

## Cerebral Venous Thrombosis - A Diagnostic Challenge

Rafaela Ianisky<sup>1\*</sup>, Thaise de Araujo Wrubleski<sup>2</sup>, Jean Rodrigo Tafarel<sup>1 2</sup>, Vitor Loureiro Dias<sup>2</sup> and Maria Cristina Figueroa Magalhães<sup>1 2</sup>

<sup>1</sup>Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

<sup>2</sup>Hospital Universitário Cajuru, Curitiba, Paraná, Brazil

### \*Correspondence to:

Rafaela Ianisky  
Rua Emiliano Pernetá  
500, Curitiba, Paraná, Brazil  
E-mail: [rafaelaiianisky@gmail.com](mailto:rafaelaiianisky@gmail.com)

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### Abstract

**Background:** Cerebral Venous Thrombosis is an underdiagnosed form of stroke. Its presentation as association of headache with visual symptoms is unusual in literature, particularly in patients without predisposing factors; so, the diagnosis is often delayed, especially by the non-neurologists. The case is discussed in the light of diagnostic challenge and how an understanding of the basic sciences can explain its clinical presentation.

**Methods:** We present a case of a 59-year-old man admitted with severe headache and visual blurring, whose complementary exams confirmed the presence of cerebral venous thrombosis in the cavernous sinuses. For his diagnose, numerous laboratorial and images exams, including contrast-enhanced MRI of the brain were performed. He was handled with dexamethasone and heparin. Later, on further investigation for thrombophilia, it was found a mutation in the prothrombin gene.

**Conclusions:** Less-common diagnoses can be easily missed or delayed if a reasonable suspicion does not exist when considering possible causes. Cerebral venous thrombosis (CVT) is one such uncommon, seldom-considered disease that carries a significant morbidity and mortality. Due to its diversity of signs and symptoms, cerebral venous thrombosis may mimic other diseases. High index of suspicion is very important for a better outcome.

### Keywords

Headache, Cerebrovascular disease, Neuroimaging, Prothrombin, stroke

### Introduction

Cerebral Venous Thrombosis is an underdiagnosed form of stroke [1, 2] representing 0.5% to 1% of cases [2], with higher prevalence in young individuals, particularly women [1]. Headache tends to be the first and most common symptom [3-5]. CVT commonly manifests itself through cerebral syndromes such as isolated intracranial hypertension, focal neurological deficits, epileptic seizures, and decreased level of consciousness [2, 4]. Due to the wide spectrum of presentations and etiologies, the diagnosis is often delayed and confirmed through neuroimaging tests [1, 5]. The general mortality or dependency rate is 15% [6], but male patients, elderly, who have mental status disorder, deep cerebral venous system thrombosis, central nervous system infection, cancer or had intracranial hemorrhage on admission have a more reserved prognosis [7]. Even so, about two thirds recover without sequelae [6], unlike those patients affected by arterial

stroke, in which between one and two thirds are permanently dependent [7].

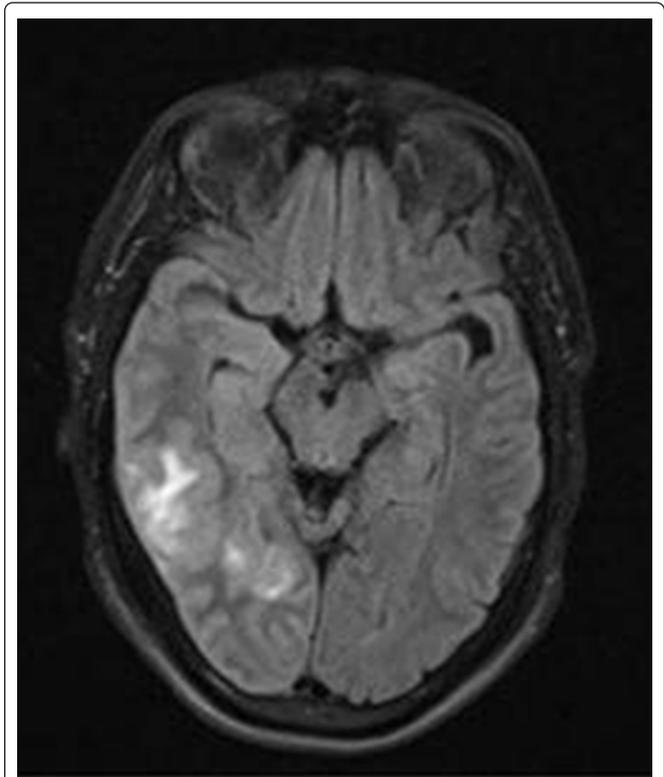
In this article, we report a previously healthy patient admitted with severe headache and visual blurring, whose complementary exams confirmed the presence of cerebral venous thrombosis in the cavernous sinuses. It is hoped that the presentation of this case will draw attention to this rare disease; helping increase clinicians' awareness and highlighting its complex process, given its non-specific and variable clinic. The case report was approved by the Ethics Committee in Research at the Pontifical Catholic University of Paraná on 30th Nov 2020 (No 40225820.6.0000.0020). Written informed consent was obtained from the patient.

## Case Report

A 59-year-old previously fit and well man presented to the emergency department of Cajuru University Hospital due to intense holocranial and periorbital headache, which started thirty days ago. In addition, he had progressive symptoms of metamorphopsia (distorted vision of objects and faces), floaters (small dark spots in vision) and photopsias (perception of flashes of light), and an episode of intense mental confusion, at which point he sought treatment. He did not take any regular medications, had a history of herpes zoster five years earlier, besides migraine since his youth. Moreover, three siblings had meningioma.

He had initially presented to an emergency care unit 15 days prior with fever and headache, where he was diagnosed with lung infection and subsequent urinary tract infection, having undergone home treatment for seven days for each of them. He evolved with improvement in fever after antibiotic therapy, but with permanence of sweating and headache. Later, he developed the ocular symptoms.

On our hospital admission, the patient was Glasgow 15 and afebrile. Clinical and neurological examination were normal, without meningeal irritation. Inspection and palpation did not show suspicious spots on the body or lymph node enlargement. Other systems without noteworthy



**Figure 1:** In the axial section of the brain MRI, one can notice areas of vasogenic edema and zones of nodulariform enhancement, compromising the temporo-occipital transition and the occipital lobe of the right cerebral hemisphere. There is also an extensive component of thrombosis of the transverse and sigmoid sinus at right associated with thickening with pathological enhancement of the tentorium

alterations. The patient remained hospitalized and further investigation was performed. Laboratory tests identified only a hemosedimentation rate of 32 mm (RV: 20 mm) and C-reactive protein of 9.4 mg/L (RV: 3 mg/L). Cytology of the cerebrospinal fluid showed mild lymphocytic pleocytosis, with negative bacterioscopy, culture and fungal tests (Table 1). Investigation with serologies for viral hepatitis, HIV, rheumatoid factor, antinuclear factor, vitamin B12 and TSH resulted in no alterations, as well as an electroencephalogram. The CT scan of the brain showed a poorly delimited hypodense corticosubcortical area in the right temporooccipital region; a contrast-enhanced MRI of the brain confirmed the CVT (Figure 1). Other diagnostic hypotheses such as paraneoplastic syndrome and Whipple's disease were also investigated and ruled out. During the hospitalization period, the headache was responsive to hourly analgesia, but the visual blurriness remained. It was then decided to start dexamethasone, with improvement of symptoms. Full anticoagulation was also performed with enoxaparin associated with warfarin, which was adjusted until the international normalized ratio (INR) reached a target between 2 and 3. Afterwards, the patient was discharged without focal neurological deficits. Outpatient follow-up was maintained and research for genetic mutations and procoagulant factors was performed. The patient presented a mutation in the prothrombin gene, possibly justifying the CVT presentation (Table 2).

**Table 1:** Results of the patient's cerebrospinal fluid examination

	Value found	References values
Proteins	23 mg/dL	20 to 40 mg/dL
Glucose	68 mg/dL	40 to 70 mg/dL
Chloride	125 mEq/L	100 to 106 mEq/L
Lactic Acid	1,7 mmol/L	1,1 to 2,4 mmol/L
RBC Count	53 /mm <sup>3</sup>	0 mm <sup>3</sup>
Leukocyte Count	21 /mm <sup>3</sup>	0 to 5 mm <sup>3</sup>
Neutrophil	1 %	2 a 5 %
Eosinophil	0 %	0 %
Lymphocyte	95 %	50 to 70 %
Monocyte	4 %	30 to 50 %

**Table 2:** The tests confirmed a mutation in the prothrombin gene, possibly justifying the CVT presentation. Anti - thrombin and functional protein C would be probable causes of the CVT if they were below reference values.

Exam	Value found	References values
Factor V Leiden(G1691A)	Normal	Normal
Protrombina (G20210A)	<b>Heterozygous</b>	Normal
Anti - thrombin	139 %	83 to 128 %
Lupic Anticoagulant - AL	1,04	Less than 1,20
Functional C - protein	Exceeding 150 %	70 to 140 %
Functional S - protein	72,0 %	63,5 to 149,0 %
Homocysteine	12,18 $\mu\text{mol/L}$	5,46 to 16,20 $\mu\text{mol/L}$
Anti Cardiolipin IgG	2,3 GPL	Less than 15,0 GPL
Anti Cardiolipin IgM	7,8 MPL	Less than 12,5 MPL

## Discussion

Cerebral venous thrombosis (CVT) is an uncommon form of stroke [1, 3, 8] caused by occlusion of the cerebral sinuses and/or veins by thrombus [2]. Its pathophysiology is still uncertain, but it is believed that from this obstruction, there is an increase in venous pressure, which decreases capillary perfusion, rising cerebral blood volume and dilating cerebral veins. Thus, there is a rupture of the blood-brain barrier and leakage of blood plasma into the interstitial space, causing vasogenic edema [2, 9]. In addition, ischemia damages the energy-dependent pumps of the cell membrane, causing intracellular swelling and cytotoxic edema [2]. The superior sagittal sinus is affected in 70 - 80% of cases, followed by the transverse and sigmoid sinus, and later the cavernous and the rectum [10]. CVT affects about five people in one million each year [8]. In about 80% of the cases, genetic or acquired prothrombotic conditions are found. Some of them are thrombophilia such as hyperhomocysteinemia, factor V Leiden mutation, and prothrombin gene mutation. Besides the use of oral contraceptives, pregnancy and puerperium, neoplasms, infections (otitis, mastoiditis, sinusitis, meningitis), [8] head trauma, vasculitis, antiphospholipid antibody syndrome, and systemic lupus erythematosus [1]. Among these, thrombophilias, which represents 34% of the CVT cases [7], and the use of oral contraceptives stands out. Fact that makes it one of the main risk factors for the development of CVT and explains its higher incidence in young women [2]. Despite all these possible causes, it can go unidentified in 15% of the cases [6]. Cerebral venous thrombosis presents a remarkably broad spectrum of signs and onsets, [3] so its diagnosis is a challenge for the medical team [4, 6, 8]. The most common symptom is headache, present in 90% of cases [2, 4, 8], probably indicative of increased intracranial pressure and distension of the sinus wall caused by local inflammation or blood leakage on

the brain surface [4]. It is described as holocranial, diffuse, and with increasing pain progression over weeks [2, 4, 8] accompanied by other symptoms of intracranial hypertension [4]. In addition, it may mimic migraine, subarachnoid hemorrhage, hypotension, or cerebrospinal fluid hypertension [4]. Other symptoms that may appear are focal or generalized epileptic seizures, seen in 30 - 40% of cases [2, 7], especially in those with upper sagittal sinus involvement [7]. While focal neurological changes are seen in 44% of patients, motor deficit, as hemiparesis, is the most frequent finding, seen in up to 40% of cases [7]. Bousser et al. described four main patterns of presentation of CVT. The most common is characterized by focal deficits and/or focal seizures. It can also appear as intracranial hypertension associated with headache, sixth cranial nerve palsy, and papilledema. Third form is manifest as a subacute encephalopathy, presenting as lowered level of consciousness and seizures, with no apparent signs of intracranial hypertension. Finally, in the last presentation, it can progress gradually and progressively with paralysis of the third to the sixth cranial nerves [9].

Until now, there is no method using clinical scores or conventional neuroimaging to predict brain lesions of CVT and if they can lead to full recovery, unlike certain cases of ischemic infarctions and hematomas [9]. As well as there are no validated pre-test scores or laboratory tests that can confidently rule out CVT [1]. Still, early diagnosis is essential because the potential for recovery is high if appropriate therapeutic measures are taken early in the course of the disease [4, 5]. Whenever a CVT is suspected, an urgent neuroimaging examination is required [1, 5]. Usually, a non-contrasted CT brain scan is the first performed in patients with suspected acute neurological diseases [5, 8,10] but it is found abnormal in only 1/3 of CVT cases [5,8]. Some of the signs that may be present include the "cord sign" - indicating hyper density of the sinuses or cortical veins [2] - and the "empty delta sign" - presents when contrast-enhanced CT is performed, in which an unopacified thrombus is seen surrounded by collateral veins in the sinus wall after contrast injection. [1] Thus, the test of choice for diagnosis and follow-up of CVT becomes magnetic resonance imaging (MRI) associated with magnetic Angio resonance [5, 6]. In MRI, the direct image of thrombosis changes with time. In the first few days, the diagnosis is hard, with an isointense signal on T1- weighted images and a hypointense signal on T2-weighted images. A few days later, the diagnosis becomes obvious, with an increased signal of the thrombus on T1- and T2- weighted images. After the first month, the diagnosis may again be difficult due to a variable signal pattern. MRI is also able to show parenchymal lesions secondary to venous occlusion: simple cerebral edema with normal signal, infarction or hemorrhagic infarction with increased signal on both sequences [5]. Intra-arterial angiography provides better details of the cerebral veins and is therefore useful in the diagnosis of rare cases of isolated cortical vein thrombosis without sinus thrombosis [2]. However, it should be reserved for cases with inconclusive or contradictory findings on other imaging modalities, to exclude a dural arteriovenous fistula, or when endovascular therapeutic intervention is planned [1]. The priority of treatment in the

acute phase is to stabilize the patient's condition and prevent or reverse the brain herniation [2]. In some cases, the use of intravenous mannitol, surgical removal of the hemorrhagic infarct, or decompressive hemicraniectomy is necessary [2]. Corticosteroids can decrease vasogenic edema but can also increase hypercoagulability [8]. Anticoagulation with heparin is performed to interrupt the thrombotic process and prevent a possible pulmonary embolism [2]. Generally, vitamin K antagonists are administered for six months after a first episode of thrombosis, or longer in the presence of predisposing factors, with a target international normalized ratio (INR) of 2. [2, 9] in patients with a poor prognosis, [1, 2] endovascular thrombolysis can be an alternative performed in specialized centers. A thrombolytic enzyme, usually urokinase, is administered to the affected sinus followed by mechanical thromboaspiration [2]. The case presented here reiterates the variability in the presentation of CVT and illustrates how patients with no apparent risk factors can develop it. Therefore, this diagnostic hypothesis should be considered by the medical team when facing neurological conditions with no defined cause. Moreover, due to its diversity of signs and symptoms, its condition may mimic other diseases and thus delay the appropriate treatment, potentially worsening the patient's prognosis.

## Conflicts of Interest

Authors declare no conflict of interest.

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