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STROKE (H ADAMS, SECTION EDITOR)

Diagnosis and Treatment of Cerebral Venous and Sinus Thrombosis

Christian Weimar

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Abstract Cerebral venous and sinus thrombosis is a still underdiagnosed cause of stroke, with an incidence of about 2.8 events per 100,000 person-years in young women and about 1.3 events per 100,000 person-years in the general population. Puerperium, oral hormonal contraception, and coagulation disorders remain the most frequently identified risk factors. Initial treatment with heparin is the only proven therapy, although the evidence is based on only two randomized placebo-controlled trials which together included 79 patients. In the case of clinical deterioration under anticoagulation, local thrombolysis and mechanical thrombectomy may be considered, but clinical efficacy is supported only by case reports. Patients with imminent lateral herniation due to large hemorrhagic infarctions should be treated with prompt surgical decompression. Following the acute phase, oral anticoagulation is recommended for 3–12 months, and only patients suffering from a severe coagulopathy or with recurrent cerebral venous and sinus thrombosis should be considered for long-term anticoagulation. Only insufficient experience is available for novel anticoagulants such as thrombin inhibitors or factor Xa antagonists.

Keywords Cerebral venous thrombosis · Dural sinus thrombosis · Venous infarction · Cerebral hemorrhage · Anticoagulation · Warfarin · Thrombin inhibitors · Factor Xa inhibitors · Secondary prevention

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C. Weimar (✉)
Department of Neurology and Stroke Center, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany
e-mail: christian.weimar@uk-essen.de

Introduction

On the basis of a previous review [1] as well as a selective literature search, this article summarizes the causes, treatment options, and controversies in cerebral venous and sinus thrombosis (CVST). It emphasizes experiences from the neurology perspective and critically discusses new developments as well as established therapies.

Epidemiology

The overall incidence of adult venous thrombosis in two Dutch provinces serving 3.1 million people was 1.32 events per 100,000 person-years [95 % confidence interval (CI) 1.06-1.61] and among women between the ages of 31 and 50 years the incidence was 2.78 events per 100,000 person-years (95 % CI 1.98-3.82) [2•]. In the Nationwide Inpatient Sample hospital discharge database comprising 11,400 patients, patients aged 15-49 years had the lowest mortality of 1.5 % compared with 2.8 % for patients aged 50-64 years and 6.1 % for patients aged 65 years or older [3•]. Cognitive impairment persists in up to one third of patients hospitalized for CVST and is more frequent in patients with deep CVST and persistent parenchymal lesions [4]. About 10 % of patients continue to have seizures, and about 50 % complain of various types of headache and/or feel depressed or anxious [5].

Etiology

The commonest condition associated with CVST in women is pregnancy/puerperium, with an incidence of around ten per 100,000 deliveries in high-income countries, accounting for 5–20 % of all CVST [6]. Except for a number of local causes, other predisposing factors of CVST do not differ between

CVST and extracerebral deep venous thrombosis (DVT). Oral hormonal contraception is frequently found in combination with coagulation disorders, but remains the sole predisposing factor in about 10 % of cases [7]. Coagulation disorders are common causes of CVST, in particular the factor V Leiden mutation with activated protein C resistance, which accounts for 10-25 % of cases [7, 8]. Additional coagulopathies associated with CVST include prothrombin G20210A mutation, antithrombin III deficiency, protein C and protein S deficiency, antiphospholipid antibody syndrome, plasminogen deficiency, hyperhomocysteinemia, dysfibrinogenemia, disseminated intravascular coagulation, and heparin-induced thrombocytopenia type 2 [5, 9]. Less common causes include malignancies (meningeoma, carcinoma, lymphoma, carcinoid, leukemia), hematological disorders (polycythemia, sickle cell disease, paroxysmal nocturnal hemoglobinuria, immune-mediated hemolytic diseases, thrombocythemia), collagenosis (systemic lupus erythematodes, Sjögren's syndrome), and vasculitis (Behçet's disease, Wegener's granulomatosis, sarcoidosis) [5].

Among rare causes of CVST are intracranial hypotension, cerebral concussion, neurosurgical interventions, obstructive hydrocephalus, impaired venous drainage (central venous catheter, dural arteriovenous malformation, strangulation), medication poisoning (chemotherapeutics, steroids, erythropoietin, androgens, drugs, vitamin A overdose), metabolic disorders (diabetes, thyrotoxicosis, uremia, nephrotic syndrome), gastrointestinal disorders (liver cirrhosis, chronic inflammatory bowel disease), and heart disease (heart failure, cardiomyopathy). Potential generalized infectious causes include bacterial septicemia, endocarditis, hepatitis, encephalitis, measles, tuberculosis, typhus, malaria, and aspergillosis. Septic CVST occurs mainly in children but also in up to 18 % of all adult cases in developing countries [10], and is associated with localized infections, such as mastoiditis, otitis media, sinusitis, tonsillitis, retropharyngeal abscess with thrombosis of the adjacent jugular vein, oral or cerebral abscesses, and meningitis. No cause of CVST can be found in about 15 % of cases, although follow-up in these patients may detect an underlying disease up to several months later [11].

Clinical Presentation

Because the ways of venous drainage are numerous and reversal of venous flow is possible, thrombosis of a cerebral sinus does not necessarily cause focal neurological symptoms but leads to impaired resorption of cerebrospinal fluid and thereby intracranial hypertension. Headache is the initial symptom in more than 70 % of cases and remains the only symptom in about 16 % of cases [12], or can be associated with other common symptoms such as nausea/vomiting, seizures, reduced consciousness or confusional state, and focal neurological deficits [11]. Papilledema can be found in about 40 % of cases, mainly in patients with a chronic course or delayed diagnosis. Initial presentation with focal or generalized epileptic seizures occurs in 30-40 % of cases. Other less frequent symptoms include thunderclap headache, subarachnoid hemorrhage, cranial nerve palsy, transient ischemic attacks, migraine with aura, psychiatric disturbances, and tinnitus. When smaller cerebral veins are involved, focal edema and venous infarctions cause neurological deficits and focal seizures which are determined by the localization of CVST and the associated lesions.

Diagnosis

Reliable identification of CVST can be achieved with the enhancement of dynamic venous CT angiography using slices of 1–1.5 mm. With application of multiplanar reconstruction, the sensitivity reaches 95 % and the specificity reaches 91 % compared with digital subtraction angiography [13]. A hypoplastic left lateral sinus is common and must be differentiated from CVST. Asymmetry of the sigmoid notches on plain brain CT is a sensitive and specific measure for differentiating an atretic transverse sinus from transverse sinus thrombosis when absence of transverse sinus flow is visualized on venous angiography [14].

Magnetic resonance (MR) angiography is superior to CT angiography in the detection of cortical venous thrombosis. Subarachnoid hemorrhage localized along a sulcus may also be indicative of a single cortical vein thrombosis [15]. Depending on the structure and localization of the thrombus, T1- or T2*-weighted sequences and susceptibility-weighted imaging are highly sensitive for direct detection of the thrombus [16, 17]. Thrombosis of the sinus does not induce signal loss in the axial and sagittal T1 and T2 sequences but may appear hyperintense because of its content of methemoglobin. Contrast-enhanced 3D gradient recalled echo T1-weighted imaging is superior to spin echo T1-weighted imaging for the detection of dural sinus thrombosis, but does not substitute for dedicated MR angiography [18].

Acute CVST presenting with neurological deficits is strongly associated with D-dimer levels of more than 500 ng/ml [19]. On the other hand, D-dimer levels below 500 ng/ml do not rule out CVST, especially when the patient presents with isolated headache only. A systematic meta-analysis found a mean sensitivity of 93.9 % and a mean specificity of 89.7 % [20]. False-negative D-dimer results were more frequent in patients with isolated headache, longer duration of symptoms, and limited sinus involvement. Therefore, although normal D-dimer levels make the presence of CVST unlikely, exclusion of CVST should not be based on D-dimer measurement only.

Treatment

In line with the therapeutic guidelines for peripheral DVT, anticoagulation is also the treatment of choice for CVST. Initial anticoagulation with heparin is thought to stop the progression of thrombosis, to reduce the risk of pulmonary embolism, and to prevent reocclusion of those vessels which have already been recanalized by internally produced fibrinolytic agents. Confirmed CVST should therefore be treated with heparin even in the presence of an associated intracranial hemorrhage.

Septic or infectious CVST is treated with antibiotics according to the underlying infectious agent and focus. In certain cases, surgical treatment can be necessary to control the focus of infection. Despite anti-infective treatment, mortality is higher compared with that in noninfectious CVST, and treatment with anticoagulation is justified even in the absence of evidence from controlled trials.

Heparin

The current guidelines for the diagnosis and treatment of CVST published by the American Heart and Stroke Association as well as the European Federation of Neurological Societies provide recommendations on anticoagulation for CVST [5, 21]. Evidence for efficacy of treatment with heparin in acute CVST comes from two small randomized placebo-controlled studies which together included 79 patients. Einhäupl et al. [22] compared dose-adapted partial thromboplastin time controlled intravenous treatment with unfractionated heparin (UFH) versus placebo in 20 patients with CVST: in the heparin group, eight patients showed complete recovery and all patients survived, with no further bleeding complications observed, whereas in the placebo group only one patient showed full recovery, three patients died, and two patients developed new intracerebral hemorrhages. De Bruijn et al. [23] investigated the efficacy and safety of treatment with subcutaneously applied nadroparin at a dosage of 90 mg/kg twice daily for 3 weeks versus placebo in 59 CVST patients. There was a nonsignificant trend in favor of treatment with low molecular weight heparin (LMWH), and neither new intracranial hemorrhage nor an increase in intracranial hemorrhage size was observed. A meta-analysis of both studies showed a 54 % relative risk reduction in mortality and severe disability with heparin treatment [24]. Although statistical significance was also not reached in this meta-analysis, the results of both studies indicate treatment of CVST with heparin is safe and reduces the risk of unfavorable progression.

It is not known whether intravenous dose-adapted treatment with UFH and weight-adapted treatment with LMWH are equivalent. A small randomized trial from India evaluated the efficacy and safety of LMWH versus UFH in 66 consecutive patients [25]. Six patients in the UFH group died and an insignificantly higher number of patients (30 versus 20) in the LMWH group fully recovered. A nonrandomized prospective observational study in patients with CVST found treatment with LMWH to be more effective and associated with fewer bleeding complications [26]. Particularly patients with hemorrhagic infarctions seemed to benefit from treatment with LMWH.

Pregnancy is not a contraindication for treatment with LMWH or UFH, but peripartal and postpartal attenuation of anticoagulative treatment should be considered individually as the risks of both bleeding and thromboembolism are increased during the peripartal phase. Anticoagulation during the acute phase of CVST is also recommended in children, whereas it may be considered individually in neonates [27•].

Thrombolysis and Mechanical Thrombectomy

Endovascular thrombolysis is composed of local application of recombinant tissue-type plasminogen activator or urokinase within the thrombosed sinuses, mechanical thrombosuction, or both. A meta-analysis of uncontrolled studies found that 12 of 156 CVST patients treated with urokinase or alteplase subsequently died and 15 had major bleeding complications [28]. Particularly patients with large space-occupying hemorrhagic infarcts do not benefit from thrombolytic therapy because an increase in hemorrhage size accelerates the imminent herniation [29]. Nevertheless, in patients with thrombosis of the inner cranial veins or extensive CVST without associated hemorrhage, locally applied thrombolysis may be an option and can be considered as an individual treatment attempt after failure of conventional heparin treatment. Probably the major indications for local thrombolysis are multiple sinus occlusions including the jugular veins with no egress of blood because these patients have very poor outcomes and markedly increased intracranial pressure (ICP). Experience with mechanical thrombectomy as a potential alternative or supplement to thrombolysis is still limited, with 64 cases summarized in a recent comprehensive review [30]. The ongoing Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (To-ACT) trial is currently randomizing CVST patients with a high probability of poor outcome (defined by the presence of at least one risk factor: mental status disorder, coma, intracranial hemorrhagic lesion, or thrombosis of the deep cerebral venous system) to receive either endovascular thrombolysis or therapeutic doses of heparin [31].

Elevated Intracranial Pressure

Increased ICP can be managed best with sufficient anticoagulation by optimizing the venous drainage, which

results in a reduction of ICP. In patients with symptomatic intracranial hypertension and imminent loss of vision, repeated lumbar punctures may be needed to drain cerebrospinal fluid (CSF) before anticoagulation can be (re)started. If clinical symptoms progress despite repeated CSF drainage, permanent CSF drainage may be necessary.

Specific ICP-lowering treatment is indicated in less than 20 % of patients. General rules of ICP-lowering treatment should be applied (upper body elevation, hyperventilation, intravenous administration of osmotherapeutic agents). However, these procedures have limited duration of action and are of little effect. The largest uncontrolled case series showed favorable outcome in 26 out of 34 patients after decompressive craniectomy despite clinical and radiological findings of herniation [32•]. In particular, patients presenting with large hemorrhagic infarctions and imminent lateral herniation should be offered prompt surgical decompression without removal of the hematoma or infarcted area [21]. Anticoagulation should be continued for 12–24 h after surgical treatment. Because of its prothrombotic activity and no proven benefit, treatment with steroids is not recommended.

Oral Anticoagulation

MR-based follow-up studies indicate that recanalization usually occurs within 3 months, irrespective of continuation of oral anticoagulation [33]. However, the recanalization rate has not been found to correlate with the risk of CVST recurrence. Despite the lack of evidence, several guidelines recommend an average duration of 3–12 months for treatment with dose-adapted vitamin K antagonists, whereas long-term anticoagulation beyond 12 months is advised only in patients with severe coagulopathies or recurrent CVST [5, 34]. In addition, children and adolescents below the age of 18 years who have heterozygote prothrombin G20210A mutation may benefit from long-term anticoagulation [35]. To date, there is not enough clinical experience and evidence for the use of novel anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) for the treatment of CVST, although rivaroxaban has been approved for treatment of acute DVT.

Secondary Prevention in Patients at Risk

The recurrence rate of CVST was investigated in a recent multicenter retrospective study including 706 patients with a first episode with CVST [36•]. After a median follow-up of 40 months (range 6–297 months), CVST recurred in 31 patients (4.4 %), whereas 46 patients (6.5 %) had a venous thromboembolism at a different site, resulting in an overall incidence of recurrence of 2.36 events per 100 patient-years (95 % CI 1.78–2.87). Because of this benign prognosis, the use of long-term anticoagulant therapy should be reserved for patients at high risk of recurrence.

Prophylaxis with weight-adapted LMWH should be given in risk situations (e.g., immobilization for more than 4 days, steroid therapy, flight longer than 4 h) in adults as well as in infants and adolescents with a history of CVST [37]. One retrospective study included 62 women aged 40 years or younger with CVST and a mean follow-up of 7.5 years [38•]. There were 45 pregnancies in 24 of the women, most of whom were receiving preventive antithrombotic medication. Only one patient, with sickle cell disease, had a recurrent CVST during pregnancy. Four patients (6.7 %) had a noncerebral venous thrombosis but did not have one during a subsequent pregnancy. Results from other case series also indicate that the risk of recurrence during pregnancy is not increased unless an inherited or acquired thrombophilia is present [39, 40]. Because the postpartum period carries the greatest day-by-day risk of developing DVT and CVST, anticoagulation with weight-adapted LMWH for 6 weeks after delivery is recommended in patients with a history of CVST in line with recommendations from the guidelines for prevention of DVT.

Conclusions

With the help of MR angiography and CT angiography, CVST is increasingly diagnosed in oligosymptomatic patients, i.e., with headache or papilledema only. Therefore and presumably owing to anticoagulation in the acute phase, the rate of death or dependency has declined from about 50 % 30 years ago to about 15 % in recent case series [41]. Nevertheless, cognitive impairment persists in up to one third of patients hospitalized for CVST, and about 10 % of patients continue to have seizures. Heparin treatment remains the baseline therapy, including in those patients with concomitant intracerebral hemorrhage. Endovascular treatment is currently being evaluated in an ongoing randomized trial and should otherwise be restricted to those patients with clinical deterioration and radiological progression of cerebral venous congestion. Oral anticoagulation with vitamin K antagonists is not indicated beyond 12 months except in patients with severe coagulopathies or recurrent CVST.

Compliance with Ethics Guidelines

Conflict of Interest Christian Weimar has received honoraria for participation in clinical trials and for contributions to advisory boards or oral presentations from Bayer Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, CoAxia. D-Pharm, Daiichi Asubio, GlaxoSmithKline, Lundbeck, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, and Sanofi-Aventis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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