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ORIGINAL ARTICLE

Diagnosis of cerebral venous thrombosis: a single centre experience

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Abstract

OBJECTIVES: Cerebral venous thrombosis is a serious cerebrovascular disease. Due to the variability of clinical symptoms and the scarcity of occurrence, this diagnosis is often delayed. The aim of the study was to describe the risk factors, the initial findings and the imaging methods that lead to the diagnosis.
METHODS: We included 34 patients treated for cerebral venous thrombosis in the years 2004–2016. We retrospectively analyzed demographic data, initial clinical symptoms, baseline D-dimer levels, risk factors, time to diagnosis, and MR findings.
RESULTS: The most common initial clinical symptom was headache (28 patients, 82.4%). Focal neurological symptoms or signs of encephalopathy developed in 22 patients (64.7%). In 26 patients, we identified at least one risk factor in their history. In women of childbearing potential, 68% of patients (15/22) were taking hormonal contraceptives; in six people the diagnosis was immediately preceded by inflammation. In all patients, the diagnosis was confirmed by MR venography. Positive hereditary thrombophilic conditions were identified in 68% and acquired in 8% of 25 examined patients. In 22 cases, baseline D-dimer levels were examined and found to be increased in 86% of them. The mean time from the first onset of symptoms to diagnosis was 6.9 days.
CONCLUSION: Cerebral venous thrombosis has a variable clinical course and the diagnosis is determined a relatively long time after the onset of symptoms. Atypical headache in the patient's history and a set of risk factors are the key findings for indication of imaging methods and confirmation of the diagnosis.

BRIEF SUMMARY

This is a retrospective observational study of 34 patients admitted for cerebral venous thrombosis in the years 2004–2016 at our institution. We analysed demographic data, initial clinical symptoms, baseline D-dimer levels, risk factors, time to diagnosis, and MR findings.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a serious cerebrovascular disease with significant long-term morbidity and high mortality rate. Due to the considerable variability of clinical symptoms and the relative scarcity of its occurrence, this diagnosis is often neglected or delayed (Peisker & Bartos, 2006; Fauknerova *et al.* 2010). The pathophysiological basis of the disease is the thrombotic occlusion of intracranial veins, which causes venous drainage from the affected vein to deteriorate. This leads to an increased intracranial pressure in less serious cases and to brain damage by oedema, haemorrhage or ischemia in more severe cases (Saposnik *et al.* 2011). The incidence of CVT in the adult population is 0.2 to 1.3 per 100,000 patients per year. Larger incidence is reported in women of childbearing potential, especially during pregnancy or in women taking hormonal contraceptives. Women are affected at a younger age than men. The occurrence of CVT in patients over 65 years of age is considered rare; while the incidence in childhood is about half that reported in adulthood (Ferro *et al.* 2001; Coutinho *et al.* 2012).

The development and course of CVT is very variable and non-specific, but often the manifestation of symptoms and the course of the disease are chronic even with relapses. The most commonly reported clinical symptom is headache, and less often eye disorders are reported.

The aim of this retrospective study is to describe our experience with the diagnosis of CVT and to compare it with data published in the literature. We focused on primary clinical symptoms (in particular headache and eye symptoms), baseline D-dimer levels, risk factors, time to diagnosis, and findings of imaging methods. Thrombophilic conditions were also evaluated in the majority of patients.

METHODS

A total of 34 patients (6 men and 28 women) treated for CVT at our facility were examined over the period from 2004 to 2016. The age range of the group was 19–79 years with the mean age of 39 years (39 years for females, and 40 years for males).

Retrospectively, we searched for initial clinical symptoms, baseline D-dimer levels, risk factors, evaluation of thrombophilic conditions, time to diagnosis, and findings of imaging methods. In all patients, the diagnosis was confirmed by MR venography.

Due to population size, only a descriptive data summary was performed. The Spearman's coefficient is used to calculate correlations.

RESULTS

Clinical manifestations

The most common early clinical sign of CVT was headache, which occurred in 28 patients (82.4 %). They suffered from hemicranial headache (11 cases) and cervicogenic headache (7 cases). Localized pain behind the eyes was reported in four patients. Diffuse headache was described in four patients. In two patients, the headache was characterized as thunderclap one. Headache was completely absent only in 6 patients. A gradual increase in severity of headache or other symptoms of intracranial hypertension was seen in 17 patients, 50 % of the whole group.

Focal neurological symptoms or signs of encephalopathy occurred in 22 cases, including paresthesia or weakness of the limbs (11 cases). Epileptic seizure occurred in 7 patients, and in 3 of them as the first symptom. Decreased psychomotor speed, mental changes, or consciousness disorders were observed in 7 patients (these symptoms occurred after severe headache in 3 cases, after epileptic seizures or weakness of the limbs in 4 cases). Visual impairment occurred only in 2 patients. Focal neurological symptoms occurred 4.4 days on average and no later than 12 days after the onset of headache, and their earliest occurrence was on the same day as the headache.

In patients without headache, the initial manifestations of thrombosis were dizziness without neurological findings in 4 cases, non-specific visual disturbances (the patient was intermittently seeing "lumps"), or a transient speech disorder of the character of expressive speech disorder.

Risk factors

A total of 27 (76.5%) patients were identified as having at least one risk factor for development of CVT in their history (one factor was present in 55.9% of patients, two factors in 14.7% and three factors in 5. 9% of patients; while 23.5% of patients had no risk factors). CVT was immediately preceded by an inflammation in the ear, nose, and throat area in 6 patients, and by a head injury in 2 patients. Two patients had a positive cancer historyPregnancy was identified in 2 women – one of them was diagnosed with CVT after a HELLP syndrome attack. Fifteen of 22 (68%) premenopausal subjects took hormonal contraceptives; and in 3 of them hormonal contraceptives were the only risk factor. Two patients took methotrexate (patients with juvenile arthritis and psoriasis). One patient treated for multiple sclerosis was diagnosed with CVT after intrathecal cytarabine administration. One patient developed problems after an airplane flight that took several hours. No other risk factors were identified in this patient.

In 25 subjects examination of thrombophilic conditions was performed to be hereditary in 68% and acquired in 8% of the examined patients (Table 1). Of the hereditary conditions, we identified MTHFR C677 mutations (32%) as the most common ones, decreased protein C levels (4%), and PAI-I mutations (24%), while Leiden mutation was found in 8 % of patients. Genetic analysis revealed at least two causes of hereditary thrombophilia in 64 % of patients. One patient was found to

Tab. 1. Frequency of occurrence of thrombophilic conditions

Hereditary thrombophilic conditions	**%**	
Leiden mutation	8	2x heterozygous
C protein deficiency	4	
PAI-I mutation	24	
MTHFR C677 mutation	32	3x heterozygous
MTHFR A1298C mutation	12	5x heterozygous
G20210A mutation	8	
Acquired thrombophilic conditions		
Increased factor VII activity	8	

have 4 causes. In patients with acquired thrombophilia, 2 patients were found to have an increased factor VIII activity.

Findings of imaging methods

In 21 patients, CVT was detected by the first imaging examination performed. In 4 of these patients, ischemia or haemorrhage were seen already at the beginning of the examination; in 1 patient, post-inflammatory changes were described in the pneumatic system of the left pyramid region. In 10 cases, CT or CT angio/venography was performed initially, 4 cases had MR scan of the brain and 7 cases had MR venography. In 13 cases, CVT was not revealed by the initial scan (10 patients with native CT scan and 3 with CT angiography); In 6 patients, the initial imaging examination was completely negative, while in an additional 7 patients, the first finding was atypical haemorrhage or ischemia. In these cases, the diagnosis of CVT was determined by MR or MR venography (Fig. 1). One patient underwent DSA – to search for a source of atypical bleeding. The mean delay in making additional imaging to confirm the CVT findings was 2.4 days. The most common sites of involvement (16 cases) were the right transverse sinus (STD), left transverse sinus (STS) and left sigmoid sinus (SSigSin). On average, the thrombosis affected 2.9 sinuses (a minimum of 1 to a maximum of 7).

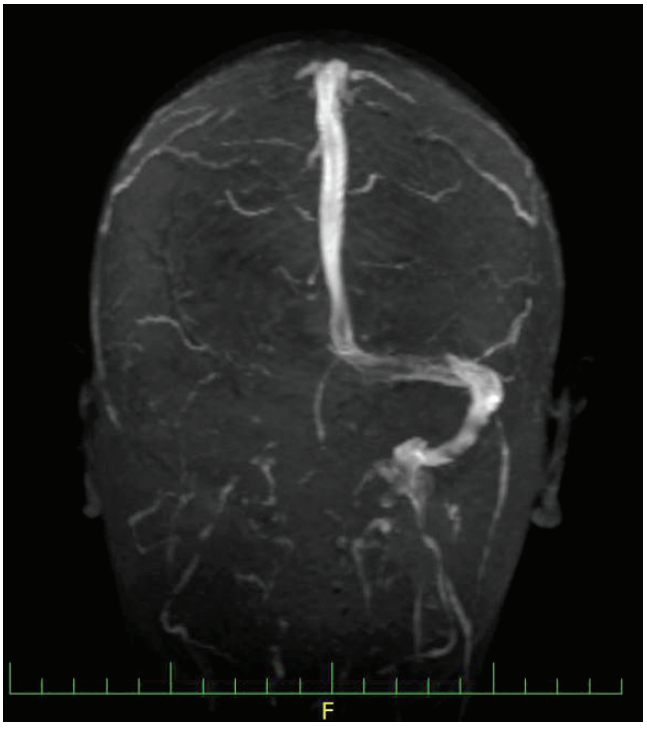

Fig. 1. MR venography without differentiable flow in sinus rectus, left transverse sinus and sigmoid sinus

D-dimer levels

Information on baseline D-dimer level was available in 22 cases. Its increase was recorded in 86 % of cases; the mean level was 1563 ng/mL (range 398–3890 ng/mL). D-dimer levels did not correlate to the speed of diagnosis or the number of affected sinuses (Fig. 2 and 3).

Time to diagnosis

The mean time from the onset of the first symptoms to the diagnosis was 6.9 days (range 0–19 days). Diagnosis was faster in women than men (mean time to diagnosis 6.6 vs. 8.8 days) and also in patients with at least one risk factor in their history (6.5 vs. 8.6 days). If CVT was clinically manifested only by headache, the mean time to diagnosis was 7.3 days (if no risk factors were present in the patient's history, the mean time to diagnosis was 9.7 days vs. 6.3 days in case of known risk factors). The mean time to diagnosis from the manifestation of focal neurological symptoms was 1.4 days; the shortest time to diagnosis was reported for epileptic seizures (0.25 days), while the longest time to diagnosis was reported for bradypsychia or consciousness disorders (2.2 days). For visual disturbances or paresthesia/paresis, the time to diagnosis was 2.0 and 1.6 days, respectively. The time to diagnosis was similar in patients younger and older than 50 years of age (6.9 vs. 6.6 days). In our group, we did not notice any tendency to a shorter time to diagnosis (Fig. 4).

DISCUSSION

Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease resulting from a thrombotic occlusion of intracranial veins. CVT is associated with increased intracranial pressure. Brain tissue damage may occur in more severe cases (Saposnik *et al.* 2011). Greater incidence is reported in women of childbearing age and is related to hormonal changes (pregnancy, contraceptives). The occurrence of CVT in patients over 65 years of age is rare. The results of our population (mean age and gender ratio) are consistent with the published data. A relatively higher incidence was reported in patients over 65 years of age, in which we found significant risk factors or their combinations (cancer history, mastoiditis or methotrexate therapy).

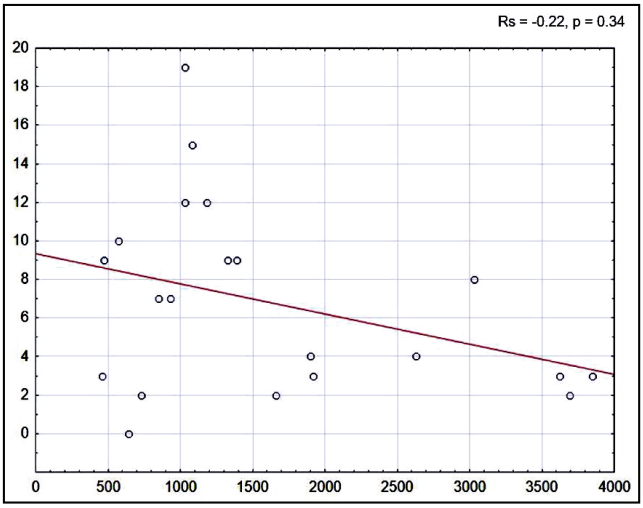

Fig. 2. Time to diagnosis(y) vs. D-dimer levels(ng/mL, x)

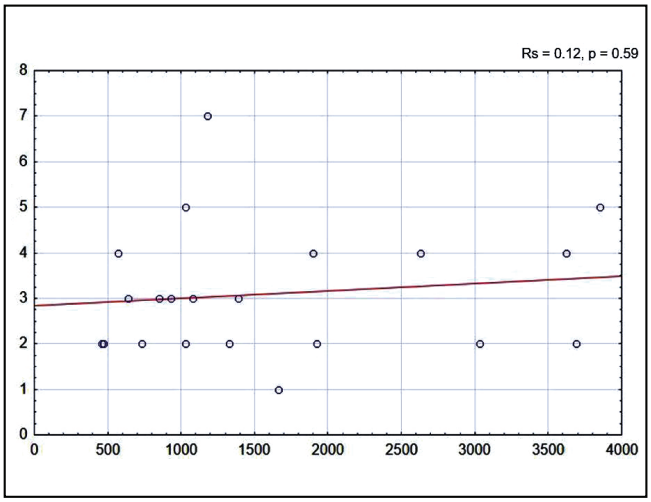

Fig. 3. Number of sinuses involved(y) vs. D-dimer levels(ng/mL,x)

The clinical picture of CVT usually consists of the classic triad of symptoms: 1) intracranial hypertension syndrome (headache, which may be accompanied by vomiting, papillary oedema and visual disturbance), 2) epileptic seizure, 3) focal neurologic deficit (Bousser *et al.* 1985). Some authors also add the symptom of encephalopathy (Stam, 2005). The manifestation of symptoms is acute (up to 2 days) in about one third of the patients, or takes up to 30 days in about one half of the patients, or has a chronic course in the remaining patients.

The most common initial clinical sign is headache, which occurs in up to 90 % of patients. It is a dull, diffuse or localized pain, gradually developing and worsening over the course of a few days, or while coughing or in the lying position. It usually reaches high intensity, but can be even mild or intermittent. In some cases, it resembles a migraine with aura or develops suddenly as thunderclap headache raising suspicion of subarachnoid bleeding (IHS, 2013). The cause of headache is probably an increase in intracranial pressure or localized mechanical irritation of dural nociceptors due to sinus wall distension. Local inflammation may also play a role. The thunderclap headache is apparently a sign of bleeding, including parenchymal haemorrhage, subarachnoid bleeding, or venous infarction (Wasay *et al.* 2010). Our study confirms that headaches are the leading symptom of CVT, but their character is very diverse. In some cases, headache may not occur at all. In our relatively small group, we diagnosed CVT even when clinical symptoms suggested other diagnoses, such as migraine or cervicogenic headache. The absence of headache does not rule out the diagnosis of CVT. Epileptic seizures and/or focal neurological or encephalopathic symptoms may occur if brain parenchyma lesions are present due to CVT. Epileptic seizure occurs in up to 40 % of patients prior to the diagnosis; and in 7% of patients within 14 days of the diagnosis. The most common are generalized or focal seizures, while convulsive status epilepticus may occur in less than 1% of patients. Epileptic seizures occur with thrombosis of the superior and inferior sagittal sinuses and thrombosis of cortical veins. They are more common in patients with motor deficits or in pregnant women (Ferro *et al.* 2004; Piazza, 2012; Ferro *et al.* 2008). The most common focal symptoms are paralysis of the limbs, which are reported in up to 37 % of the patients as a manifestation of the involvement of the superior or inferior sagittal sinus and sinus rectus. Left sigmoid sinus thrombosis is manifested by a speech disorder in 19 % of cases, while visual field disturbances (13 %) have been reported to occur in patients with a transverse sinus involvement (Ferro *et al.* 2004). The most serious symptoms of CVT are signs of encephalopathy, such as apathy, delirium, cognitive impairment, and consciousness disorders. These are manifestations of extensive neural tissue involvement by oedema or venous infarction or occur in patients with sinus rectus thrombosis.

In our group, we recorded focal or encephalopathic symptoms and in particular epileptic seizures at a lower frequency than in other studies. Apparently, we managed to capture earlier stages of CVT, when the brain parenchyma was not already damaged. In addition, we diagnosed less frequently thrombosis of the superior sagittal sinus and cortical veins, which are associated with the occurrence of epileptic seizures (Wasay *et al.* 2010).

In patients with suspected CVT, we carry out a targeted search for risk factors. At least one risk factor is present in 85 % of patients. The most common risk factors are thrombophilic conditions, whether hereditary or acquired. Hereditary thrombophilic conditions include deficit of antithrombin, protein C and protein S, factor II (prothrombin) mutations, and factor V (Leiden) mutation. The acquired thrombophilic conditions may also include hyperhomocysteinemia and presence of antiphospholipid antibodies. Additional risk factors include pregnancy, postpartum period

or use of contraceptives. And moreover, infections, systemic and especially localized (otitis, mastoiditis, meningitis), cancer, chronic inflammatory disease and some haematological diseases (polycythemia). Cranial trauma or lumbar puncture (Ferro *et al.* 2004) may also act as a risk factor.

We identified risk factors in a total of 76.5 % of patients. In line with previous studies, our study demonstrated that taking hormonal contraceptives is a significant risk in women. According to a recent meta-analysis, the use of hormonal contraceptives is associated with a 7.6-fold increase in the risk of CVT compared to women not using hormonal contraceptives (Amoozegar *et al.* 2015). The incidence of thrombosis may be even higher for women with congenital haemostasis disorders (Martinelli *et al.* 2003). Surprisingly, smoking does not increase the risk of CVT (Ciccone *et al.* 2005) in patients taking hormonal contraception.

An additional significant risk factor acquired in our patients was an inflammatory involvement in the ENT area (Bălaşa *et al.* 2014). Its occurrence was quite considerable in our group. It is possible that some of our patients were not treated with antibiotics fast enough.

For one patient, the only risk factor was a several-hour airplane flight. This factor is associated with lower vein thrombosis but it has been described in the literature also with the development of CVT. Unlike our case, other factors were also present in patients, such as dehydration, hereditary thrombophilia, or hormonal contraceptive use (Güngör & Onar, 2007). In our population, we recorded higher number of thrombophilic conditions compared to the ISCVT study (Ferro *et al.* 2004). This is mainly due to the fact that we also examined mutations in the methylene-tetrahydrofolate reductase gene MTHFR C677T or A1298C and PAI-I (Plasminogen activator inhibitor-I) mutations that were not tested in the ISCVT study. The relationship between MTHFR and PAI-I mutations and development of thrombosis has not been demonstrated by some authors, and is therefore considered controversial(Gouveia & Canhão,2010; Habib *et al.* 2015; Ringelstein *et al.* 2012). After their exclusion, the percentage of hereditary thrombophilic conditions in our population was comparable to the published data.

The first imaging technique used in clinical practice in a patient with symptoms of CVT is native CT scan of the brain, which provides typical findings only in 30 % of cases. In some patients we observed hyperdensity at the site of the thrombus (cord sign, delta sign). In most cases, only indirect signs of CVT are seen, including focus of ischemia non-respecting the arterial territory, or less commonly, intracerebral or subarachnoid haemorrhage. Another non-specific sign is intraparenchymal hypodensity corresponding to oedema.

Magnetic resonance imaging (MRI) is the gold standard in the diagnosis of CVT. During the first days, the thrombotic sinus appears isointense in the T1 sequence and hypointense in the T2 sequence. During the second week, methemoglobin deposition occurs, and the thrombus appears hyperintense in the T1 and T2 images. Chronic thrombosis may appear isointense or hypointense.

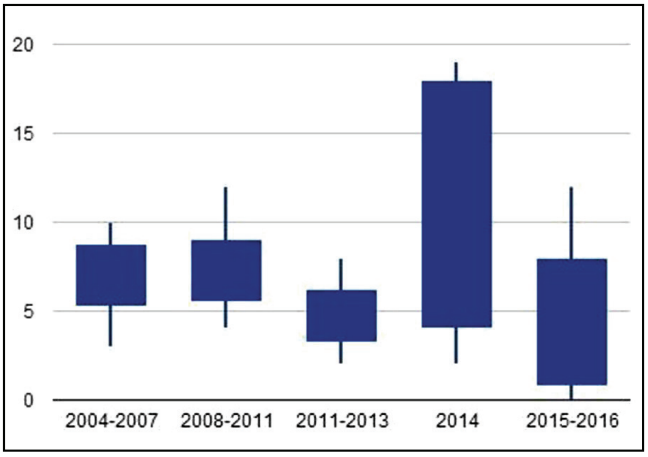

Fig. 4. Number of days needed for diagnosis(y) in different years (x)

Negative CT or MR scans do not rule out CVT, and CT or MR venography is required in patients with clinical suspicion. MR and CT venography has a comparable precision (Khandelwal *et al.* 2006). The advantage of MR imaging (especially time-of-flight MR venography and T2*-weighted images) is ability to better visualize the surface and deep vein system and cerebral parenchyma. The yield of the examination can be increased if 2D phase-contrast venography or diffuse-weighted images are included in the CVT diagnosis protocol (Vymazal *et al.* 2007). CT venography takes precedence when MR is contraindicated or when we need to know the result quickly. Both methods are also recommended to monitor the development of cerebral venous thrombosis, and according to the American Heart Association (AHA) guidelines, follow-up imaging should be performed after 3 months (Saposnik *et al.* 2011). Our experience confirms that baseline imaging, especially a native CT scan of the brain, does not necessarily lead to the detection of CVT. Therefore, CT venography or MRI of the brain (or MR venography) should be indicated when CVT is suspected.

As with deep vein thrombosis, increased D-dimer levels above 500 ng/mL are found in CVT. When CVT is strongly suspected (headache and presence of epileptic seizure or focal neurological symptoms), the D-dimer level is increased in 96 % of cases. Conversely, in subacute or chronic cases or when CVT is manifested by headache only, the D-dimer level is often within normal ranges (Crassard *et al.* 2005; Meng *et al.* 2014). In our study, we confirmed the high negative predictive value of the D-dimer level. An increase in D-dimers above 500 ng/mL was present in most patients. This level is generally used for CVT diagnosis but has not been validated for this disease. Some authors compared the occurrence of CVT even with lower D-dimer levels (Crassard *et*

al. 2005). When using the cut-off of 400 ng/mL in our group, the result of the test would be negative only in one patient, who had the chronic course of the disease.

The most common time to diagnosis was 7 days (range 3–16 days) in the study with the largest group of CVT patients (ISCVT) (Ferro *et al.* 2004). The diagnosis is faster in women, in patients with severe clinical manifestations of CVT (consciousness disorder, epileptic seizure), and if venous infarction is present on the initial imaging. The speed of diagnosis at our site was comparable to other studies. Even in our group, the diagnosis was obtained more quickly in women and in the case of more severe clinical course of CVT. We did not confirm the tendency to a shorter time needed to diagnosis (Nzwalo *et al.* 2015).

The presence of a focal neurological deficit (motor impairment, sensitivity or speech disorder), risk factors or precipitating factors, and the number of venous sinuses and veins involved had no influence on the time to diagnosis (Ferro *et al.* 2004).

CONCLUSION

Our experience confirms that CVT has a highly variable clinical course and diagnosis is often established over a relatively long time span since the onset of the problem. Careful consideration of the medical history, especially atypical headaches and presence of risk factors, are of crucial importance for early indication of imaging methods, confirmation of CVT and its treatment.

AUTHOR CONTRIBUTIONS

MP manuscript writing, data collection, statistical analysis.
PT study design, data collection, manuscript writing.
VP study design, manuscript review.
ŠI study design, manuscript review.

CONFLICT OF INTERESTS STATEMENT

The authors state that there are no conflicts of interest regarding the publication of this article.

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