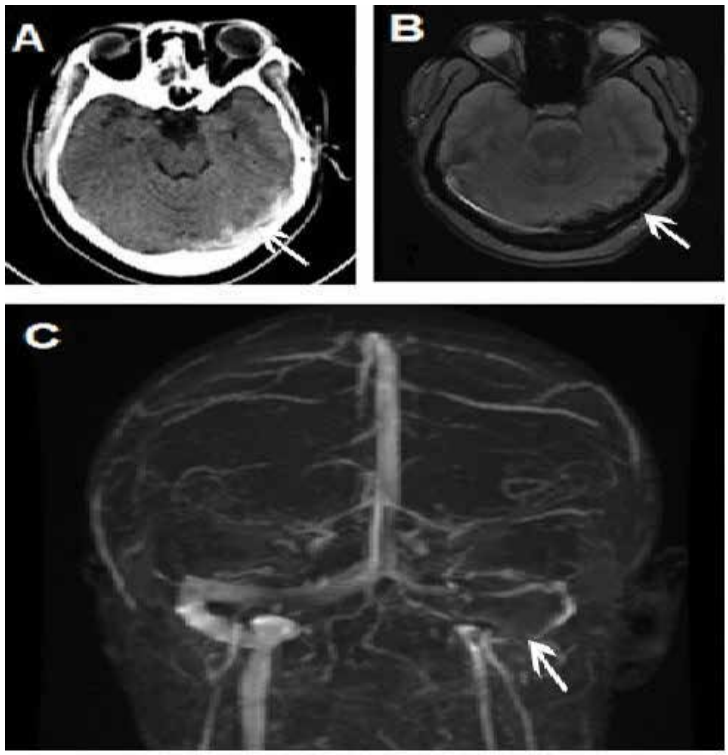

Figure 3. (A) Nonenhanced computed tomography (CT) in the axial plane demonstrating spontaneous hyperdensity of the left lateral sinus (white arrow). (B) Magnetic resonance (MR) T2*SW imaging in the axial plane demonstrating left LS hyposignal (white arrow). (C) Magnetic resonance (MR) venography in the coronal plane noting absence of flow in the left LS (thrombosis of the left LS) (white arrow) [46].

The cord sign (visible on unenhanced CT scans) is found in 25% of CVT patients and is defined as a homogeneous hyperdense appearance of a thrombosed cortical or deep vein. It reflects a newly formed thrombus in a cerebral vein and is best seen within the first week of the disease. After 7–14 days, the clot becomes isodense and then hypodense. It is known that slow flow can also produce this sign, thus its specificity is considered to be rather low [1, 6, 52].

The "dense triangle sign" (seen on no contrast CT scans) was reported in less than 2% of cases; it is characterized by the hyperdense appearance of the thrombosed sinus and can be seen during the first 2 weeks of the disease. Mimicking occurs in patients with increased hematocrit or dehydrated [1, 3, 6, 9].

The empty delta sign (seen after injection of contrast agent) is present in about 35% of reported cases and only in patients with SSS thrombosis. The empty delta sign reflects a lack of contrast enhancement within the posterior 1/3 of the SSS that is surrounded by contrast enhancement of the wall of the sinus due to the presence of collateral tributaries. It is absent when the test is performed either in the first 5 days or more than 2 months after onset of symptoms. An early division of the SSS can appear as a false delta sign [1–5, 20].

b. *Indirect signs of CVT* are more frequent and include the following findings. Intense contrast enhancement of the falx and tentorium or areas of gyral enhancement can be observed in

the region of a thrombosed dural sinus; it is seen in 20% of CVT cases [1, 5, 20]. The presence of brain edema with small, compressed ventricles can be found in 20–50% of CVT patients. This sign can be difficult to differentiate from normal brain, especially in young patients. The opposite finding (enlarged ventricles) does not exclude the diagnosis considering that it can be associated with cerebellar vein thrombosis [1, 20]. Cortical veins may appear dilated on contrast-enhanced scans due to dilatation of collateral tributaries [20]. Localized or diffuse areas of white matter hypodensity without contrast enhancement are present about 75% of cases; they suggests cerebral edema (sometimes associated with mass effect) or venous infarction which usually do not respects the arterial boundaries. Venous infarcts can be unilateral or bilateral, single or multiple; venous infarcts are usually hemorrhagic, being described on CT as spontaneous hyperdensity (10–50%); In most CVT patients, parenchymal lesions manifests on CT as large subcortical often multifocal hematomas and petechial hemorrhages within large hypodensities. No hemorrhagic venous infarcts are considered to be equally frequent. In serial CT scans some lesions may disappear ("vanishing infarcts") and new others may appear [1, 5, 20]. In less than 1% of cases, CVT is associated with a subarachnoid hemorrhage, usually found in the vicinity of the venous occlusion. Subdural hematomas are also infrequent [1, 2, 14, 20].

Particular forms of CVT may present with some distinctive features. On post-contrast CT scans of patients with cavernous sinus thrombosis can be found multiple irregular filling defects with bulging cavernous sinuses and enlarged orbital veins. Cerebellar venous infarction can be associated with hydrocephalus and compression of the forth ventricle. In case of deep venous system thrombosis the characteristic findings may include: the presence of bilateral hypodensities involving the thalami and basal ganglia, hyperdensities in these same regions (hemorrhages or hemorrhagic infarction), severe edema with compression of the third ventricle and hyperdense appearance of the occluded sinuses and deep veins on unenhanced CT scans [1, 20].

It is important to emphasize that CT is normal in up to 30% of CVT cases and most of the findings are nonspecific. Anatomic variability of the cerebral venous system makes CT diagnosis of CVT insensitive, results on no contrast head CT being abnormal only in 30% of CVT cases. Therefore, a negative CT examination will not exclude a diagnosis of CVT; in suspected cases, an MRI or angiographic examination is necessary for further confirmation [4, 5, 14, 53].

Nevertheless, the distribution of the parenchymal abnormalities, including diffuse edema, bilaterally infarcts or hemorrhages, predominance of hemorrhagic changes and the presence of a lesion which crosses usual arterial boundaries should always raise the suspicion of CVT [14, 20].

CT angiography (helical CT venography) with bolus injection of contrast material gives excellent details of venous circulation anatomy and pathological changes including: filling defects in the occluded sinus or veins, sinus wall enhancement, increased collateral venous drainage and tentorial enhancement [1, 5]. CT venography is especially useful in the acute setting because it provides a rapid (it can be performed immediately after brain CT) and reliable method for detection of CVT, particularly in patients with contraindications to MRI. Also, it allows the diagnosis of sub-acute or chronic CVT because it can detect thrombus of

heterogeneous density. CT venography is less invasive, less expensive and offers a better visualization of the cavernous and inferior sagittal sinuses then intra-arterial angiography; it is comparable to MR venography for the diagnosis of cerebral venous thrombosis. Limitations of CT venography include: limited visualization of skull base structures in 3D display, contrast allergy, contrast nephropathy and radiation exposure, which may limit its use in pregnant women, children and patients with renal failure [4, 5].

Magnetic resonance imaging. The combination of MRI showing the thrombosed vessel and MR venography (MRV) demonstrating the no visualization of the same vessel is currently the most sensitive (90%) method to confirm the diagnosis of CVT in the acute, subacute, and chronic phases. Therefore, the combination of an alteration of signal intensity in a dural sinus and a corresponding absence of flow on MRV supports the diagnosis of CVT [2, 4, 14, 53, 54].

MRI pathological signs in patients with CVT include those seen in the venous channels and those seen in the brain parenchyma [14].

The signal intensity of the thrombus on T1- and T2-weighted MR images varies according to the age of the thrombus [5, 6, 14]. In the acute stage (0–5 days), flow void is absent and the occluded vessel appears isointense with brain parenchyma on T1-weighted and hypointense on T2, due to the appearance of deoxyhemoglobin in red cells within the thrombus. In the sub-acute phase (6–15 days), the absence of flow void persists, but, the thrombus appears hyperintense in both T1- and T2-weight images due to the accumulation of methemoglobin in the venous thrombus. These intermediate pattern (increased signal on T1- and T2-weighted images) is characteristic for CVT. In chronic stages, recanalization of the previously occluded vessel results in reappearance of the flow void; the thrombus can be heterogeneous with variable intensity on T2-weighted and isointense on T1-weighted images, related with the presence of the deoxygenated hemoglobin and methemoglobin products. At 6 months, more than 2/3 of cases still show some heterogeneous localized signal abnormalities which can persist for years [1, 4, 53, 54].

MRI shows a variety of focal parenchymal changes in up to 40% of patients; they include: edema, brain swelling and/or hemorrhage. The presence of edema is suggested by increased signal on T2-weighted images and isointense or hypointense signal on T1- weighted images. An increased signal in both T1- and T2-weighted images is indicative for parenchymal hemorrhage and can be seen in about 30% of the CVT cases [1, 6, 14, 53].

The SSS thrombosis is typically associated with flame-shaped, irregular areas of lobar hemorrhage in the parasagittal frontal and parietal lobes; temporal or occipital lobe parenchymal changes correspond to lateral (transverse and sigmoid) sinus thrombosis; deep parenchymal abnormalities, including thalamic hemorrhage, edema, or intraventricular hemorrhage are suggestive for thrombosis of the vein of Galen or SS [6, 14].

After contrast (gadolinium) administration, marked contrast enhancement and flow voids may be observed within the thrombosed sinuses, slow flow in dural and intrathrombus collateral channels or recanalization [2, 5].

Diffusion-weighted imaging (DWI) allows the direct visualization of the clot as a high signal intensity within the affected vein or dural sinus. However, the major interest of DWI is to

show, in the venous infarcts, a diffusion pattern significantly different from that in arterial infarcts. The DWI most common pattern of brain lesions in CVT is a heterogeneous signal intensity with normal or increased apparent diffusion coefficient (ADC) corresponding to vasogenic edema, and thus, markedly different from that of arterial infarcts [1, 5, 19].

*Echo-planar T2 susceptibility weighted imaging (T2*SW) sequences* are useful in the diagnosis of isolated cortical venous thrombosis and during the very early days of acute CVT when T1 and T2 are less sensitive. This diagnosis technique identifies the intraluminal thrombus as a hypointense area [2, 5, 19].

Hydrogen 1 magnetic resonance spectroscopy (MRS) shows a normal N-acetyl aspartate (NNA) peak and a small lactate peak, suggesting that the functionally impaired neurons are still viable in CVT; these findings also, emphasize the difference between venous and arterial infarcts [1].

The MRI advantages in CVT diagnosis include sensitivity to blood flow, ability to visualize the thrombus itself and noninvasiveness. However, its use is limited in some situations, such as comatose patients or in dubious cases (e.g. isolated cortical vein thrombosis), when intra-arterial angiography is necessary to confirm the diagnosis [1, 5].

Magnetic resonance venography (MRV) has become the imaging modality most widely used in CVT diagnosis, being easily repeatable and noninvasive [1, 3, 20]. Several methods can assess venous or dural sinus flow: two-dimensional time-of-flight (2D-TOF), three dimensional time-of-flight (3DTOF) and phase contrast; contrast enhancement MR venography with elliptic centric ordering is a newer technique which allows superior assessment of smaller venous channels [1, 5, 20]. The 2D-TOF technique is the most commonly used method for the diagnosis of CVT, showing abnormalities in the normal flow signals, no opacification of sinuses and collateral venous channels; the absence of flow signal indicates a complete intraluminal thrombosis [1, 14, 20]. The indirect signs of cerebral venous disease include delayed emptying, collateral venous pathways, venous dilation and tortuous cortical collateral veins (corkscrew veins) [3]. Contrast-enhanced MRV is also useful in distinguishing anatomic variants such as a hypoplasic sinus from CVT. Nevertheless, MRV has a limited role in diagnosing partial thrombosis, cortical vein and cavernous sinus thrombosis; also it has limited utility in patients with renal disease (risk of nephrogenic systemic fibrosis) [1, 3, 4]. In order to assess the recanalization of the occluded cortical vein/sinuses it is recommended to perform a follow-up CT or MR venography at 3–6 months after diagnosis (IIa/ C) [1, 14].

Cerebral angiography and direct cerebral venography are invasive diagnostic techniques, being reserved for rare situations when the clinical suspicion of CVT is high, but MR or CT venography results are inconclusive or if an endovascular procedure is planned. For example, it may be useful in cases of isolated cortical vein thrombosis or when is necessary to exclude a dural arteriovenous fistula or distal aneurysm [4, 5, 14].

Cerebral angiography. The partial or complete lack of opacification of veins or sinuses is the best angiographic evidence of CVT. Other signs present and suggestive for venous occlusive disease are: venous congestion with dilated cortical, scalp, or facial veins, dilatation of collateral venous channels ("corkscrew" veins) and reversal of venous flow [1, 14, 20]. CVT is easy to recognize on angiography when it affects the posterior or whole SSS, both LSs or the

deep venous system, but it can be confused with hypoplasia when the anterior third of the SSS or the left LS are occluded. In such cases, in order to establish the diagnosis of CVT is necessary to find additional evidences: involvement of another sinus or delayed emptying and dilated collateral veins in occlusion of the anterior part of the SSS and absence of filling of the whole sinus or its sigmoid portion in LS thrombosis. The presence of collateral veins pathways usually indicates SSS thrombosis and is found in about 50% of CVT cases [1]. The limitations of this technique include the facts that it does not show the thrombus itself, has a traumatic effect, is associated with the usual risk of complications during surgery, involves a certain amount of radiation, requires a higher technical competency and may only be performed in a qualified hospital. Also, certain individuals are allergic to the iodine contrast material [1, 53].

Direct cerebral venography is usually performed during endovascular therapeutic procedures; it allows the visualization of the intraluminal thrombus either as a filling defect within the lumen (no occlusive thrombosis) or as complete no filling (occlusive thrombosis). Complete thrombosis may also present a "cupping appearance" within the sinus [14].

10. Management

The treatment of cerebral venous disease focuses on a combination of symptomatic, etiologic and antithrombotic medications on a case-by-case basis. The therapeutic measures used in clinical practice are based on anticoagulation, control of seizures, and management of increased intracranial pressure. Any underlying cause or risk factors should be managed appropriately. Patients with CVT should be admitted in a stroke unit and the treatment, started as early as possible [1, 9, 15].

10.1. Acute phase therapy

10.1.1. Antithrombotic treatment

There is now ample evidence that heparin is safe even when CT or MRI demonstrate a hemorrhagic lesion. The aims of antithrombotic treatment in CVT are to recanalize the occluded sinus or vein, to combat the propagation of the thrombus, and to treat the underlying prothrombotic state-in order to prevent venous thrombosis in other parts of the body-and to prevent the recurrence of CVT [1, 5, 19].

A meta-analysis shows that, with heparin, there is an absolute risk reduction in mortality of 14% and in death or dependency of 15%, with relative risk reduction of 70 and 56%, respectively [1, 55]. In ISCVT cohort, more than 80% of the patients were treated with anticoagulants, indicating a consensus on the efficacy and safety of anticoagulation in the acute phase of CVT [16]. Despite the fact that new or increased hemorrhages do indeed occur after heparin treatment for cerebral venous disease, their frequency is low. The risk for intracranial and systemic hemorrhages is as well, low and such hemorrhages did not influence the outcome. Anticoagulant therapy is also safe in children [5].

Thus, current guidelines recommend immediate treating patients with acute CVT with heparin, as a bridge to oral anticoagulation with a vitamin K antagonist. Heparin is either subcutaneously administered low–molecular weight heparin (LMWH) (180 anti-factor Xa U/kg/24 h administrated by two subcutaneous injections daily) or dose adjusted intravenous (IV) unfractionated heparin (UFH), titrated to an activated partial thromboplastin time (APTT) of twice the upper limit of normal. This recommendation also applies to patients with an intracerebral hemorrhage at baseline (Ia/A). LMWH should be preferred in uncomplicated CVST cases considering that LMWHs have a longer-life, more predictable clinical response and less interaction with platelets compared with standard heparin. However, this recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or in cases when fast reversal of the anticoagulant effect is necessary (e.g. patients who have to undergo neurosurgical intervention) [2, 15, 19, 51].

Although the majority of patients recover with anticoagulant therapy, a subset of patients with CVT have poor outcomes despite anticoagulation. Local IV thrombolysis (catheter-directed fibrinolysis), with or without mechanical thrombectomy are invasive therapeutic procedures which have been considered only in acute patients with CVT and large hemorrhagic infarcts, without impending herniation, who deteriorate despite adequate anticoagulation and symptomatic treatment (III/B) [1, 2, 19]. These procedures may be performed in selected expertise centers in interventional radiology [5, 19].

Thrombolysis can be done through peripheral veins or through selective cannulation. In direct catheter thrombolysis, a microcatheter and microguide wire are sent to the occluded dural sinus through a guiding catheter from the jugular bulb. Mechanical manipulation of the thrombus with the guidewire can potentially reduce the amount of fibrinolytic agent required for sinus recanalization [14]. *Balloon-assisted thrombolysis* may be more efficient because the inflated balloon may reduce washout of fibrinolytic agent, thus lessening the dose used and the risk of its eventual side effects. The balloon may be used to perform partial thrombectomy before pharmacological thrombolysis [14]. It is important to emphasize that, currently there is no evidence to support the routine use of thrombolysis, considering that both local urokinase and r-TPA carry an undeniable risk of hemorrhagic complication and may require continuous infusion [1, 5, 15, 56, 57].

Catheter thrombectomy. Currently there is no endovascular device specifically designed to treat CVT [57]. *The AngioJet system*, which was designed for use as a thromboaspiration catheter in cardiovascular indications, is not sufficiently supple to be easily passed through the tortuous intracranial sinuses. Although, the walls of the sinuses are thick enough to allow catheterization, the AngioJet device should be removed after partial recanalization of the thrombosis and follow-up with additional local thrombolysis [14, 58, 59]. *The Merci* retrieval is a snare-type device that removes thrombus in a corkscrew fashion using a series of coiled wires. This device may be used in combination with local thrombolysis in order to avoid damaging the wall or trabeculae of the dural sinus [58, 60]. *The Penumbra System* is a new-generation neuroembolectomy device helpful mainly in arterial thrombus extraction [14, 61, 62]. It uses a separator wire under vacuum suction in order to destroy the clot. In CVT patients, it may be performed in combination with continuous infusion of local urokinase [58, 63] or with an

adjuvant balloon angioplasty (without local thrombolysis) [58, 64]. The risks associated with the Penumbra System use in CVT treatment are similar to those seen with the Merci and AngioJet systems [14].

10.1.2. Symptomatic treatment

Early initiation of antiepileptic drugs is recommended in patients with acute CVT presenting a single seizure with or without supratentorial lesions, in order to prevent early recurrent seizures. The routine use of antiepileptics in CVT patients without seizures is not recommended (III/C) [14, 19, 51]. However, antiepileptic drugs could be considered as an option for patients with either acute seizures, supratentorial lesions or motor deficits. Any of the major antiepileptic agents can be used, however valproate is preferred to phenytoin and carbamazepine because it causes less interference with oral anticoagulants. If it is not tolerated other antiepileptic (lamotrigine, levetiracetam) can be used [1, 5, 51].

10.1.3. Treatment of intracranial hypertension

Brain swelling is observed in about 50% of all CVT on CT scan, however minor brain edema needs no treatment than anticoagulants, considering that heparin improves the venous outflow and, thus reduce intracranial pressure in most patients. Antiedema treatment is required in only 20% of patients [15, 19].

General recommendations in the acute stage of CVT include: elevating the head of the bed, osmotic diuretics (e.g., mannitol), intensive care unit admission with sedation, hyperventilation to a target $PaCO_2$ of 30–35 mmHg and ICP monitoring [5]. In cases associated with *severe headache* with or without papilledema, the symptoms can be ameliorate with analgesics or through a therapeutic lumbar puncture (LP) (before starting heparin) when not contraindicated by parenchymal lesions. Administration of a diuretic as acetazolamide or furosemide is a therapeutic option [1, 5]. In patients with isolated intracranial hypertension *and threatened vision,* a LP should be performed with sufficient CSF removal to obtain a normal closing pressure. Acetazolamide may be an option in patients with papilledema [15, 19]. If severe headaches persist or vision continues to deteriorate despite the correct treatment, there should be considered shunting procedures (lumboperitoneal, ventriculoperitoneal shunts or optic nerve fenestration) [5, 15]. If *consciousness becomes abnormal,* mannitol is usually added; however, shunting or barbiturate-induced coma might be necessary in more severe cases [1].

In patients with CVT and large hemorrhagic infarcts, with imminent unilateral hemispheric herniation, decompressive surgery, such as hemicraniectomy or hematoma evacuation can be life-saving, with improved clinical outcomes (III/B) [2, 4, 19].

10.1.4. Etiologic treatment

In CVT patients with a suspected local or systemic infection the treatment should include administration of the appropriate antibiotics and the surgical drainage of infectious sources. (I/C) [1, 14].

10.2. Management after the acute phase

In order to prevent recurrent CVT and other venous thrombosis, *the anticoagulation* should be continued after the acute phase of CVT [19]. There are no controlled data on the required duration of oral anticoagulation. Thus, the guidelines recommend anticoagulation with an oral vitamin K antagonist and a target INR between 2 and 3 for 3–6 months in patients with provoked CVT (septic thrombosis) and 6–12 months in patients with idiopathic CVT and in those with "mild" thrombophilia. Patients with recurrent CVT, deep vein thrombosis, or pulmonary embolism complicating CVT or initial CVT in the setting of "severe" thrombophilia (homozygosity for prothrombin gene mutation 20,210 or factor V Leiden; combined thrombophilias; deficiencies of antithrombin, protein C, or protein S; or antiphospholipid antibodies), should be considered for indefinite duration anticoagulation (III/B) [2, 4, 17, 19].

Prevention of seizures. Seizures occur in 11% of the patients, more so if the patient had seizures in the acute phase or had a hemorrhagic parenchymal lesion. Such patients can be placed on antiepileptic drugs to prevent seizure recurrence [19]. Then, anticonvulsants can be progressively discontinued 1 year after CVT in patients with normal EEG and no recurrent seizures [1].

Acetazolamide might be helpful in patients with milder pressure elevation found during follow-up, but if *visual acuity decreases and the headaches* persist despite to these measures, CSF shunting procedures should be considered [9, 19].

It is important to know that steroids are not useful and should be avoided in patients with cerebral venous disease, unless they are needed to treat an underlying disease. (IIa/B). Current guidelines recommend using steroids in patients with acute CVT and Behcet's disease or other inflammatory diseases (e.g. SLE) to improve outcome [2, 19, 51].

Contraception and future pregnancies. Anticoagulation for CVT during pregnancy and early in the puerperium consists of full-dose LMWH in the majority of women, considering that, in contrast to UFH, LMWH is not associated with teratogenicity or a higher risk of fetal bleeding (IIa/C) [5, 14, 17]. If there is needed, a regional anesthesia should be performed 10–12 h after the last prophylactic dose of LMWH and 24 h after the last therapeutic dose of LMWH. If there are used prophylactic UFH doses (5000 units twice daily), regional anesthesia can be safely placed, but in cases which require higher doses (10,000 units twice daily or greater), an individual assessment is usually necessary [65–67].

The anticoagulant therapy with LMWH or vitamin K antagonist with a target INR of 2.0–3.0 should be continued for ≥6 weeks postpartum (for a total minimum duration of therapy of 6 months) (I/C). Women who have suffered CVT in the setting of hormonal contraceptive therapy should use other contraceptive methods apart from oral or parenteral agents. Emergency contraception and hormonal replacement therapy are also contraindicated. Women with a history of CVT while receiving OC, during pregnancy, or during the postpartum period have an increased risk of recurrence during subsequent pregnancies. Thus, prophylactic anticoagulation with LMWH during future pregnancies and the postpartum period is reasonable for women with previous history of CVT (IIa/C) [4, 5, 17]. It is essential to know that CVT and pregnancy and puerperium-related CVT are not contraindications to future pregnancy.

Nevertheless, further investigations regarding the underlying cause and a consultation with a hematologist or maternal fetal medicine specialist are indicated. Women of fertile age with past CVT should be advised not to become pregnant while taking an oral anticoagulant because of its teratogenic effects [5, 17, 19].

11. Prognosis

The clinical course of CVT is unpredictable and the individual prognosis is difficult to predict, but the overall vital and functional prognosis of this condition is far better than that of arterial stroke, with about two-thirds of patients recovering without sequelae [5, 17, 19]. In a meta-analysis of 1180 patients with CVT, the mean 30-day mortality rate was 5.6%, that of death at the end of follow-up was 9.4% and that of complete recovery was 88% [4, 5, 68]. Approximately 4% of patients with CVT die within 30 days from symptom onset [14, 16]. The primary cause of death in acute CVT is transtentorial herniation secondary to a large hemorrhagic lesions, followed by herniation due to multiple lesions or to diffuse brain edema. Other causes of early death include status epilepticus, medical complications, and pulmonary embolism [4, 14, 19]. A high mortality rate within the first months is associated with depressed consciousness, altered mental status, thrombosis of the deep venous system, right hemisphere hemorrhage and posterior fossa lesions [9, 14, 19].

According to ISCVT results, about 1/4 of CVT patients deteriorate after their initial presentation, developing seizures, coma, worsening of or a new focal deficit, increased headaches or vision loss. Among these patients, about 1/3 will have new parenchymal lesions if neuroimaging is repeated [2, 9, 16].

Predictors of poor outcome derived from the ISCVT cohort are: central nervous system infections, malignancy, deep cerebral venous system thrombosis, hemorrhage at admission CT/MRI, GCS score on admission less than 9, poor mental status, age older than 37 years and male gender [16, 51]. Death after the acute phase is predominantly due to the underlying conditions, in particular malignancies [2, 19]. Based on this results, the ISCVT study group developed a risk score for poor outcomes which range from 0 (lowest risk) to 9 (highest risk) with a cut-off ≥3 points indicating a higher risk of death or dependency at 6 months. Two points were assigned for the presence of malignancy, coma, or thrombosis of the deep venous system and 1 point for male sex, presence of decreased level of consciousness, or intracerebral hemorrhage (ICH) [14, 69].

If the patient with CVT survives, the prognosis for recovery is much better (about 80%) than for patients with arterial stroke. A minority (10%) of patients are found to have permanent neurological deficits by 12 months of follow-up. About 44% of the CVT patients have some degree of handicap or significant cognitive impairment after 1–4 years [1, 4, 16]. Sequelae of CVT include cognitive and motor impairments, seizures, headaches, visual loss and an increased risk for further venous thrombotic events. Also, approximately one half of survivors feel depressed, anxious or experience minor cognitive or language deficits [4, 5]. Residual epilepsy has been reported in 10% of the patients. Other thrombotic events such as

deep vein thrombosis and pulmonary embolism occur in about 5% of patients and mostly within the first year [4, 16]. The risk of VTE is increased in patients with severe thrombophilia. Recurrence of CVT is rare (2.8%) and tends to occur within the first year of evolution, especially after anticoagulation discontinuation [4, 17]. Severe visual loss due to intracranial hypertension is infrequent [5]. It was suggested that LS thrombosis can later induce arteriovenous malformations affecting the transverse sinus [1].

The CVT associated with postpartum state has a survival rate of 90% [1, 36]. It is considered that the absence of sex-specific risk factors is a strong and independent predictor of poor outcome in women with CVT [17]. The large majority (88%) of the pregnancies ends in normal births, the remaining being prematurely terminated by voluntary or spontaneous abortion; nevertheless, the rate of spontaneous abortion was found to be higher in CVT female patients [5]. In neonates, the functional outcome is usually normal if asphyxia is not associated [1].

It has been estimated that recanalization of the thrombosed cerebral vein and sinus occurs in 40–90% of CVT patients, mostly within the first 4 months, being limited thereafter [4, 5, 9]. The deep venous system and the cavernous sinus have a higher rate of recanalization; the lowest rates were observed in LS thrombosis. Recanalization of the occluded sinus is not related to outcome after CVT [5, 9, 14].

Author details

Dragoș Cătălin Jianu[1,2]*, Silviana Nina Jianu[3], Georgiana Munteanu[2], Flavius Traian Dan[2] and Claudia Bârsan[2]

*Address all correspondence to: dcjianu@yahoo.com

1 Department of Neurology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

2 Department of Neurology, Clinical Emergency County Hospital, Timisoara, Romania

3 Department of Ophthalmology, Military Emergency Hospital, Timisoara, Romania

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Chapter 4

Intravenous Thrombolysis for Acute Ischemic Stroke in a High Complex Regional Hospital

Álvaro Soto Venegas

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79544

Abstract

Background: Intravenous thrombolysis (IVT) with alteplase (tissue plasminogen activator) is the standard pharmacological treatment in acute ischemic stroke (AIS), reducing disability in patients.

Aim: To report the results of a thrombolysis protocol taken during 6 years in a regional public hospital at Temuco, Chile.

Material and methods: Data from 231 consecutive patients aged 67.1 ± 13.1 years (58.9% men) who were treated with IVT, from May 2012 until April 2018, were analyzed.

Results: The median door-to-needle time was 71 min (interquartile range = 53–102). The median National Institute of Health Stroke Scale (NIHSS) scores on admission and at discharge were 13 and 4 points, respectively. At discharge, 27% of hospitalized patients had a favorable outcome, defined as having 0 to 1 points in the modified Rankin scale. Symptomatic intracerebral hemorrhage and mortality rates were 5.7 and 13.1%, respectively. The thrombolysis rate rose from 0.7% in 2012 to 5.5% in 2018.

Conclusions: The implementation of 24/7 neurology shifts in the Emergency Department allowed us to increase the amount and quality of IVT in our hospital, as measured by the rate of thrombolysis and by process indicators such as door-to-needle time.

Keywords: fibrinolytic therapy, stroke, time-to-treatment, thrombolytic therapy, tissue plasminogen activator, alteplase

1. Introduction

Stroke is the leading cause of disability and the second cause of death worldwide [1]. More than two-thirds of the global burden of stroke occurs in developing countries, where

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the average age of patients is 15 years younger than in developed countries [2]. In the period 2000–2008, the total incidence rates in low- and middle-income countries exceeded the level of stroke incidence in high-income countries by 20% for the first time [3]. Stroke has become one of the main health problems in many countries of Latin America and the Caribbean [4].

In Chile, cerebrovascular diseases (CBVD) are the leading cause of death, with a rate of 50.6 deaths per 100,000 inhabitants in 2011. In addition, they are the first specific cause of disability-adjusted life years (DALY) in older than 74 years and the fifth between 60 and 74 years [5]. Acute ischemic stroke (AIS) is the most frequent cause of CBVD in Chile and represents approximately 65% of all cerebrovascular events [6]. CBVD is the leading cause of death in Chile and accounted for 9% of all deaths in 2010 [6]. About 8888 people died in Chile in 2010 due to CBVD, and 26,072 were hospitalized with the diagnosis of CBVD in Chile in 2009.

The PISCIS population study conducted in Iquique during 2000–2002 gave the following information: the total incidence adjusted for age for a first stroke was 140.1 per 100,000 inhabitants. The incidence rates per 100,000 inhabitants according to the type of stroke were: 87.3 for cerebral infarction, 27.6 for intracerebral hemorrhage, and 6.2 for subarachnoid hemorrhage. About 93% of the new brain strokes occur in people older than 45 years: the average age was 66.5 years and 56% of them were men. Mortality at 1 month after a first cerebral infarction was 19% and mortality at 6 months was 28%. About 18% of people are left with a moderate or severe dependence at 6 months after a cerebral infarction [7]. The prevalence of CBVD, according to the National Health Survey (NHS) in 2016–2017 is 2.6% in the general population, and rises to 8.2% in ≥65 years [8]. A slight increase was observed when comparing the prevalence estimated in the 2009–2010 NHS, with 2.2 and 8.1%, respectively [9].

2. Stroke in the Araucanía region

The incidence rate of CBVD, calculated as a diagnosis of hospital discharge, in the period 2001–2010, in the Araucanía Sur Health Service, was 961.3 per 100,000 inhabitants/year [10].

According to the data from the 2017 census, the largest number of indigenous people in Chile is concentrated in the Araucanía Region. About 34.0% of respondents mentioned belong to an indigenous or native people, which is significantly higher than 12.8% at national level [11]. Furthermore, according to the 2009–2010 ENS, the Araucanía region has the highest prevalence of high systolic blood pressure compared to the other regions. On the other hand, the Ninth region (Araucanía), along with the Fifth, Seventh, and Eighth, presents double the mortality by stroke compared with the rest of the regions of Chile. Most of the increased risk would be given by the prevalence of poverty, diabetes, sedentary lifestyle, and overweight [12].

AIS is the most frequent reason for neurological consultation in the adult emergency service (AES) of the Dr. Hernán Henríquez Aravena Hospital (HHHA) in Temuco-Chile, accounting for 30.7% of the attentions performed by the neurologist [13]. The HHHA is located in the heart of the city of Temuco (310,020 inhabitants), capital of the Ninth region of Araucanía, about 670 km south of Santiago de Chile, has 730 beds, and is the only hospital of high complexity of the Araucanía region, and serves a beneficiary population of approximately 800,000 inhabitants. The HHHA neurology unit does not have its own service and depends on the internal medicine service. Our hospital lacks a stroke unit [14].

3. Intravenous thrombolysis in acute ischemic stroke

Intravenous thrombolysis (IVT) with alteplase (tissue plasminogen activator), administered up to 4.5 h from the onset of symptoms, is the reference pharmacological treatment in AIS, reducing the likelihood of dependence patients [15, 16]. The effectiveness of IVT is highly time dependent. Around one in three patients treated with alteplase within 3 h of symptom onset, and one in six treated within 4.5 h, achieves significant benefit [17, 18]. Since 1996, IVT has been the standard management for acute AIS in developed countries. However, IVT has been used in the treatment of AIS on small scale in Latin America and the Caribbean but not on a national basis. The time from stroke onset to hospital arrival is crucial for thrombolysis to be effective, and studies in Lima-Peru, Montevideo-Uruguay, and Joinville-Brazil reported delays in hospital admission. Cost is also an issue, especially for public-health systems, which hampers planning of thrombolysis for a subgroup of patients with ischemic stroke in Latin America [4]. Although the implementation of IVT was rapid in the Chilean private health system [19] since 1997, it was not until 2011 that the first experience of an IVT protocol was reported in a public hospital in the country [20]. Currently, the rate of thrombolysis in large private clinics in Santiago-Chile is 12%, but in public hospitals, it is 6% [5]. This gap seems significant because 80% of the population in Chile is served in the public health system.

4. Intravenous thrombolysis in the HHHA

Since May 2012, IVT has been performed in the HHHA, which has face-to-face neurologists 24/7 in the emergency department since July 2013 [14]. The following is a series of consecutive patients who received IVT, between May 2012 and April 2018. The IVT protocol was based on the NINDS (1995) and ECASS III (2008) studies, that is, thrombolysis within 3 h, and between 3 and 4.5 h, respectively [15, 16]. In addition, modifications were made considering the most recent medical literature [21] and local experience, particularly in relation to age (over 80 years) and the relevance of some relative contraindications [22, 23]. **Table 1** shows the inclusion, exclusion, and precaution criteria of the IVT protocol.

Inclusion criteria

- Neurological symptoms for a period less than 4.5 h, with defined start time
- Neurological deficit measurable by the NIHSS scale[a]
- Computed tomography of the brain without signs of intracranial hemorrhage
- Signed informed consent

Exclusion criteria

- Ischemic stroke within the last 3 months
- Traumatic brain injury or central nervous system surgery in the last 3 months
- Acute myocardial infarction within the last 21 days
- Major surgery in the last 14 days or organ biopsy
- History of intracranial hemorrhage
- History of coagulopathy (hemophilia, von Willebrand)
- Gastrointestinal or urinary tract bleeding in the last 21 days
- Use of oral anticoagulants with INR[b] > 1.7 or new anticoagulants in the last 48 h
- Seizure at the onset of symptoms (except diffusion confirms infarction)
- Noncompressible arterial puncture in the last 7 days
- Lumbar puncture in the last 7 days
- Pregnancy or delivery during the last month
- Known antecedents of neoplasia with risk of bleeding
- Systolic BP[c] > 185 mmHg and/or diastolic BP > 110 mmHg refractory to intravenous medication
- Evidence of systemic bleeding
- Suspicion of septic embolism or infectious endocarditis
- Rapidly improving symptoms
- NIHSS score < 4
- Glucose concentration < 50 or > 400 mg/dl
- Prolongation of partial-thromboplastin time > 40%
- Platelet count < 100,000/mm^3
- Hematocrit < 25%
- Prothrombin time > 15 s
- Hemorrhage or early hemorrhagic transformation
- Extensive constituted infarction

Caution criteria

- Age over 80 years
- Severe neurological deficit (NIHSS score > 22)
- Early signs of extensive infarction (ASPECTS[d] score < 7)

[a]National Institute of Health Stroke scale
[b]International Normalized Ratio
[c]Blood pressure
[d]Alberta Stroke Program Early CT Scan score.

Table 1. Criteria for inclusion, exclusion, and precaution for intravenous thrombolysis [14].

5. Results

In total, 231 patients were treated in the period May 2012–April 2018. The average age of the patients was 67.7 years (SD = 12.6), with a median of 69 years and about 56.6% of the patients were male (N = 136). The clinical characteristics of the thrombolysed patients are shown in **Table 2**.

Regarding the time parameters, the median of the start-to-door time was 105 min interquartile range (IQR): 70.5–156.5. The median door-to-needle time (DNT) was 71 min (IQR: 53–102). The median onset-to-needle time was 185 min (IQR: 136–235). The median of the NIHSS scale at admission was 13 points (IQR: 8–18). In 79 patients (34.2%), the DNT was ≤60 min. Likewise, there was a constant decrease in DNT and a progressive increase in the percentage of patients treated in less than 60 min from their admission to emergency (**Table 3**). In 110 patients (47.6%), thrombolysis was started within 3 h of evolution of the AIS.

For the first 106 patients treated until April 2016, the clinical classification of the AIS, according to the Oxfordshire criteria, was: 44.3% of TACI (total anterior) infarcts stand out, 35.9% of PACI (partial anterior) infarcts, 15.1% of POCI (posterior) infarcts, and 4.7% of LACI (lacunar) infarcts. The etiologies of the AIS, according to the TOAST classification, are the following: 23.4% of atherothrombotic cause, 35.9% of cardioembolic cause, 5.7% by arterial dissection, 5.7% of lacunar infarctions, and 29.3% of indeterminate cause. Regarding the functional result of the intervention measured with the modified Rankin Scale (mRS) at discharge (**Figure 1**), it is noteworthy that 27.3% of the patients were discharged without disability (mRS = 0–1). For

Characteristics	**Patients**
	N = 231
Age (average ± SD[a])	67.1 ± 13.1
≥ 65 years (%)	143 (61.9%)
Male gender (%)	136 (58.9)
Mapuche ethnicity (%)	20 (8.7)
Discharge mRS 0–1[b] (%)	42 (26.1%)
Discharge mRS 0–3[b] (%)	76 (47.2%)
Start-to-door time (median, IQR[c])	105 (70.5–156.5)
Door-to-needle time (median, IQR[c])	71 (53–102)
Start-to-needle time (median, IQR[c])	185 (136–235)
Door-to-needle time ≤ 60 min (%)	79 (34.2)
Start-to-needle time ≤ 180 min (%)	110 (47.6%)

[a]Standard deviation.
[b]modified Rankin Scale.
[c]Interquartile range.

Table 2. Clinical characteristics of thrombolysed patients.

Year	N	Rate IVT[a] (%)	Median SDT[b] (minutes)	Median DNT[c] (minutes)	Median SNT[d] (minutes)	% DNT ≤ 60 min
2012	5	0.7	24	85	154	0
2013	11	1.2	93	111	200	36.4
2014	24	2	79	97	180.5	8.3
2015	44	3.6	91	71	182.5	43.2
2016	65	5.4	132.5	71.5	207	27.7
2017	58	4.8	104	57	156.5	44.8
2018	24	5.5	153	56	163	41.7
Total	231	3.2	105	71	185	34.2

[a]Intravenous thrombolysis.
[b]Start-to-door time.
[c]Door-to-needle time.
[d]Start-to-needle time.

Table 3. Evolution of the thrombolysis rate, time parameters, and percentage of patients who received thrombolysis in ≤60 min.

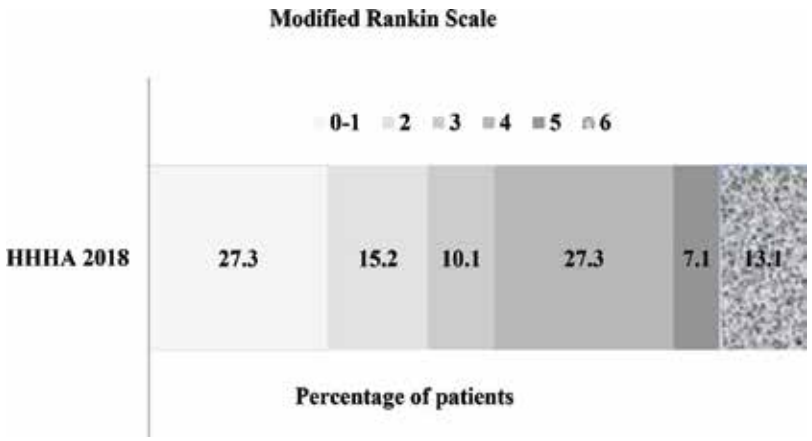

Figure 1. Evaluation of disability at discharge in patients with acute ischemic stroke who received intravenous thrombolysis [14].

this subgroup of patients (N = 106), the median of the NIHSS scale at discharge was 5 points (IQR 1–14). The mortality rate was 13.1%. In relation to the causes of death, in seven patients, it was due to the AIS. Two cases were due to symptomatic hemorrhagic transformation and four patients due to complications not related to the AIS: bronchial cancer, cutaneous focus sepsis, pulmonary focus sepsis, and severe pneumonia. In addition, 13 patients with hemorrhagic transformation (12.3%) were registered, of whom 6 (5.7%) were symptomatic. Four patients

developed an intrahospital AIS, with a 66-year-old man who suffered cerebral infarction after a coronary angiography. On the other hand, IVT plus mechanical thrombectomy was performed in four patients. In this subgroup, a 51-year-old patient died as a result of a malignant infarction of the right middle cerebral artery due to an occlusive carotid dissection [14].

In our hospital 1200, AIS is diagnosed per year approximately. Therefore, the rate of thrombolysis increased from 0.7% in 2012 to 5.5% in 2018. **Table 3** shows the evolution of the number of patients treated per year, the DNT, and the percentage of subjects treated who were thrombolysed within 60 min.

6. Discussion

Intravenous thrombolysis in AIS is feasible to be performed in public hospitals, and particularly in regions of our country. In our series, the median DNT was 71 min. The possible causes for the result of this indicator are: emergency service collapsed, delay in prioritization, delay in the evaluation by neurologist, delay in the taking of neuroimaging, lack of space in the resuscitation box, waiting for the result of exams (INR), etc. In our series, it was not possible to assess the disability of the subjects at 3 months. In this sense, early outcome evaluations have been used, such as the score on the NIHSS scale on the second and seventh day of evolution of the AIS, which have been shown to predict, with adequate accuracy, the functional results at 3 months [24, 25]. In our study, the median of the NIHSS score at discharge was 4 points, with a prethrombolysis score of 13 points (**Figure 2**). The greater severity of the AIS, compared with

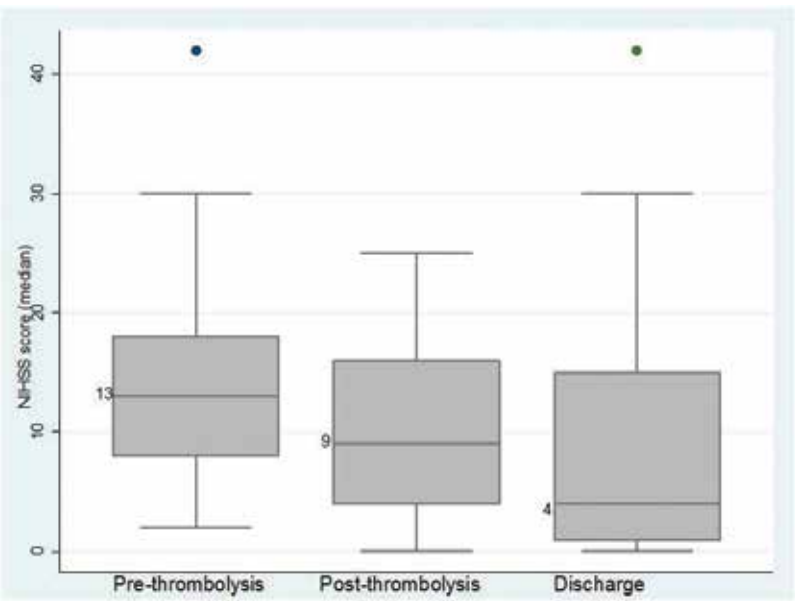

Figure 2. Evolution of the NIHSS score in 231 patients with acute ischemic stroke treated with intravenous thrombolysis.

other series, could be explained by the high percentage of TACI infarcts and cardioembolic AIS. The 5.7% of symptomatic intracerebral hemorrhages (sICH) observed in our series are comparable to that reported in national and foreign studies. For example, a recent meta-analysis of 12 randomized clinical trials of IVT up to 6 h from the onset of symptoms, which included 7012 patients, reported an ICH rate of 7.7%, with a fatal ICH rate during the first 7 days of 3.6%, and a mortality of 8.9% within 7 days, and of 19.1% until the end of the follow-up period [26]. When presenting our results, we must emphasize that the HHHA does not have a specific infrastructure to attend to neurological patients, that is, a stroke unit. These units have demonstrated their cost-effectiveness in decreasing mortality and disability due to stroke [27]. In our reality, not all thrombolysed patients access the intensive care unit and complete 24–48 h of observation in the emergency service, being later hospitalized in the internal medicine service.

The developing world carries the highest burden of stroke mortality and stroke-related disability. The number of stroke patients receiving alteplase (r-tPA) in the developing world is extremely low. Prehospital delay, financial constraints, and lack of infrastructure are main barriers of thrombolysis therapy in developing countries [28]. Stroke thrombolysis is currently used in few developing countries like Brazil, Argentina, Chile, Senegal, Iran, Pakistan, China, Thailand, and India. Most of the centers with the infrastructure to deliver thrombolysis for stroke are predominantly private sector, and only available in urban areas [29].

The rate of thrombolysis that started with 0.7% for the period May-December 2012 rose to 5.5% in the period January-April 2016 (**Table 3**). For this change, we consider that the presence of the neurologist, since July 2013, in the emergency service in the 24/7 modality has been fundamental.

Our thrombolysis rate is comparable with that observed in other Chilean public hospitals, but it is very low compared to national private clinics that have reported a rate greater than 10% [5]. According to our records, 19.1% of patients with AIS consult within 3 h of the start of symptoms, with a median of approximately 10 h, until the consultation. We believe that with educational campaigns aimed at the community, and the socialization of our IVT protocol to the hospitals and health centers of the Araucanía region, we can increase the rate of thrombolysis in the medium term. The thrombolysed patients had a shorter duration of hospitalization (median of 8 days), considering that the average stay of patients who do not receive IVT has been estimated between 14 and 15 days in other public hospitals [30, 31]. Our results, which constitute the largest reported series of IVT in AIS, in Chilean public hospitals, fill us with satisfaction and optimism. They are also an enormous incentive to continue increasing the number of patients treated and continue to improve the quality of care.

7. Future of the acute management of ischemic stroke in the Araucanía region

About 80% of the population in Chile is treated in the public health system. On the other hand, it is expected that the incidence of stroke will increase significantly in our country due to the aging of the population. This is why we see the need to set a reperfusion protocol for acute ischemic stroke in the 24/7 modality that includes intravenous thrombolysis and mechanical

thrombectomy in selected cases. On the other hand, node hospitals in the region are expected to have a scanner in the medium term, which would allow telethrombolysis. We also consider the need to have a stroke unit and/or a neurological intermediate unit in our hospital for the adequate management of patients with acute stroke. In short, we hope that the HHHA will become a comprehensive stroke center.

8. Conclusion

Intravenous thrombolysis in acute ischemic stroke is feasible to be performed in public hospitals, and particularly in regions of our country. The presence of neurologists 24/7 in the Emergency Department has allowed us to increase the quantity and quality of IVT in our hospital, measured by thrombolysis rate and by process indicators such as door-to-needle time.

Acknowledgements

Funded by the University of La Frontera, DIUFRO Project DI15-0081. We thank Gladys Morales Ph.D. for her statistical work.

Conflict of interest

Álvaro Soto has received honoraria and travel grants from Boehringer Ingelheim.

Author details

Álvaro Soto Venegas[1,2,3]*

*Address all correspondence to: alvaro.soto@ufrontera.cl

1 Department of Medical Specialties, Faculty of Medicine, Universidad de La Frontera, Temuco, Chile

2 Unit of Neurology, Dr. Hernán Henríquez Aravena Hospital, Temuco, Chile

3 Center for Research in Cardiovascular and Nutritional Epidemiology (EPICYN), Universidad de La Frontera, Temuco, Chile

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Chapter 5

Complementary Therapy with Traditional Chinese Medicine for Neonatal Hypoxic Ischemic Encephalopathy

Chun-Ting Lee, Yu-Chiang Hung and Wen-Long Hu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76373

Abstract

Hypoxic ischemic encephalopathy (HIE) is one of the most significant causes of morbidity, mortality, and lifelong disability in newborns. The diagnosis of neonatal HIE is based on the dysfunction of neurogenic signs and classification according to the Sarnat staging system, which evaluates conscious level, neuromuscular control, complex reflexes, autonomic function, seizures, electroencephalogram readings, and duration of neurologic sign. There is no standard treatment for neonatal HIE, but it is widely accepted that hypothermia therapy is a safe and effective method for treating neonates with HIE. Traditional Chinese medicine (TCM) has recently been used to treat cases of neonatal HIE, especially herbal medicine prescriptions. Acupuncture is a common method used in TCM and is another promising therapy for neonatal HIE due to its demonstrated effective treatment of the disease in animal models. While there is a lack of direct evidence in clinical practice, we have observed acupuncture to be useful in adult HIE and in animal studies; therefore, we believe a clinical trial designed to evaluate the effectiveness of acupuncture in neonatal HIE treatment is worthwhile. Taken together, TCM is a promising technique that can be integrated into the conventional therapies for neonatal HIE.

Keywords: acupuncture, complementary therapy, herbal medicine, neonatal hypoxic ischemic encephalopathy, traditional Chinese medicine

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1. Introduction

1.1. Definition and epidemiology of neonatal hypoxic ischemic encephalopathy

Hypoxic ischemic encephalopathy (HIE) occurs when the cerebral blood flow is disrupted, causing a subsequent lack of oxygen to the affected brain area. Neonatal HIE is one of the most significant causes of morbidity, mortality and lifelong disability of newborns, which can include visual impairment, learning impairment, epilepsy, mental retardation, blindness, and cerebral palsy (CP) [1–3]. The incidence of HIE is approximately in 2–9/1000 live births and its frequency increases up to 26/1000 newborns in developing countries [1, 3–10]. Nearly 40% of HIE newborns cannot survive the neonatal period and another 30% suffer from long-term neurological disorders [4, 11, 12].

1.2. Cause of neonatal HIE

HIE is caused by a number of reasons, including severe hypoxia, hypotension, or infection during prenatal development; uterine rupture, cord occlusion or prolapse, abruption or placental insufficiency during perinatal development; shock; and respiratory or cardiac arrest during postnatal periods [3, 13].

1.3. Pathophysiology of neonatal HIE

The pathogenesis of HIE can be divided into the following steps after injury (**Figure 1**) [1, 3, 4, 9, 10]:

- **i.** First 60 min: Due to lack of glucose and oxygen delivery to the brain, anaerobic respiration cannot produce sufficient adenosine triphosphate (ATP) and causes failure of ATP-dependent Na^+/K^+-pumps [1, 3, 4, 9, 10]. This phenomenon results in Ca^{2+} and Na^+ influx and cell membrane depolarization [1, 3, 4, 9, 10]. When the membrane depolarizes, the cells release excitatory glutamate [1, 3, 4, 9, 10]. Glutamate can activate N-methyl-D-aspartate (NMDA) and a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, which increases Ca^{2+} influx into cells and causes cell apoptosis [1, 3, 4, 9, 10]. Furthermore, hypoxia inducible factor-1α (HIF-1α) is also upregulated in these conditions, which will then bind to HIF-1β to form HIF-1α/β complex and traffic to nucleus, where it activates downstream genes, such as erythropoietin (*EPO*) and vascular endothelial growth factor (*VEGF*), to rescue this situation after brain injury [9]. Hydrogen sulfide (H_2S) is a novel neuromodulator that is produced by cystathionine β-synthase (CBS) in brain tissue, especially the hippocampus, and can modulate NMDA receptor activity [14]. H_2S plays an important role in ischemic brain damage and the inhibition of H_2S levels could serve as a therapeutic strategy to protect neuron damage in HIE [15].
- **ii.** Between 1 and 48 h: Acute inflammation, oxidative metabolism, and continuation of activated apoptotic cascades take place in this stage of HIE [1, 3, 4, 9, 10]. Because of the Ca^{2+}

accumulation in cells, production of nitric oxide (NO) by neuronal nitric oxide synthase (nNOS) is elevated and generates reactive oxygen species (ROS) caused by mitochondria (mt) injury [1, 3, 4, 9, 10]. Furthermore, lipid peroxidation is induced by intracellular ROS level elevation [1, 3, 4, 9, 10], and *Bcl-2* expression levels are reduced, while *Bax* expression is increased, leading cells to undergo apoptosis [9]. Carbon monoxide (CO) is an endogenous molecule that is generated from the degradation of heme by heme-oxygenase (HO) might serve as an neuroprotective reagent because it can reduce inflammation, anti-apoptosis, and induce vasodilation in HIE rats [16].

iii. Days to months: At this point, chronic inflammation, late cell death, remodeling and repair of the injured brain tissue, and astrogliosis (abnormal increase of astrocytes due to brain damage) occur [1, 3, 4, 9, 10]. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are two important factors that have beneficial effects on brain repair and remodeling in HIE [17–20].

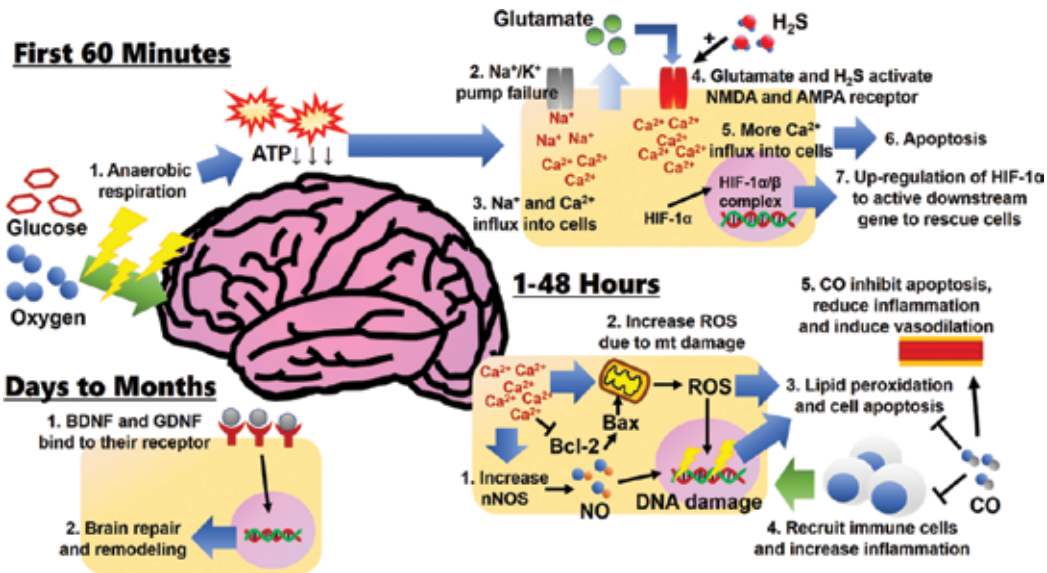


Figure 1. Pathophysiology of neonatal hypoxic ischemic encephalopathy. Generally speaking, the pathophysiology of neonatal HIE can be divided into three major steps. **(1) In the first 60 min:** HIE is caused by reduced glucose and oxygen delivery to the brain, which causes anaerobic respiration. This phenomenon will reduce ATP production from one molecule of glucose (38 ATP → 2 ATP). The reduction of ATP will initially influence the ion content in cells, and then glutamate will accumulate outside the cells and induce cell apoptosis by activating the NMDA and AMPA receptors to transport more Ca^{2+} into cells. However, HIF-1α will be upregulated to modulate downstream genes involved in cell rescue. **(2) In the next 1–48 h:** due to Ca^{2+} accumulation in cells, nNOS and ROS increase, which causes lipid peroxidation and induce cell apoptosis. Furthermore, excess Ca^{2+} will reduce *Bcl-2* expression and increase *Bax* expression, also leading cells to undergo apoptosis. In addition, CO might play an important role in preventing immune cell recruitment, decrease the inflammatory response, inhibit cell apoptosis, and promote vasodilation. **(3) In the days to months following the initial HIE onset:** BDNF and GDNF might be involved in many signaling cascades responsible for brain tissue repair and remodeling. * Partial figure design was provided by Hsiao-Han Hsu.

1.4. Diagnosis and classification of neonatal HIE

Any abnormal heart rate or other signs of neonate distress during delivery and respiratory problems, improper Apgar scores, seizures, unconsciousness and so on after birth are warning sings to suspect neonatal HIE. There is no currently available bedside test for accurate diagnosis of neonatal HIE [1]. The diagnosis of HIE is based on the signs of neurogenic dysfunction such as abnormality of muscle power and tone, reduced consciousness and respiration, functional disruption of the cranial nerve, and seizures [1, 21]. Metabolic acidosis and low Apgar scores are associated with neuronal dysfunction; moreover, metabolic acidosis is significantly related to HI injury [1, 21]. Furthermore, the image pattern of magnetic resonance imaging (MRI) may provide further evidence for HIE diagnosis [1]. Classification of neonatal HIE follows the Sarnat staging system, which is divided into three categories—stage I (mild), stage II (moderate), and stage III (severe)—that are used to evaluate the following parameters: level of consciousness, neuromuscular control, complex reflexes, autonomic function, seizures, electroencephalogram readings, and duration [1, 22].

1.5. Treatment of neonatal HIE

1.5.1. Systemic support

The basic care of neonatal HIE is systemic support, which is very important to maintain the cerebral blood flow that ensures glucose and oxygen supply to the brain to prevent further injury [1]. Neonates with HIE produce less carbon dioxide (CO_2) due to changes in energy metabolism and need less ventilator support to maintain suitable levels of CO_2 [1, 23]. Insufficient CO_2 (hypocapnia) is related to high mortality and poor development of neuron function [1, 23, 24]. In addition, too much oxygen (hyperoxia) is also hazardous in neonates with HIE because it can enhance oxidative stress and free radical formation that might increase mortality and poor outcome [1, 24]. Therefore, maintaining suitable CO_2 and O_2 levels at $PaCO_2$ 40–55 mmHg and PaO_2, 50–100 mmHg, respectively, may prevent further brain injury in neonates with HIE [1]. Blood pressure must also be maintained to avoid hypotension in newborn HIE because it could prevent further ischemic brain injury [1]. Unfortunately, there is no evidence of what the ideal mean arterial blood pressure (MAP) is in cases of neonatal HIE [1].

1.5.2. Fluids and nutrition

For the best long-term outcomes, the initial optimal rate of fluid therapy is not established but the most common practice is to start intravenous 10% dextrose solution combined with sodium and add proper electrolytes based on the results of serum electrolytes [1]. It is suggested that carefully managing fluid therapy in neonates with HIE is helpful in preventing brain edema [1, 25]. Research has shown that hypoglycemia is associated with a high Sarnat stage grade and is an important factor for severe brain injury [1, 26, 27]. Under normal physiological conditions, the adult brain uses nearly 100% glucose as an energy source, but in

http://dx.doi.org/10.5772/intechopen.76373

neonate brains, glucose may account for only 70% [1, 28]. Despite neonate brains being able to use other substrates as energy such as lactate or ketones, these alternative substrates may not compensate for the lack of glucose [1, 28]. In other words, monitoring fluid and glucose strictly is very important in preventing brain edema and hypoglycemia in newborns with HIE and might be helpful in reducing further brain damage [1].

1.5.3. Hypothermia

It is widely accepted that hypothermia therapy is a safe and effective way to treat neonatal HIE and could reduce morbidity and mortality [1, 3, 29–31]. Many studies have shown that keeping neonatal HIE subjects 2–3° below the normal brain temperature can prevent further neurological damage; one of the possible mechanisms for this might be associated with reduce carbon biomass related to acetyl moieties such as pyruvate and acetyl-CoA [3, 32–34]. Other possible mechanisms of neuroprotection from HIE symptoms like inactive microglia cells could be the reduction of apoptosis pathways by decreased caspase-3 activity, decreased NMDA receptor activity, preservation of lipoprotein membrane integrity, and decreased inflammatory responses [35–40]. Therapeutic hypothermia is a part of current standard treatments of neonates with moderate to severe HIE [41].

1.5.4. Medication for seizure control

The best medication for seizure control in neonates with HIE is not well standardized [1]. Phenobarbital, a frequently prescribed drug by physicians, can only control seizure attacks in 27% of patients [1]. Two promising anti-seizure drugs, topiramate and levetiracetam, need more clinical trials to prove their efficacy in neonates with HIE [1]. In one animal study and one human pilot clinical trial, topiramate was shown to work synergistically with hypothermia therapy [1, 42]. Levetiracetam is reported to reduce neuron cell apoptosis and decrease excitotoxicity in general, and one animal study showed these effects are also appearing in neonatal HIE rats [1, 43].

2. Traditional Chinese medicine in the treatment of neonatal HIE

2.1. TCM perspective of neonatal HIE

Neonatal HIE can be classified into "tai jing, 胎驚", "tai shian, 胎癇", "jing feng, 驚風", and "huan mi, 昏迷" in TCM. In mild and moderate grades of neonatal HIE, the common TCM diagnostic pattern are "deficiency of qi and blood, 氣血不足" and "qi obstruction and blood stasis, 氣滯血瘀". The best therapeutic principles are "supplementing qi and nourishing blood, 益氣養血" and "promoting qi circulation to remove blood stasis, 行氣化瘀". In severe grade one, the most common diagnostic pattern is "phlegm stasis causing wind, 痰瘀生風" and the therapeutic principle is "tranquilize mind and arresting convulsion, 化痰定驚". To

reach this goal, TCM physicians can use herbal medicine or acupuncture in the treatment of neonatal HIE, which we will discuss in the following section.

2.2. Acupuncture therapy for neonatal HIE

2.2.1. Clinical trial

Currently, there are no suitable clinical trials that have demonstrated that acupuncture can improve the prognosis of neonatal HIE, as acupuncture has only been evaluated in older infants who survived HIE [44]. CP is one of the consequences of HIE that acupuncture might have some beneficial effects in children [45–49]. Clinical evidence showed that acupuncture therapy intervention could improve the quality of life and promote improvements in speech and language impairment, neural function, motor disability, and cognition [45, 46, 50–53]. Although there is no current clinical trial evidence that acupuncture therapy could be used in neonates with HIE, there are many basic research studies have already demonstrated that acupuncture has the potential to be an intervention option for neonatal HIE.

2.2.2. The possible mechanism of acupuncture therapy for neonatal HIE

Because it is widely accepted by patients, physicians and scientists that acupuncture therapy can be used to improve many brain-related diseases such as stroke and Alzheimer disease [54, 55], many researchers are devoted to investigating the possibility of treating neonates with HIE with acupuncture therapy (**Table 1**).

In 2010, Liu et al. [56] showed that electro-acupuncture (EA) could protect against brain damage caused by HIE by reducing hydrogen sulfide (H_2S) generation in neonatal rats. In this study, they treated acupoints Dazhui (DV14, 大椎) and Baihui (DV20, 百會) using needles 0.25 mm in diameter and 10 mm long and an electrical wave frequency 2/100 Hz at an intensity of 3 mA for 30 min/day with 14 continuous days starting the second day after the neonatal HIE rat model was established [56]. The results showed that EA could increase cerebral blood flow and motor function when compared to the no treatment group [56]. They also measured the expression of CBS, an enzyme that can produce H_2S in brain tissue and is elevated in HIE, in the EA-treated group and found reduced expression compared to the untreated control [56]. In 2011, the same therapeutic protocol was also associated with the NO/nNOS system; EA could reduce NO levels and nNOS expression of the cortex compared with the no treatment group [57]. In addition, the expression of nNOS might be related to the nuclear factor-κB (NF-κB) pathway that EA could reduce the nNOS expression level via reducing the NF-κB generation [58]. In 2014, DV14 and DV20 stimulated by EA elevated CO levels and HO-1 in HIE neonatal rats, which might protect against neuron damage [59]. Chao et al. [60] showed that applying manual acupuncture (MA) using needles 0.18 mm in diameter and 13 mm long at Baihui (DV20, 百會) and Shuaigu (GB8, 率谷) for 30 min/day with 30 s twirling and rotation every 5 min during each MA treatment, 2 days before HIE established and 7 days after HIE was induced, could reduce neonatal rat brain injury. They found that this treatment protocol could balance K^+ after HIE, probably through activation of the δ-opioid receptor (DOR) in the brain [60].

Acupoints	Treatment protocol	Possible mechanism	Reference
Dazhui (DV14, 大椎), Baihui (DV21, 百會)	Needles: 0.25 mm in diameter and 10 mm long Method: EA with electrical wave frequency 2/100 Hz and intense 3 mA Treatment time: 30 min/day with 14 days	**1.** Reduce H_2S level by decreasing the expression level of CBS **2.** Reduce NO level by decreasing the expression of nNOS through the NF-κB pathway **3.** Increase CO level in cortex by enhancing HO-1 expression	[56–59]
Baihui (DV20, 百會), Shuaigu (GB8, 率谷)	Needles: 0.18 mm in diameter and 13 mm long Method: MA with twirling and rotating for 30 s every 5 min during each MA treatment Treatment time: 30 min/day, 2 days before established HIE and 7 days after established HIE	Attenuating ischemic disruption of K^+ homeostasis via activated DOR	[60]
Baihui (GV 20, 百會), Dazhui (GV 14, 大椎), Quchi (LI 11, 曲池), Yongquan (KI 1, 湧泉)	Needles: 13 mm long, diameter not available in Ref. Method: EA with asymmetric bidirectional continuous pulse wave frequency 5–10 Hz and intensity 3–5 V at GV20 and LI11 Treatment time: 10 min/day with 21 days	GDNF, RET receptor and Akt were increased expression	[61]
Baihui (GV 20, 百會), Si shencong (Ex-HN 1, 四神聰)	Needles: 0.3 mm in diameter and 25 mm long Method: MA with twirling at a rate of 2 spins/s for 15 s when needles insertion in each acupoint and the needles were twirled for 3 min every 10 min Treatment time: 30 min/day with 28 days (MA performed for 5 days and 2 days of rest)	**1.** Attenuated brain cell apoptosis **2.** Up-regulated BDNF and GDNF expression level	[62]

Table 1. The commonly used acupoints and possible mechanisms of neonatal hypoxic ischemic encephalopathy acupuncture.

An article published by Xu et al. [61] showed that EA could protect against neuron damage after HIE and might be associated with the GDNF/rearranged during transfection (RET) receptor pathway. This study choose Baihui (GV 20, 百會), Dazhui (GV 14, 大椎), Quchi (LI 11, 曲池), and Yongquan (KI 1, 湧泉) for acupuncture therapy using needles 13 mm long, and EA with asymmetric bidirectional continuous pulse waves with a frequency of 5–10 Hz and an intensity 3–5 V, which was performed at GV20 and LI11 for 10 min/day for continuous 21 days [61]. These results showed that after treatment, the RET receptor and its key downstream phosphatidylinositol 3 kinase (PI-3 K)/protein kinase B (Akt), increased in expression in a dose dependent manner (sham EA compared with EA treated for 1, 3, 7, and 21 days) [61].

Based on these data, the authors suggested that the longer duration acupuncture treatment had better therapeutic effects on reducing neuron damage after HIE [61].

Zhang et al. [62] found that acupuncture at Baihui (GV 20, 百會) and Si shencong (Ex-HN 1, 四神聰) could reduce neuron damage after HIE. One day after neonatal HIE rat model was established, therapy included 0.3 × 25 mm needles that were twirled at a rate of two spins per second for 15 s, and then retained for 30 min at GV20 and Ex-HN1 [62]. At the needle retention interval, the needles were twirled three times for 3 min [62]. The acupuncture therapy was performed for five consecutive days followed by 2 days of rest and was performed over a total of 28 days [62]. The results showed that neurobehavioral function, and learning and memory abilities were improved after 20 days of treatment [62]. In addition, this study suggested that the possible mechanism of the acupuncture treatment might be associated with anti-apoptosis and upregulated GDNF and BDNF expression levels in the brain [62].

2.3. Herbal medicines for neonatal HIE

2.3.1. Clinical trial

Herbal medicines, including single herb and formulas (combination with different ingredient herb), have beneficial effects on brain HI injury. For example, treating neonates with HIE with a combination of Panax notoginseng saponins and conventional therapy can significantly reduce central respiratory failure, circulation dysfunction and gastrointestinal symptoms when compared to neonates treated only with conventional therapy [63]. Furthermore, the level of Ca^{2+} in red blood cells decreased significantly in the Panax notoginseng saponins treated group [63]. Research has also shown that conventional therapy combined with *Salvia miltiorrhiza*, *Ligusticum chuanxiong*, *Ginkgo biloba*, and *Astragalus propinquus* can improve the clinical outcome of HIE [64]. Some formulas such as Xuefu Zhuyu Decoction (血府逐瘀湯), Sheng Mai Yin (生脈飲), and An Gong Niu Huang Wan (安宮牛黃丸) are also known to improve the prognosis of neonates with HIE when combined with conventional therapy [64]. Considerable research has provided us a possible mechanism for how these herbal medicines and formulas work in HIE treatment, and we discuss this in the following sections.

2.3.2. Possible mechanisms of different single herbs for neonatal HIE remedies

In this section, we briefly discuss and summarize some single herbs and their possible pharmacological mechanism on neonatal HIE (**Table 2**).

i. *Panax ginseng* (人參)

Ginseng, the root and rhizome of *Panax ginseng* C A Meyer, has been used as a tonic herb for over 2000 years [65]. Ginsenoside Rg1 is one of the ingredients that is extracted from Ginseng and might improve brain repair after HIE [65]. Rg1 could increase neural viability, promote angiogenesis, and induce neurogenesis by increasing HIF-1α expression [65]. In addition, the expression of HIF-1α expression by Rg1 via cellular signaling pathway such as PI-3 K/Akt and extracellular signal-regulated kinase (ERK) was demonstrated [65].

ii. *Salvia miltiorrhiza* (丹參)

Salvia miltiorrhiza is a common drug used for promoting blood circulation and removing blood stasis "活血化瘀" [66, 67]. Research has shown that tanshinone IIA, an important component of *Salvia miltiorrhiza*, might have neuronal protective, anti-apoptosis effects by inhibiting caspase-3 activity after HIE [66]. In addition, tanshinone IIA can reduce inflammation by decreasing the expression level of TNF-α and IL-1β in HIE brain tissue [67].

iii. *Ligusticum chuanxiong* (川芎)

Ligustrazine, a component extracted from *Ligusticum chuanxiong*, has known to have effect of neuron protection [68, 69]. *Ligusticum chuanxiong* is a herb which is widely used to active blood and promote qi circulation "活血行氣" [68, 69]. In modern research, ligustrazine can increase the expression level of HIF-1α, which can activate many downstream pathways that protect neuron damage in HI conditions [68]. Furthermore, ligustrazine can reduce neuron cell apoptosis through increasing the *Bcl-2* gene expression and decreasing the *Bax* gene expression [69].

iv. *Astragalus propinquus* (黃耆)

Astragalus propinquus is a tonic herb that is used to invigorate qi for ascending "補氣升陽", and nourish blood and promote granulation "養血生肌" [70]. In a recent study, it was demonstrated that *Astragalus propinquus* can improve neural behavior by increasing the expression level of VEGF and VEGF receptor-2 (VEGFR-2) [70], which play important roles in ameliorating cognitive impairment in ischemic brain tissue *in vitro* and *in vivo* by improving neuronal cell viability and function [71].

v. *Radix Puerariae* (葛根)

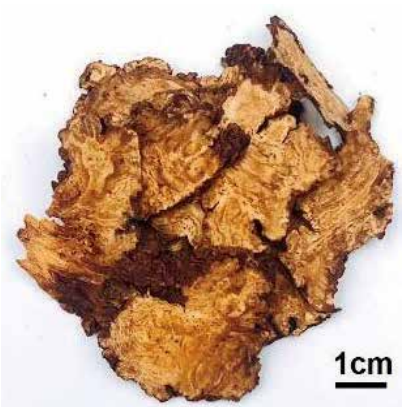
Puerarin is extracted from *Radix Puerariae*, which has been demonstrated to reduce neuronal apoptosis after HI injury [72, 73]. The possible mechanism of puerarin is the downregulation of Bax and Caspase-3 levels by increasing the expression of BDNF [72]. In addition, puerarin can reduce ROS, prevent excess Ca^{2+} reflux into cells, and decrease inflammatory responses caused during HI injury [72]. Furthermore, the Bim protein can promote cell apoptosis and can also be downregulated by puerarin [73].

vi. *Gastrodia elata* (天麻)

Gastrodia elata belongs to *Orchidaceae* family and is used as a herbal medicine for its pharmacologic function of relieving convulsion and spasm "息風止痙", suppressing liver yang "平抑肝陽", and expelling wind evil and channel "祛風通絡" [74]. It is a promising neuroprotective herb that might have been used in many incurable neural diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and seizure because this herb was demonstrated that could reduce neuron cell apoptosis via reducing neuron cell damage by free radical, inhibiting Ca^{2+} influx into cells and decreasing the neuron toxicity by counteracting glutamate effect [75]. The expression of doublecortin in brain tissue can be upregulated by *Gastrodia elata*, and this phenomenon is beneficial for brain injury because it can increase neuron cell migration and differentiation [74].

vii. *Ginkgo biloba* (銀杏)

The extractions from the *Ginkgo biloba* leaf are widely used in the treatment of aging-related diseases such as AD, cerebrovascular disease, and macroangiopathy [76]. The possible mechanism of *Ginkgo biloba* leaf extraction might be associated with its anti-oxidative properties such as scavenging free radicals, regulation of oxidative stress, and anti-lipid peroxidation;

Herbal medicine	Possible mechanism	Reference
Panax ginseng (人參) 	**1.** Increases neural viability, promotes angiogenesis, and induces neurogenesis by targeting hypoxia HIF-1α. **2.** Involves the cellular signaling pathway PI-3 K/Akt and ERK upstream of HIF-1α.	[65]
Salvia miltiorrhiza (丹參) 	**1.** Neuronal protective effect by inhibiting caspase-3 activity after HIE, which inhibits apoptosis. **2.** Reduces inflammation by decreasing the expression level of TNF-α and IL-1β in HIE brain tissue.	[66, 67]
Ligusticum chuanxiong (川芎) 	**1.** Increases the expression of HIF-1α, which can activate many downstream pathways that can protect neuronal damage in HI conditions. **2.** Reduces neuron cell apoptosis by increasing *Bcl-2* gene expression and decreasing the *Bax* gene expression.	[68, 69]

http://dx.doi.org/10.5772/intechopen.76373

Herbal medicine	Possible mechanism	Reference
Astragalus propinquus (黃耆) 	Improves neural behavior by increasing the expression level of *VEGF and VEGFR-2, which might be associated with* ameliorating cognitive impairment in ischemia brain tissue *in vitro* and *in vivo* through improvement of neuron cell viability and function.	[70, 71]
Radix Puerariae (葛根) 	**1.** Decreases apoptosis by down-regulating the level of Bax and Caspase-3, which increases the expression of BDNF. **2.** Reduces ROS, prevents excess Ca^{2+} influx into cells, and decreases the inflammatory response to HI injury. **3.** Prevents apoptosis by down-regulating the Bim protein.	[72, 73]
Gastrodia elata (天麻) 	Increases neuron cell migration and differentiation by elevating the expression of doublecortin.	[74]
Ginkgo biloba (銀杏) 	**1.** Associated with anti-oxidative properties, protection against oxidative DNA damage, and regulation of mt damage. **2.** Promotes brain tissue repair by increasing nestin protein expression and inducing neural stem cell proliferation.	[76, 77]

Herbal medicine	Possible mechanism	Reference
Rhodiola rosea (紅景天) 	Increases the expression level of HIF-1α in endothelium cells of brain vessels, cerebral cortex, and hippocampus.	[80]
Panax notoginseng (川七) 	**1.** Reduces the damage caused by free radicals and decreases Ca^{2+} influx into neuron cells. **2.** Promotes blood circulation in the brain by a vessel dilating effect.	[81]

*All herbal medicine samples were kindly provided by Long Zhi De Chinese Medicine and Biotechnology Co., Ltd.

Table 2. Possible mechanisms of herbs used for neonatal HIE treatment.

protecting DNA damage from oxidative damage; regulating mt damage such as inhibiting mt-induced ROS, and decreasing mt-related apoptosis [76]. In addition, the extract of *Ginkgo biloba* leaves can increase nestin protein expression, which can promote brain tissue repair by inducing neural stem cells proliferation [77].

viii. *Rhodiola rosea* (紅景天)

Rhodiola rosea is a widely used herbal medicine in Asia and Eastern Europe for enhancing physical and mental performance [78]. More recently, this plant has been used as an additive in food, beverages, and dietary supplements [78, 79]. *Rhodiola rosea* extract might function as an HIE treatment by increasing the expression level of HIF-1α in the endothelium cells of brain vessels, cerebral cortex, and hippocampus [80].

ix. *Panax notoginseng* (川七)

Panax notoginseng saponins are important components in *Panax notoginseng* that are a promising reagent for HIE therapy because they have a protective effect that is associated with the

reduction of free radicals and Ca^{2+} influx into neuron cells, which can limit cellular damage after HIE onset [81]. Furthermore, it can also serve as a vasodilator and increase the circulation in the brains of HIE patients [81].

2.3.3. Possible mechanism of different herbal formulas for neonatal HIE

Formula is a combination of different single herbs used to treat many kinds of diseases. The beneficial of formula is that after combing different herbs together which could reduce toxicity and side effect if we only used too many same single herbs. Here we briefly introduce some herbal formulas that are beneficial in neonatal HIE therapies (**Table 3**).

i. Xuefu Zhuyu Decoction (血府逐瘀湯)

Xuefu Zhuyu Decoction is from "Correction on Errors in Medical Classics (醫林改錯)" written by Qing-Ren Wang (王清任) [64]. Because this formula is widely used to promote blood circulation and remove blood stasis "活血化瘀", this formula could reduce the viscosity of blood and lead to an increase the blood circulation [64]. Studies have shown that this formula could improve neural behavior in neonatal rats with HIE on day 6 after neonatal HIE rat model was established, compared to the saline treated control group [82]. In addition, Xuefu Zhuyu Decoction could maintain or slightly increase nerve growth factor (NGF) expression on day 6, while NGF expression levels decreased in the saline-treated control group [82]. These results suggest that Xuefu Zhuyu Decoction might protect neuron cells after HI injury by up-regulating NGF expression [82]. NGF is a neurotrophy, which can support the differentiation and survival of neuron cells and have anti-apoptotic and anti-oxidative effect which is showed to have beneficial effects on neonatal HIE rat [83].

ii. Sheng Mai Yin (生脈飲)

This formula consists of *Panax ginseng* (人參), *Liriope spicata* (麥門冬), and *Schisandra chinensis* (五味子) and is widely used to supplement qi and nourish yin "益氣養陰", reduce resuscitation and recuperate depleted yang "回陽固脫", and promote blood circulation and remove blood stasis "活血化瘀" [64]. A pharmacologic study showed that this formula can eradicate free radicals, inhibit lipid peroxidation, improve microcirculation, and increase

Formulas	Possible mechanism	Reference
Xuefu Zhuyu Decoction (血府逐瘀湯)	**1.** Increases blood circulation by decreasing blood viscosity. **2.** Improves neural behavior by up-regulating NGF expression.	[64, 82]
Sheng Mai Yin (生脈飲)	**1.** Eradicates free radicals, inhibits lipid peroxidation, improves microcirculation, and increases cell resistance to hypoxia. **2.** Rescues brain hypoxia and ischemic injury by improving the metabolism of the heart, increasing myocardial cells contraction, and cardiac output.	[64]
An Gong Niu Huang Wan (安宮牛黃丸)	Eradicates free radicals and reduces edema in the brain by decreasing vascular permeability and increasing hypoxia resistance.	[64, 84]

Table 3. Possible mechanisms of herbal formulas for neonatal HIE treatment.

neuron cell resistance to hypoxia and other cellular stress [64]. In addition, Sheng Mai Yin can also improve the metabolism of heart and increase myocardial cells contraction and cardiac output to rescue hypoxia and ischemic injury of the brain [64]. Taken together, Sheng Mai Yin can prevent nerve cells damage after HIE via reducing neuron cell apoptosis, increasing neuron cell resistance to hypoxia and stress, increasing brain circulation [64].

iii. An Gong Niu Huang Wan (安宮牛黃丸)

An Gong Niu Huang Wan is a formula that can remove qi and blood obstruction, smooth circulation, and stop pains with aromatics "芳香開竅", awaking brain and reliving spasm "醒腦止痙", clear away heat and toxic materials "清熱解毒" and cool blood and promoting qi circulation "涼血行氣" [64]. A biomedical study showed that An Gong Niu Huang Wan could eradicate free radicals in brain tissue and reduce brain edema by decreasing vascular permeability and increasing neuron cell resistance to hypoxia [64, 84].

3. Discussion and conclusion

Current advances in medical technology have increased, but there is still no standard and effective treatment for neonatal HIE. The widely accepted treatment for neonatal HIE is hypothermia therapy that has been demonstrated to reduce morbidity and mortality in newborns [1, 3, 29–31]. Many researchers and physicians hope to find the best way to treat this disease and devote themselves to the investigation and development of new therapeutic agents and stem cells transplantation therapy [1]. Recently, many basic researches showed that TCM (including herbal medicine and acupuncture) treatment was involved in many molecular pathways which might be beneficial to neonatal HIE for example, reducing H_2S and NO level, increasing CO level, keeping ion homeostasis, up-regulating BDNF, GDNF and NGF, scavenging free radicals and so on in neural cells to prevent cells apoptosis and further damage. Due to abovementioned reasons, integrating Chinese Medicine to treat neonatal HIE is one promising method toward a better prognosis. Here we review many kinds of herbal medicines and formulas used in clinical practice in China and show that in with standard treatment, these herbs and formulas can improve the prognosis of neonatal HIE. In addition, acupuncture therapy is also a promising method to treat neonates with HIE, but unfortunately there are no suitable clinical trials that report the effect of acupuncture on neonatal HIE. However, it is worth mentioning that acupuncture therapy of adults with HIE is very useful [85]. In our experience, the Acupoints of Regain Consciousness (ARC) "醒腦開竅方" and Acupoints of Recover from Paralysis (ARP) "疏經活絡方" established by Dr. Wen-Long Hu are very useful in cases of adult HIE, and these acupoints are listed as the following: ARCs including 12 Jing-Well points (十二井穴), Frontal-top belt (額頂帶), Top-temporal belt (頂顳帶) and Renzhong (DU 26, 人中); and ARPs including Quchi (LI 11, 曲池), Hegu (LI 4, 合谷), Zusanli (ST36, 足三里), Sanyinjiao (Sp 6, 三陰交), Yanglingquan (GB 34, 陽陵泉) and three brain needle (腦三針) [85].

To conclude, although there is still a lack of clinical studies for demonstrating that acupuncture is suitable and beneficial for the treatment of neonates with HIE, many animal studies have demonstrated that acupuncture has potential as a treatment for neonatal HIE in clinical

practice, and its effectiveness for treating the symptoms of neonatal HIE should be evaluated. Based on current research and our clinical practice, we believe integrating conventional therapy with TCM is a promising therapeutic method for neonatal HIE.

Author details

Chun-Ting Lee[1], Yu-Chiang Hung[1,2] and Wen-Long Hu[1,3,4]*

*Address all correspondence to: oolonghu@gmail.com

1 Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan

3 Fooyin University College of Nursing, Kaohsiung, Taiwan

4 Kaohsiung Medical University College of Medicine, Kaohsiung, Taiwan

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Edited by Pratap Sanchetee

The stroke is the third leading cause of death and disability across the globe. We have evolved from a sense of frustration and helplessness to proactive and effective management in the hyperacute and acute phase of a stroke. The aim is to salvage the ischemic brain and turn it again into a viable and functional one. Advances in imaging and newer therapeutic strategies of this devastating illness have changed our outlook. The modern management of an ischemic stroke involves intravenous thrombolysis within a window period of four and half hours. Endovascular management with newer stent retrievers has a higher rate of recanalization with an extended therapeutic window.

A new era has emerged in the management of ischemic stroke treatment. This book, written by experts, aims to improve the understanding of stroke medicine for postgraduate medical students in medicine and neurology who have an interest in stroke care.

Published in London, UK
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ISBN 978-1-83881-709-1