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Subjective Visual Complaints After Cerebral Venous Thrombosis

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THESIS OUTLINE

This Master thesis in Medicine consists of an Original Scientific Article, written between March 2019 and November 2019, with bibliographic research until September 2019.

This article was written with the goal of submission to the Journal of Stroke and Cerebrovascular Diseases. Therefore, the instructions for the authors of this journal were followed and are presented in Appendix 1.

RESUMO

Introdução

Na avaliação inicial de doentes com diagnóstico provável de trombose venosa cerebral, os sintomas visuais são muitas vezes negligenciados e subvalorizados. O objetivo deste trabalho é descrever as alterações visuais encontradas antes e após o diagnóstico de trombose venosa cerebral. Adicionalmente, abordamos outras manifestações clínicas, fatores de risco, meios de diagnóstico, tratamento e seguimento destes doentes.

Métodos

Neste trabalho, realizámos um estudo retrospetivo de doentes internados no Serviço de Neurologia do Centro Hospitalar e Universitário de Coimbra, Portugal, entre dia 1 de janeiro de 2012 e 31 de maio de 2019, diagnosticados com trombose venosa cerebral. Foram recolhidas múltiplas variáveis, incluindo dados demográficos, fatores de risco, sinais e sintomas, meios de diagnóstico, tratamento e seguimento. Focámo-nos principalmente nas alterações visuais destes doentes e para isso recolhemos informações relativas à função visual tanto na fase aguda como na crónica.

Resultados

Durante o seguimento, foram identificadas alterações visuais em 25 doentes (19.1%), tendo estas surgido 22.43 meses (DP 19.59) após o diagnóstico. A presença de papiledema, diminuição da acuidade visual, zumbidos pulsáteis, e obscurações visuais transitórias na fase aguda associaram-se a maior prevalência de alterações visuais durante o seguimento. Nos casos em que houve transformação hemorrágica ou na ausência de recanalização total, verificou-se maior prevalência de alterações visuais durante o seguimento.

Conclusão

As alterações visuais, ainda que subvalorizadas, são comuns na fase aguda e crónica da trombose venosa cerebral. Algumas particularidades clínicas podem predizer a sua ocorrência na fase crónica, podendo mesmo possibilitar um diagnóstico mais precoce e melhor orientação terapêutica.

Palavras-Chave: *Trombose venosa cerebral, hipertensão intracraniana, perda visual, papiledema, neuro-oftalmologia*

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Subjective Visual Complaints After Cerebral Venous Thrombosis

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ABBREVIATIONS

APLS: antiphospholipid syndrome

CT: computed tomography scan

CTV: computerized tomography venography

CVT: cerebral venous thrombosis

DSA: digital cerebral angiography

ICH: intracranial hypertension

INR: international normalized ratio

ISCVT: International Study on Cerebral Vein and Dural Sinus Thrombosis

LMWH: low-molecular weight heparin

MRI: magnetic resonance imaging

MRV: magnetic resonance venography

mRS: modified Rankin Scale

MTHFR: methylenetetrahydrofolate reductase

NOACs: new oral anticoagulants

OR: odds ratios

PAI: plasminogen activator inhibitor

SSS: superior sagittal sinus

VTE: venous thromboembolism

ABSTRACT

Introduction

In the evaluation of a patient with a probable diagnose of cerebral venous thrombosis, visual symptoms are often overlooked and undervalued. We sought to describe visual complaints in patients diagnosed with cerebral venous thrombosis, both in acute and chronic phases. Additionally, we report clinical features, risk factors, imaging techniques, treatment and follow-up of those patients.

Methods

We conducted a retrospective study of consecutive patients admitted to the Neurology department of Coimbra University and Hospital Centre, Portugal, between January 1st, 2012 and May 31st, 2019, diagnosed with cerebral venous thrombosis. We collected multiple variables comprising demographics, risk factors, clinical features, diagnostic tools, therapeutic approaches and follow-up. Our main focus was the study of visual impairment and to do so, we reviewed clinical information regarding visual function in the acute and chronic phases.

Results

Visual features were identified during follow-up in 25 patients (19.1%). The mean time of onset of visual alterations was 22.43 months (SD 19.59) after diagnosis. The presence of papilledema, visual loss, pulsatile tinnitus and transitory visual obscurations in acute phase predicted the existence of visual changes on follow-up. The presence of hemorrhagic infarction at baseline and the absence of total venous recanalization on follow-up favored the existence of visual abnormalities post-cerebral venous thrombosis.

Conclusion

Visual changes, although usually overlooked, are quite common in acute and chronic phases of cerebral venous thrombosis. Specific clinical particularities may predict their occurrence in chronic phase, possibly allowing early diagnosis and directed treatment approaches.

Key Words: *Cerebral venous thrombosis, intracranial hypertension, visual loss, visual impairment, papilledema, neuro-ophthalmology*

INTRODUCTION

Cerebral venous thrombosis (CVT) results from thrombosis of the cerebral venous system [1]. It can have immediate consequences, like edema, hemorrhage and infarction, or more dreaded ones, like intracranial hypertension (ICH) that can lead to papilledema and other neurological signs and symptoms [2].

Though uncommon, CVT is an important cause of stroke, accounting for about 0.5 to 1% of all strokes in the adult population [3] and its incidence appears to be growing [4]. In a cooperative study of Neurology centers in Portugal, it was reported an annual incidence of 0.22 per 100,000 [5]. However, the true prevalence may be substantially higher, because some cases go undetected due to its unpolished clinical manifestations [6]. CVT may be observed in all age groups, but it is more common between the ages of 20-50 and there is a clear female predominance [7, 8].

Although there are some discrepancies in etiology [1, 9], several risk factors are present most of the times [6] and in about 85% of the cases, at least one risk factor can be found. The most frequent are gender-specific risk factors, such as oral contraceptives, puerperium, pregnancy and hormonal replacement therapy; genetic or acquired prothrombotic disorders; infections; inflammatory diseases and malignancies [2, 5, 8, 10, 11].

The clinical presentation varies [10, 12] and the mode of onset can be acute, subacute or chronic. The signs and symptoms are not specific and may resemble other cerebral diseases. These can be grouped as four major different syndromes, which can appear separately or combined: isolated intracranial hypertension, focal neurologic abnormality, seizures and encephalopathy [5, 10]. Isolated intracranial hypertension commonly leads to a broad spectrum of visual symptoms, including visual transitory obscurations, metamorphopsia, visual field defect, and, in more chronic and later presentations, papilledema and decreased visual acuity [13, 14]. The intracranial pressure will be higher if the extent of thrombosis is greater and if there is a parenchymal lesion [15]. On the physical examination, some fundus changes can occur which will be evidenced as papilledema, optic disc hemorrhage, retinal hemorrhage, retinal varices, macular edema and optic atrophy [3, 16]. Encephalopathy is the most severe syndrome as it can lead to herniation, which is the major cause of death in CVT [17].

In order to avoid misdiagnosis, a high clinical suspicion must be allied with accurate imaging techniques [5, 12]. This can be done using cranial computed tomography scan (CT), computerized tomography venography (CTV), magnetic resonance imaging (MRI), magnetic resonance venography (MRV) and digital cerebral angiography (DSA) [3]. There is no laboratory test to establish the diagnosis of CVT. D-dimer measurements may be used, but still, they produce both false positive and false negative results [3,6,10,18].

The initial approach should be broad and cover not only antithrombotic and symptomatic treatment, but also prevention and treatment of associated conditions, risk factors, complications and advising on a healthy lifestyle [10]. Regarding anticoagulation, the recommended treatment in the acute phase is heparin, preferably low-molecular weight heparin (LMWH), if there is no contraindication against it [19]. Once the patient is clinically stable, there should be a switch to warfarin. Some new oral anticoagulants (NOACs), such as dabigatran and apixaban, are apparently safe and effective as an alternative [19, 20]. They have been used off-label over the last years but, until further studies, they should not be prescribed [21]. It is generally recommended that oral anticoagulation is maintained for 3 to 12 months, aiming an international normalized ratio (INR) of 2-3 [10, 19, 22]. If oral anticoagulation fails to dissolve the venous clot, direct endovascular thrombolysis or mechanical thrombectomy could be considered [23]. In case there is increased intracranial pressure, it can be rapidly relieved by a therapeutic lumbar puncture, ventricular shunting, or by taking acetazolamide [6, 24, 25]. A complete neuro-ophthalmological evaluation, covering visual acuity and visual field testing, should be performed in patients with papilledema or visual complaints [26]. After the treatment, an underlying etiology, such as thrombophilia, should be searched, since it increases the risk of recurrence [23, 27].

As for the prognosis, CVT has been known to be an “all or nothing disease”, since it evolves either to complete recovery or death [8, 28]. Usually, CVT has a favorable prognosis with death rates ranging from 4-8% [29, 30], most of which occur during acute phase. Severe visual loss, though rare, is a problem. Resorting the use of optical coherence tomography, significantly axonal loss was demonstrated in CVT patients despite having bilateral vision 10/10, normal fundoscopy and visual field tests, probably as a result of subclinical increased intracranial pressure and chronically undetected papilledema [22, 31].

While papilledema and other ocular symptoms seem to be common in CVT, the literature does not include detailed account on ocular manifestations and there are scarce case reports. Hence, the real incidence of visual loss after CVT is still unknown. Besides, unlike idiopathic intracranial hypertension, which has a straight and well described correlation with visual loss, a reason was not found to why and how this happens in CVT-related intracranial hypertension [32]. Therefore, many physicians are performing off-label approaches to deal with visual impairment during the follow-up of CVT.

In this study, we describe visual complaints in patients diagnosed with CVT, both in acute and chronic phases. Additionally, we report clinical features, risk factors, imaging techniques, the treatment and the follow-up of those patients.

METHODS

This is a retrospective study of consecutive patients admitted to the emergency department of Coimbra University and Hospital Centre, Portugal, between January 1st, 2012 and May 31st, 2019, diagnosed with cerebral venous and dural sinuses thrombosis.

All clinical records were carefully reviewed, including demographics, initial clinical signs and symptoms, radiological evaluations, etiological factors, acute and maintenance treatments, and follow-up results, regarding not only motor function, but also visual outcome. Specifically, data regarding subjective visual complaints following a CVT diagnose was actively searched, not only on neurology follow-up appointments, but also in family doctor appointments. Additionally, ophthalmology and neuro-ophthalmology referrals were reviewed.

The diagnosis of CVT was documented based on both clinical presentation of the patients and detection of thrombosis in cerebral venous sinuses on cranial computed tomography scan (CT), computerized tomography venography (CTV), magnetic resonance imaging (MRI), magnetic resonance venography (MRV) and digital cerebral angiography (DSA), according to established diagnostic criteria [33].

The type of onset was considered acute if the duration of the symptoms was less than 72 hours on admission, sub-acute if the duration was between 72 hours and 1 month, and chronic if the symptoms persisted for longer than 1 month. A list of associated illnesses or conditions that might predispose to CVT was registered. Clinical symptoms and signs were recorded, including headache, seizures, altered consciousness, visual field disturbances, cranial nerve involvement and focal neurological deficits, such as hemiparesis or hemiplegia. The number of involved sinuses or veins, location of thrombus and lesions at admission on imaging techniques such as presence of parenchymal involvement, ischemic infarction, hemorrhagic infarction or ICH were obtained. All treatment modalities and duration were recorded, based on physician's preference. Since the frequency and etiology of CVT may vary according to sex and age, patients were compared by sex and age groups for clinical symptoms, etiological factors, vascular involvement, and frequency of parenchymal involvement. Patients were divided into 2 categories: under and over 55 years of age, regarding postmenopausal period.

Functional outcome in the follow-up was categorized with the modified Rankin Scale (mRS). Patients with mRS scores of 0-1 were classified as independent (favorable outcome), mRS score of 2 as minimal disability, and mRS scores of 3-6 as dependent or dead (poor outcome). Follow-up visits were recorded after 3, 6 and 12 months after the initial diagnosis of CVT.

Visual Function outcome was assessed through patient's complaints and clinical assessments reported in follow-up visits, such as new-onset monocular or binocular vision loss and visual

field defect. Additionally, disk optic abnormalities in follow-up visits were also identified, including papilledema and optic disk atrophy.

Our Local Ethics Hospital Committee approved the study protocol. Informed Consent was not collected as it was a retrospective study and all patient information was kept anonymous, respecting all ethic and deontological aspects.

Statistical Methods

Continuous data were summarized as mean ± standard deviation or median with interquartile range, and categorical data were presented as frequency and percent. Independent sample t-test was used to compare groups for continuous variables. Categorical data were analyzed by using Pearson chi-square or likelihood ratio test statistics. Odds ratios (OR) were calculated for the possible prognostic factors using the multivariate logistic regression analysis.

RESULTS

A total of 136 patients were diagnosed with CVT between January 1st, 2012 and May 31st, 2019. A total of 130 patients were enrolled (mean age 43.75, SD 16.86, range 17-86 years, 34 males [26.0%]), and six patients were excluded, as their data were inconclusive.

The female rate was 73.3% in general population, whereas the percentage of male patients was higher in the older age group (63.6%).

Acute mode of onset is the most common setting, regardless of the age group (55.6% in patients younger than 44 years old, 56.0% in 44 – 54 years old patients and 54.5% in patients older than 55 years).

Clinical and Neuroimaging Features

The onset mode was acute in 72 patients (55.0%), sub-acute in 49 (37.4%), and chronic in 9 (6.9%) (Table I and Figure 1).

Table I. Number of cases according to age group, mode of onset and gender.

		Gender				**Total**	
		Female		Male			
		n	%	**n**	%	**n**	%
Age Group	18 - 54	**81**	83.5	**11**	33.3	**92**	70.77
	≥55	**16**	16.5	**22**	66.7	**38**	29.23
Mode of Onset	Acute	**54**	55.7	**18**	54.5	**72**	55.38
	Sub-acute	**40**	41.2	**9**	27.3	**49**	37.69
	Chronic	**3**	3.1	**6**	18.2	**9**	6.92

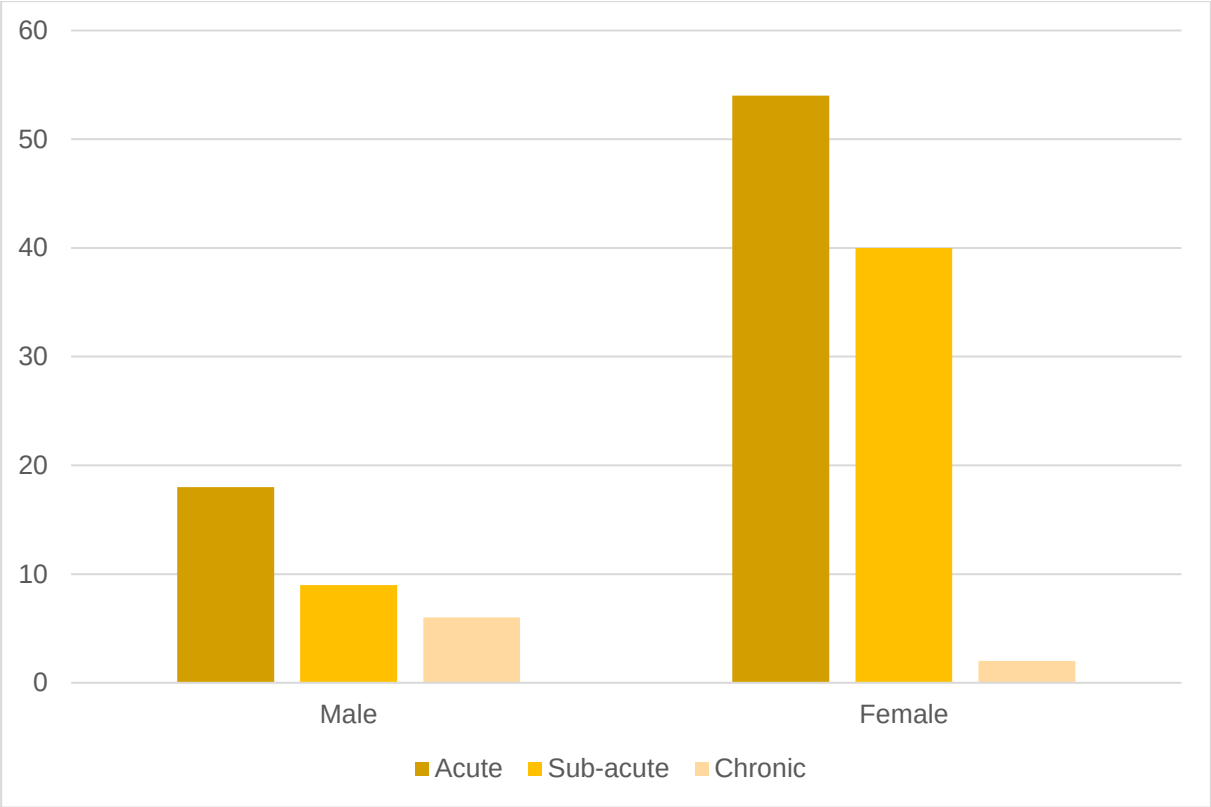

Figure 1. Mode of onset according to gender.

The median delay from onset of symptoms to diagnosis was 3 days (mean 7.85; SD 17.75 days).

The most common symptoms were headache (n=108 cases; 83.1%) and epileptic seizures (n=19, 14.6%), while the most frequent signs on neurological exam were motor weakness (n=38, 29.2%) and papilledema (n=31, 23.8%) (Table II and Figure 2 and 3).

Table II. Clinical symptoms and signs of CVT.

		Gender				
		Female		Male		
		n	%	**n**	%	p
Clinical Symptoms	Headache	**83**	86.5	**25**	73.5	0.085
	Diplopia	**7**	7.3	**2**	5.9	0.783
	Transitory Visual Obscurations	**1**	1.0	**1**	2.9	0.865
	Pulsatile Tinnitus	**13**	13.5	**2**	5.9	0.775
	Epileptic Seizures	**16**	16.7	**3**	8.8	0.187
Clinical Signs	Altered consciousness	**14**	14.6	**5**	14.8	0.995
	Papilledema	**24**	25.0	**7**	20.6	0.607
	Language deficit	**14**	14.6	**8**	23.5	0.235
	Motor weakness	**28**	29.2	**10**	29.4	0.979
	Visual Field Defect	**7**	7.3	**3**	8.8	0.775

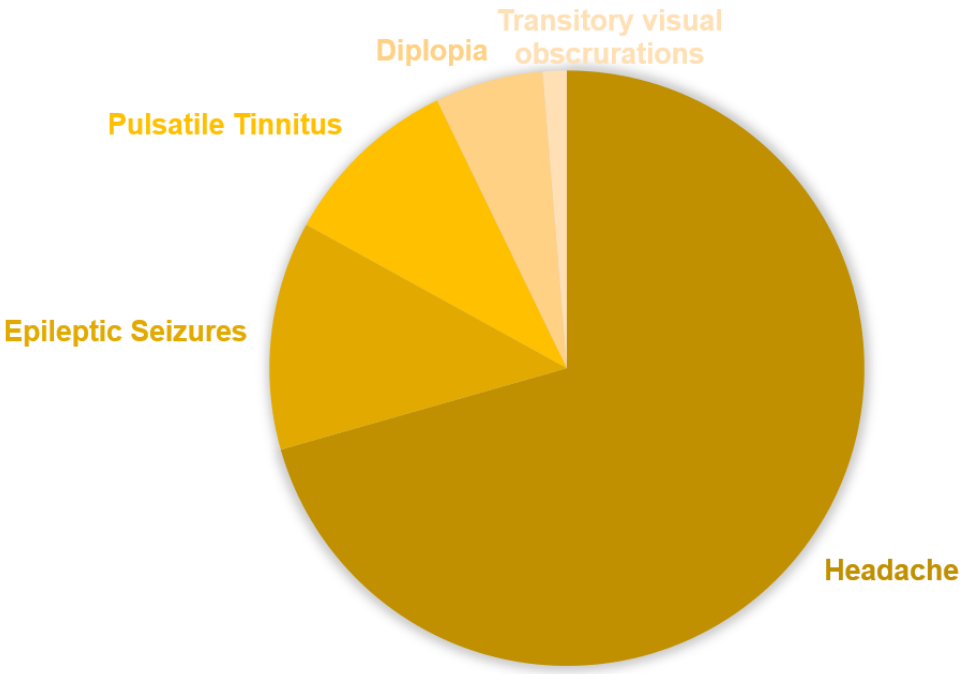

Figure 2. Clinical symptoms of CVT.

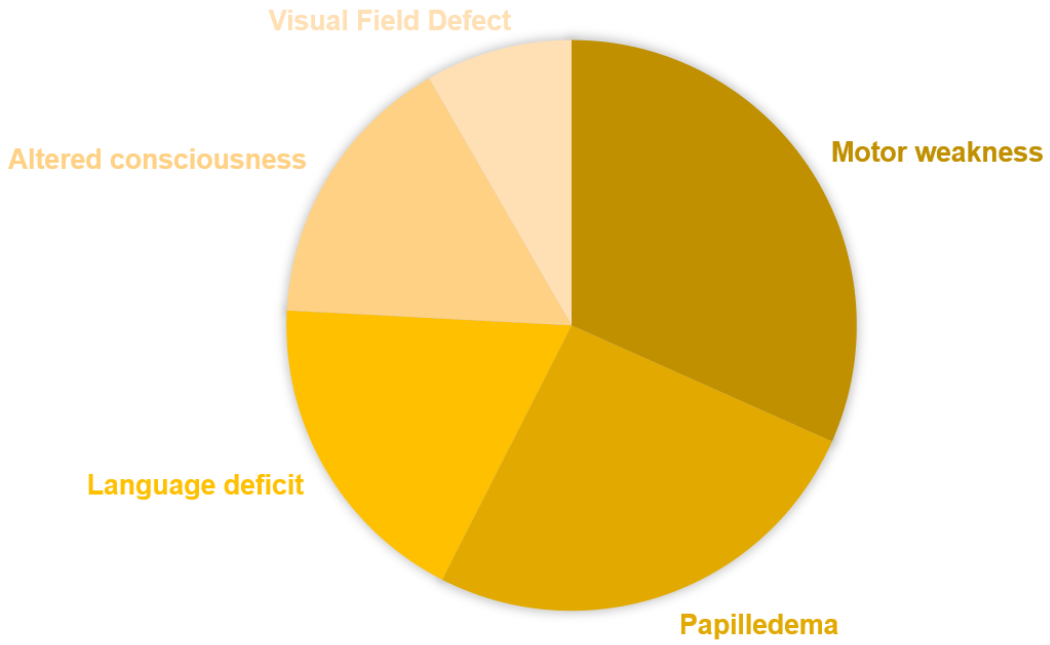

Figure 3. Clinical signs of CVT.

The first approach to diagnosis of CVT was established by cranial MRI/MRV in 9 patients (6.9%), by CTV in 30 (23.1%), and by cranial CT in 88 patients (67.69%).

Radiological imaging revealed parenchymal lesions in 50 patients (38.46%). From those, 26 (20.0%) had infarction at diagnosis, and 24 (18.46%) had hemorrhagic transformation. Parenchymal lesion involvement was observed in all group ages in a similar fashion (Table III).

Table III. Parenchymal involvement in CVT.

	Group Ages			
	18 - 49		**≥ 50**	
	n	%	**n**	%
Parenchymal infarction	**16**	17.4	**10**	26.3
Hemorrhagic infarction	**16**	17.4	**12**	31.6

Venous involvement was found in 1 sinus in 34 patients (26.0%), in 2 sinuses in 49 patients (37.4%) and in more than 2 sinuses in 42 patients (32.1%). More than half of the patients had multiple sinuses involved. The transverse sinus, either isolated or in multiple involvement, was the most common site of thrombosis (76.2%, n = 99), followed by the sigmoid sinus (56.2%, n = 73) and the superior sagittal sinus (SSS) (43.8%, n = 57). By location, 11 patients (8.46%) had thrombosis in isolated transverse sinus, 14 (10.8%) in isolated SSS, 3 (2.3%) in isolated sigmoid sinus, and 12 (9.2%) in isolated cortical venous thrombosis (Table IV). There were no sex differences in terms of the involvement of the sinuses (P = .271).

Table IV. Imaging techniques performed, number of sinus involved, site of thrombosis and parenchymal involvement.

		Gender				
		Female		Male		
		n	%	n	%	Total
Radiological Work-up	Cranial CT	**86**	89.6	**2**	5.9	**88**
	Cranial CTV	**7**	7.3	**23**	67.6	**30**
	Cranial MRI	**3**	3.1	**4**	11.8	**7**
	Cranial MRV	**0**	0	**2**	5.9	**2**
Number of Sinuses Involved	1 sinus	**23**	24.0	**11**	32.4	**34**
	2 sinuses	**35**	36.5	**14**	41.2	**94**
	> 2 sinuses	**35**	36.5	**7**	20.6	**42**
Sinuses	Transverse Sinus	**68**	70.8	**31**	64.7	**99**
	Superior Sagittal Sinus	**43**	44.8	**14**	41.2	**57**
	Sigmoid Sinus	**56**	58,3	**17**	50.0	**73**
	Cortical Veins	**21**	21.9	**5**	14.7	**26**
	Cavernous Sinus	**2**	2.0	**1**	2.9	**3**
	Internal Jugular Veins	**45**	46,9	**18**	52.9	**63**
	Deep veins	**17**	17.7	**4**	11.8	**21**
Parenchymal Involvement	No lesion	**76**	79.2	**28**	82.4	**104**
	Infarction	**20**	20.8	**6**	17.6	**26**
	Hemorrhagic infarction	**20**	20.8	**4**	11.8	**24**
	Intracerebral hemorrhage	**1**	1.0	**3**	8.8	**4**

During the follow-up, 77 patients (56.15%) repeated neuroimage: 14 patients (11.0%) were submitted to a new brain CT, 32 (24.4%) to CTV, 21 (16.0%) to MRI, 7 (5.3%) to MRV, and 3 (2.3%) to DSA. From those, only 1 had a complete resolution of CVT, 15 had a partial recanalization and 1 patient had no change regarding CVT. The second exam was performed in a mean time of 7.32 months (SD 6.37) after CVT diagnosis. Regarding CVT status, 45 patients (34.4%) had a partial recanalization, 23 (17.6%) had a complete resolution, and 9 (4.6%) had no change regarding CVT.

Etiology and Risk Factors

Among our study population, gynecological causes comprised the majority of possible causes identified (60.8%), including 74 patients (56.92%) using oral contraceptives, 2 patients (1.54%) in puerperium, and 3 patients (2.30%) on hormone substitution therapy. A positive previous history of deep venous thromboembolism was observed in 3 cases (2.3%). In 26 patients (20.0%), prothrombotic conditions were found. These causes included methylenetetrahydrofolate reductase (MTHFR) homozygote mutation in 6 patients (4.61%); prothrombin gene mutation in 1 (0.73%), and plasminogen activator inhibitor (PAI) mutation in 1 (0.73%); protein S or protein C deficiency in 3 patients (2.17%); activated protein C resistance in 1 (.73%); and antithrombin III deficiency in 1 (.73%).

Fourteen patients (10.77%) were malignancy related. The most frequent malignancies consisted of breast cancer in 8 patients, hematological malignancies in 7 patients, colon cancer in 4 patients, central nervous system malignancy in 4 patients, and lung cancer in 3 patients. History of malignancy was found to be significantly higher in cases involving patients over 50 years old ($P < .001$) (Table V). In 10 patients (7.69%) a mechanical precipitant was found. Seven patients (8.1%) were diagnosed with a paracranial infection, including sinusitis, otitis media, and mastoiditis. In 8 patients (6.15%) there was a systemic infection (Table V).

Table V. Etiology and risk factors.

	Age Group			
	18 - 54		≥ 55	
	n	%	n	%
Gynecological causes				
Oral contraceptive use	72	78.3	2	5.3
Puerperium	2	2.2	0	0
Hormone substitution therapy	2	2.2	1	2.6
Smoking	**16**	17.4	**4**	10.5
Infections				
Paracranial	6	6.5	1	2.6
Systemic	6	6.5	2	5.3
History of VTE				
Deep venous thrombosis	1	1.1	2	5.3
Cerebral venous thrombosis	1	1.1	0	0
Malignancy	**4**	4.3	**10**	26.3
Mechanical precipitant				
Lumbar puncture	4	4.3	0	0
Traumatic brain injury	4	4.3	3	7.9
Jugular vein puncture	0	0	1	2.6
Prothrombotic causes				
MTHFR mutation homozygote	3	3.26	3	7.89
Hyperhomocysteinemia	2	2.17	1	2.63
Prothrombin mutation	1	1.1	0	0
Protein C/ S deficiency	3	3.26	0	0
PAI mutation	1	1.1	0	0
Antithrombin III deficiency	1	1.1	0	0
Activated protein C resistance	1	1.1	0	0

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; PAI, plasminogen activator inhibitor; VTE, venous thromboembolism.

Treatment

All patients started anticoagulation therapy: 109 patients (83.85%) with warfarin, 16 (12.31%) with NOACs, and 5 patients (3.85%) with acenocoumarol. Regarding the duration of the treatment, 42 patients (32.31%) were under anticoagulation for 6 months, 53 (40.77%) for a year, and 35 patients (26.92%) were anticoagulated for over a year.

Functional Outcome

Functional outcome was assessed with Modified Rankin Scale (mRS) within one, three and twelve months after the diagnosis. At one month post-diagnose, 92 patients (93.8%) had mRS 0-1, 3 patients (2.3%) had mRS 2, and 5 patients (3.9%) had mRS 3-5. In the follow-up, there was a tendency to motor improvement (Table VI).

Table VI. Functional Outcome according to mRS scale.

	Group Ages			
	18 - 49		≥ 50	
	n	%	**n**	%
1 month mRS				
0-1	**88**	95.7	**33**	89.5
2	**1**	1.1	**2**	5.3
3-6	**3**	3.3	**2**	5.3
3 months mRS				
0-1	**90**	97.8	**35**	92.1
2	**1**	1.1	**1**	2.6
3-6	**1**	1.1	**2**	5.3
6 months mRS				
0-1	**90**	97.8	**35**	92.1
2	**1**	1.1	**2**	5.3
3-6	**1**	1.1	**1**	2.6
12 months mRS				
0-1	**91**	98.9	**38**	100
2	**0**	0	**0**	0
3-6	**1**	1.1	**0**	0

Patient's age was a determinant factor regarding motor outcome, as younger patients had a more favorable outcome (p=.076).

Patients presenting motor weakness (B=0.155, 95% CI -0.013 – 0.322, p=0.070) and impaired consciousness (B=0.445, 95% CI 0.297 – 0.594, p<0.001) had a worse motor outcome.

Regarding venous sinus impairment, patients with circumflex, transverse and lateral sinuses involvement had a worse 1-year outcome.

Visual Outcome

During follow-up, visual symptoms or signs were identified in 25 patients (19.1% from total population). From those, 4 patients (3.1%) had a monocular vision loss, 7 (5.3%) had a visual field defect, 2 (1.6%) had optic disc atrophy, 4 (3.1%) complained about binocular vision loss, and 12 patients (10.1%) had papilledema (Table VII and Figure 4). The mean time of onset of visual signs and symptoms was 22.43 months (SD 19.59) after CVT diagnosis.

Table VII. Visual signs and symptoms prevalence after CVT treatment.

	Group Ages			
	18 - 49		≥ 50	
	n	%	**n**	%
Visual symptoms				
Visual fields defects	**4**	4.3	**3**	7.9
Monocular vision loss	**2**	2.2	**2**	5.3
Binocular vision loss	**3**	3.3	**1**	2.6
Visual signs				
Papilledema	**7**	7.6	**5**	13.2
Optic disk atrophy	**0**	0	**2**	5.3

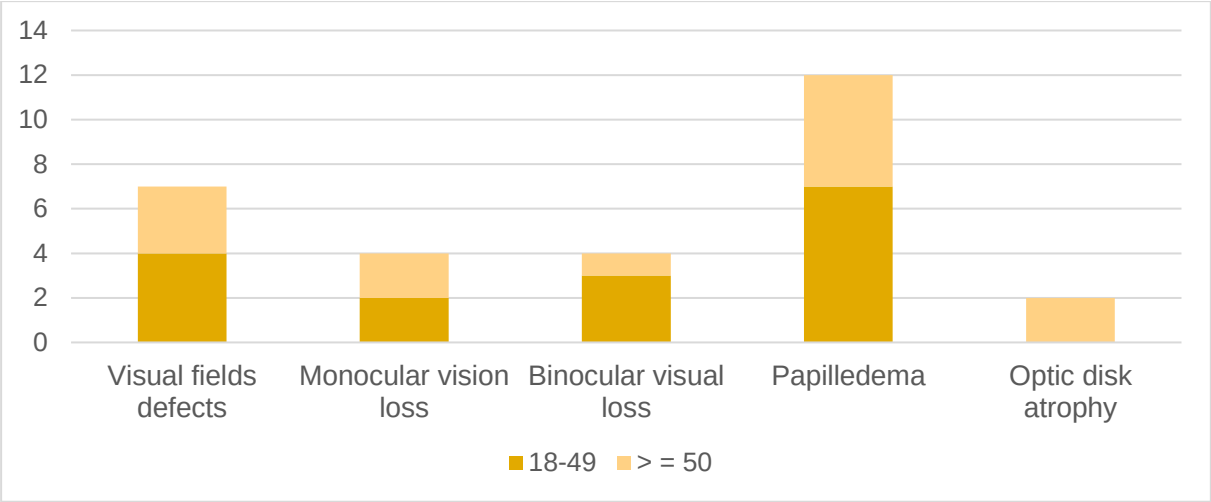

Figure 4. Visual signs and symptoms prevalence after CVT treatment according to age group.

Patients with visual complaints on follow-up had a lower CVT imagiological resolution rate than patients without visual complaints (Table VIII and Figure 5).

Table VIII. Visual symptoms in second neuro-imaging results (n=77).

	With visual symptoms		**Without visual symptoms**		**p**
	n	**%**	**n**	**%**	
CVT total resolution	1	4.0	22	21.0	**<0.001**
Partial recanalization	17	68.0	28	26.7	**0.001**
No changes	2	8.0	7	6.7	0.782

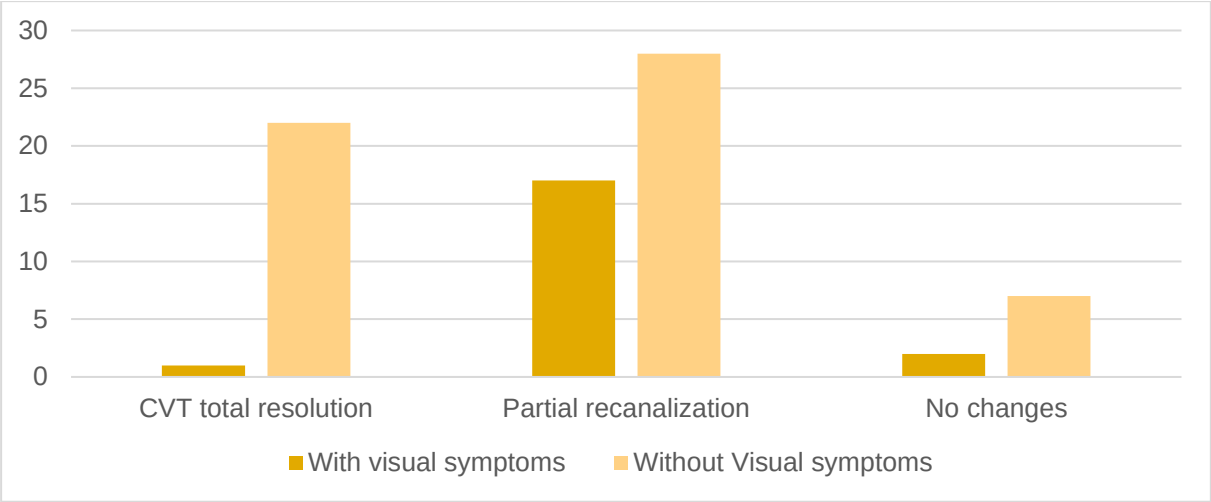

Figure 5. Visual symptoms and signs in second neuro-imaging results.

The presence of papilledema, visual loss, pulsatile tinnitus and transitory visual obscurations in acute phase predicts the existence of visual changes such as new-onset monocular or binocular vision loss, visual field defects papilledema and/or optic atrophy on follow-up. Imagiological evaluation may also aid to predict visual outcome: the presence of hemorrhagic infarction at baseline and the absence of total venous recanalization on follow-up favor the existence of visual abnormalities post-CVT (table IX). There are no specific guidelines for the treatment of papilledema in the context of CVT. For that reason, the treatment performed was individualized based on the best clinical evidence.

Table IX. Univariate Binary Logistic Regression for Predictors of Visual Outcome.

	Total Population (n=130)	Univariate association with visual symptoms/signs β (95% CI)	P Value
Age, y, mean ±SD	43.75 ± 16.86	1.004 (0.978 – 1.030)	0.767
Female gender, n (%)	97 (74.61)	0.664 (0.256 – 1.722)	0.400
Headache, n (%)	108 (83.08)	1.086 (0.333 – 3.548)	0.891
Altered consciousness, n (%)	19 (14.62)	0.450 (0.114 – 1.779)	0.255
Motor weakness, n (%)	38 (29.23)	0.545 (0.188 – 1.579)	0.264
Papilledema at onset, n (%)	31 (23.85)	4.178 (1.651 – 10.576	**0.003**
Vision loss at onset presentation, n (%)	13 (9.9)	4.421 (1.337 – 14.620)	**0.015**
Pulsatile Tinnitus at onset, n (%)	15 (11.54)	0.999 (0.998 – 1.000)	**0.021**
Transitory Visual Obscurations at onset, n (%)	2 (1.54)	0.999 (0 .998 – 1.000)	**0.015**
Superior Sagittal Sinus n (%)	57 (43.85)	1.835 (0.761 – 4.426)	0.176
Transverse Sinus n (%)	99 (76.15)	2.000 (0.692 – 5.777)	0.200
Sigmoid Sinus n (%)	73 (56.15)	1.216 (0.500 – 2.953)	0.667
Venous infarction n (%)	26 (20.0)	0.133 (0.017 – 1.036)	0.054
Hemorrhagic infarction n (%)	24 (18.46)	0.120 (0.016 – 0.933)	**0.043**
1 month mRS, mean ±SD	0.42 ± 0.82	1.045 (0.624 – 1.749)	0.868
Partial recanalization (follow-up neuroimaging) n (%)	45 (34.62)	5.869 (1.548 – 22.251)	**0.009**
Complete CVT resolution (follow-up neuroimaging) n (%)	23 (17.69)	0.084 (0.010 – 0.670)	**0.019**

DISCUSSION

We were able to gather data from 130 patients that were admitted to Coimbra University and Hospital Centre, and evaluated initial clinical signs and symptoms, radiological findings, etiological factors, acute and maintenance treatments and follow-up results, regarding both motor function and, most importantly, visual outcome. To the best of our knowledge, the present study is the biggest retrospective study to be done on this subject. Key take-home points from this study are as follows.

In our population, the most affected age group was from 18 to 55, accounting for 70.77% of cases. Besides, we found a female predominance of 73.3%, which is likely related to gender specific risk factors, such as oral contraceptive use, pregnancy and puerperium [8]. Therefore, as previous studies have reported [7, 8, 10, 11, 34], we concluded that CVT affects mostly young and middle-aged females, being infrequent in older patients. Thus, unlike other subtypes of stroke, its incidence seems to decrease with age.

As for the onset mode, the most common was acute (55.0%) and the less common was chronic (6.9%). In another study, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), symptoms onset was most commonly sub-acute [3, 28]. This difference can be explained based on the time interval we used to classify these events. Whereas we considered type of onset as acute if duration of symptoms was less than 72 hours on admission, ISCVT considered it was less than 48 hours. Thereupon, more patients were classified as acute in our study. Besides, we must consider that Coimbra's Hospital receives emergency cases from all over central region of the country and, for that reason, the rate of acute cases is much higher.

Regarding initial symptoms, headache was by far the most frequent (83.1%). These results were consistent with other studies [28, 34, 35]. This symptom has no characteristic pattern and for that reason it is not distinguishable from other primary or secondary headaches [6, 34]. Therefore, when a patient presents a headache, it is important to establish early and differential diagnosis, making use of different complementary diagnostic tests [5]. Moreover, as shown in our study, papilledema is also highly prevalent, affecting almost one-fourth of the patients. Papilledema consists on the swelling of the optic disc, and it can be identified by fundoscopy [21]. Just as headache, it may also be the first manifestation of CVT. Even so, we must keep in mind that it is neither sensitive nor specific [5, 22]. It takes time to develop and, for this reason, it is present in only 50% of the patients at the time they seek medical help [21]. The most common site of venous thrombosis in patients with papilledema is within the junction of the transverse and sigmoid sinus [36]. Besides papilledema, an increased intracranial pressure may manifest with other visual alteration such as blurred vision and diplopia, due to sixth

cranial nerve palsy [31, 32]. If intracranial pressure remains high, there's a risk of visual loss and, therefore, it should be promptly treated with acetazolamide [6, 25]. This drug has shown great results on improving visual fields and retinal nerve fiber layer thickness on optical coherence tomography in other entities such has idiopathic intracranial hypertension [37, 38].

Most of the risk factors are present in the adult life [32]. Evidence has shown that there are many risk factors associated with this condition, including coagulopathies, oral contraceptive use, pregnancy, puerperium, systemic or intracranial infections, trauma, lumbar puncture, malignancy, other thromboembolic events, severe dehydration, connective tissue diseases, nephrotic syndrome, and inflammatory diseases, such as Behçet disease and sarcoidosis [2, 3, 5, 8, 10, 23, 39]. Among our study population, gynecological causes comprised most of the possible causes identified (60.8%). In addition, one fifth of the patients had prothrombotic conditions, such as MTHFR homozygote mutation, prothrombin gene mutation, PAI and antithrombin III deficiency. Moreover, 14 patients (10.77%) were malignancy related. Other data showed that a history of cancer increases the risk of CVT, approximately fivefold [11]. Thence, search for an occult neoplasm should be considered, especially in an elderly patient, since CVT can be the first manifestation of a solid cancer.

Due to a wide variety of presentations, diversity of the underlying risk factors and, sometimes, non-specific imaging findings, the diagnosis ends up being delayed, and that will affect not only the treatment approach, but also the prognosis. In our study, the median delay from onset of symptoms to diagnosis was 3 days. In fact, statistically speaking, only 30% of cases are diagnosed within the first 2 days [21]. In Coimbra University and Hospital Centre, the most used imaging technique for the first assessment was the CT scan (67.69%). In the emergency setting, CT is often performed, and it is useful to rule out other cerebral disorders that may mimic CVT. It will demonstrate focal edema in about 8% of the cases, and one-third will demonstrate parenchymal hemorrhage [40]. However, most of the times, CT provides non-specific findings, and it can be normal in up to 30% of the cases, especially in patients with a chronic disease course [10, 14]. In patients with normal unenhanced brain imaging, especially if there is bilateral papilledema, CVT should always be considered and research should continue [14]. Therefore, a second contrast-enhanced imaging technique was rightly performed most of the times, usually a computerized tomography venography. Erstwhile, traditional angiography was the main tool to diagnose CVT. With time, MRI, MRV and CTV replaced it and are now considered the modern golden-standard [12, 21]. Regarding the site of thrombosis, more than half of the patients had multiple sinuses involved. The transverse sinus, either isolated or in multiple involvement, was the most common site of thrombosis (76.2%), followed by the sigmoid sinus (56.2%) and the superior sagittal sinus (43.8%). Curiously, there were no sex differences in terms of the involvement of the sinuses, showing

that there is no preferential site of thrombosis in each gender. In previous studies, the most common site of thrombosis was set to be the superior sagittal sinus, followed very closely by transverse sinus [15, 28, 35].

As stated in the European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis [19], after the acute treatment with heparin, there should be a switch to oral anticoagulation, preferably, vitamin K antagonists, among which warfarin is the most acclaimed. In our population, 109 patients (83.85%) were hypocoagulated with warfarin. NOACs were selected in 16 patients (12.31%). Although they are not yet approved for treatment, NOACs are yielding good results and looking promising [19, 20, 41]. Lastly, 5 patients (3.85%) were treated with acenocoumarol, which is also a vitamin K antagonist. Concerning the duration of treatment, it needs to be individualized based on risk factors for recurrent thrombosis, taking into consideration prothrombotic predispositions, such as factor V Leiden mutation and antiphospholipid syndrome (APLS) [15, 42]. For patients with CVT provoked by a transient risk factor, anticoagulation is recommended for 3-6 months. In our study, 42 patients (32.31%) were under anticoagulation for 6 months. If CVT is idiopathic, even after studies conducted after the episode, or if it is due to a mild thrombophilia, anticoagulation may be considered for 6-12 months. Most of our patients fell in this category, accounting for 53 patients (40.77%). Lastly, if there is an underlying thrombophilic condition, or if there is recurrent CVT, the therapy should be over one year and, sometimes, it may be lifelong [2, 5, 10, 19, 42]. Among our patients, 35 (26.92%) were anticoagulated for over a year.

Functional outcome was assessed with modified Rankin Scale (mRS) [43] at one, three and twelve months after diagnosis. There were some patients who had no motor evaluation in follow-up, but among those who had, at 1 month post-diagnosis, 92 patients (93.8%) had mRS 0-1, 3 patients (2.3%) had mRS 2, and 5 patients (3.9%) had mRS 3-5. Thus, we identified a clear tendency to motor improvement. This reflects the normally good prognosis associated with CVT. Patient's age was a determinant factor regarding motor outcome, as younger patients had a more favorable outcome. We found that patients presenting with motor weakness and impaired consciousness had a worse motor outcome. Regarding venous sinus impairment, patients with circumflex, transverse and lateral sinuses involvement had a worse 1-year outcome. Similarly, previous studies on the prognosis of CVT identified this risk factors as being related to an unfavorable outcome [15, 28].

The long-term effects of CVT on optic nerve and visual function remain uncertain [31], and for that same reason, besides motor outcome, we also assessed visual outcome during the follow-up. We verified that 25 patients (19.1%) had visual complaints. The most common findings were papilledema, in 12 patients (10.1%), and visual field defect, in 7 patients (5.3%). The

symptoms installed in approximately 22 months after the diagnosis. According to our results, the existence of visual changes on the follow-up may be predicted by the presence of papilledema, visual loss, pulsatile tinnitus, and transitory visual obscurations in acute phase. Imagiological evaluation may also aid to predict visual outcome since the presence of hemorrhagic infarction at baseline and the absence of total venous recanalization on follow-up favored the existence of visual abnormalities post-CVT. Also, in patients with visual symptoms after the diagnosis, only 1 had complete CVT resolution on the second neuro-imaging results, compared to 22 patients without visual symptoms. To summarize, patients with visual complaints on the follow-up had a lower CVT imagiological resolution rate than patients without visual complaints. Considering these results, we can assume that the presence of visual symptoms at follow-up probably indicates that there was no complete resolution of the thrombotic event. Papilledema is one of the risk factors that may predict deterioration after CVT. Others include seizure activity, decreased mental status, number of involved sinus, low serum sodium level, and low platelet count [44].

Strengths of the study include its considerably large sample, considering that it is a rare disease and it involved patients from a single country. This allowed us not only to better understand the clinical and etiological features and outcome of the disease but also to reduce potential bias. Besides, the selection of our patients is not biased. Out of the 136 patients selected, only 6 were not included in the study because their clinical reports were inconclusive. CVT was confirmed in all cases with current technology, and established consensus criteria. Completeness of the follow-up was satisfactory. Nevertheless, our study has several limitations that warrant comment. Firstly, our analysis is limited by the nature of the retrospective study. Secondly, the sample could have been even larger, but given the rarity of the disease, and the fact that the data came from a single hospital, it is justifiable. Thirdly, we decided to include 9 cases of chronic CVT, although we know that it has a different pathophysiology and evolution pattern. As it is a small group, it doesn't alter our outcome and results due to our considerably large sample size. The follow-up was satisfactory, but even so, we had patients that did not complete it, either because they stopped attending the appointments, migrated to other country or died. Besides, some patients did not have all the necessary information on their clinical files, and, for that reason, we did not collect all relevant variables. Being a central hospital, Coimbra's university Hospital takes charge of more severe cases that were referred from other smaller hospitals. Therefore, our findings might not be generalizable to centers that see less severe cases of CVT. In addition, we only took Portuguese population, mainly from the central region, so, even though it covers a board demographic area, our results may not apply to other populations. However, considering all

these aspects, there are no significative differences compared to other studies [1, 2, 3, 4, 7, 8, 9, 10, 11, 15, 18, 22, 23, 28, 29, 33, 35].

Our results have implications for clinical practice concerning the investigation, treatment, and prognosis of patients with CVT. Despite the limitations, the highly significant correlation between visual impairment and CVT, suggesting a cause-effect relationship, merit further studies to provide more insight to understand why it occurs in CVT. Understanding what contributes to visual impairment and its pathophysiology might help adopting different approaches in the future, allowing an earlier diagnosis and a better follow-up.

Soon, more studies should be performed, with a larger amount of population, in different countries, and with a prospective design. Raising awareness to the visual outcome within the medical community and reinforcing the need for neuro-ophthalmological surveillance after CVT is an important goal of this project. Although this is an observational study, its results will improve current knowledge about CVT effect on visual function and will also open pathways to future prospective treatment trials, aiming to prevent visual loss after CVT. It becomes critical to identify and characterize the incidence of visual dysfunction after CVT and its imagiological and clinical predictors in order to design therapeutic studies directed to CVT-related visual impairment.

In conclusion, we were able to enroll a large number of patients which corroborated the results of previous studies regarding epidemiology, risk factors, clinical signs and symptoms, diagnostic tools, therapeutic approaches, and prognosis. Additionally, we focused on the study of visual impairment both before and after the diagnosis of CVT. The literature included scarce information on this, and our results helped understanding it better and settled precedents for future studies. Our data clearly indicate a relation between visual complaints, imaging findings, and its implications on future prognosis. Even though we consider CVT as a disease within the scope of neurology, papilledema and intracranial hypertension may be its first and only manifestations. Thence, ophthalmologists should be able to promptly identify them, as these visual complaints may bring afflicted patients to them first. Besides being relatively infrequent, CVT entails a considerable morbidity and mortality burden and, therefore, an early and accurate diagnosis of these conditions will certainly help to prevent long-lasting deterioration of visual disfunction and, in more severe cases, death. Nevertheless, in order to clarify all these, new multicentered studies, with different designs and a higher number of patients, should be done.

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APPENDICES

APPENDIX I

Journal of Stroke and Cerebrovascular Diseases

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The abstract is limited to 250 words. Do not use abbreviations, footnotes, or references in the body of the abstract. Include a brief description of the goal, materials and methods, findings, and conclusion of the study.

Introduction, Materials and Methods, Results, and Discussion

Include within the body of the text a description of the ethical guidelines that were followed for human and animal studies. If appropriate, provide citation of institutional review by human or animal research committees. Also describe any hazardous procedures or chemicals involved in the studies and what precautions were taken to avoid injury to subjects or investigators. Within the Materials and Methods section, provide a brief but complete description of the statistical methods used, including which tests were used for analysis of which variables. Drugs, medications, or other material should be listed as generic items. If brand names are used, they should be placed after the generic name in parentheses with the manufacturer's name, city, and state or country.

Restrict all comments and discussion to the Discussion section. Results presented in the Results section should not be repeated in the Discussion section.

References

Cite references in text in order of appearance using Arabic numerals in parentheses for citations. Place the reference list at the end of the final text page. References should be listed in text citation number order and must be double spaced. Include the names of all authors up to a total of three before resorting to the use of "et al." All published material, including brief communications and letters to the editor, must be cited in the References section. References to unpublished material, such as personal communications and unpublished data, must be placed within the text and not cited in the References section. Personal communications and unpublished data must include the individual's name, location, and month and year of communication as appropriate. In the reference list, use only abbreviations approved for use in the latest edition of *Index Medicus* and conform style and punctuation to the requirements listed below:

Journal article

Bontia R, Ford MA, Stewart AW. Predicting survival after stroke: A three-year follow-up. Stroke 1988;19:669-673.

Book chapter

Whyte J, Robinson KM. Pharmacologic management. In: Glenn MB, Whyte J, eds. The practical management of spasticity in children and adults. Philadelphia: Lea & Febiger, 1990:201-226.

Complete book

Brooks VB. The neural basis of motor control. New York: Oxford University Press, 1986.

Special type of article

Schmidt R, Fazekas F, Horner S, et al. Lipoprotein (a) serum levels of normals are not associated with carotid atherosclerosis and microangiopathy-related cerebral damage. J Stroke Cerebrovasc Dis 1995;5:116 (abstr).

Tables

Tables must be cited in text and numbered according to order of appearance. Explanatory matter and source notations for borrowed or adapted tables should be placed in a table footnote, not in the title or table body.

Figure Legends

Figure legends should allow interpretation of the figures without reference to the text.

Figures

All figures must be cited in the text and numbered in order of appearance. Computer-generated figures should use solid fills or cross-hatching, not tonal shading. Figure legends should be presented separately and placed in the manuscript after the list of references. Figure legends should be brief and not repetitive of description in the text. Color figures may be accepted but any cost related to reproduction is the responsibility of the author. However, color figures may be published in the electronic version of The *Journal* at no cost to the authors. Authors should consult Elsevier's website for guidelines for preparing electronic artwork: *http://www.authors.elsevier.com/artwork*

Special Sections in the Journal of Stroke and Cerebrovascular Diseases

Controversies: A Controversies Section will appear several times yearly and serve as a medium for communicating controversy in the field of stroke and cerebrovascular disease. Authors will be selected for their expertise or outspoken positions or for their objectivity and analysis of a chosen subject. The Editor of the Controversy Section will oversee the preparation of the submitted manuscripts. They or an invited Guest Editor will add their commentary.

Rapid Communications: The Editor will provide the most rapid turnaround time possible in the review process. Authors may request rapid review of material found to be of critical importance to the field. The authors should accompany their manuscript with a letter stating clearly why they consider their work is appropriate for that request. These manuscripts will be published in the next subsequent issue of the Journal at the Editor's discretion.

Case Reports: Reports of clinical interest should contain no more than 400 words of text and one table or figure. The reference list should be limited to 10. The authors should also limit their case reports to new materials, rare clinical conditions, or cases that provide insight into controversial disease states. They should provide their reason for the case report in a separate cover letter to the author.

Journal Club: Journal Club will appear several times yearly. This section provides the opportunity for authors to publish journal clubs conducted in their own institutions on articles of recent interest from peer-reviewed medical literature. The authors should review no more than two articles and provide a summary of each article. This should be followed by their critical review of the paper, followed by the voiced opinion of named commentators in the audience. The authors should then summarize their conclusions at the end of the article. This section provides an opportunity for residents in training and students of clinical cerebrovascular disease to communicate their opinions of the stroke literature.

Methodologic and Technical Reports: The Journal will accept the full description of clinical trials prior to publication of results. The paper must include comprehensive details of the methodologic design. Publications are expected to enhance the science of clinical trials design and to provide extensive detail of these methods. It is hoped that authors will follow up with publication of some, if not, all aspects of the results of the clinical trial.

The Technical Note section will permit publication of innovative techniques in neurology, neurosurgery, and interventional radiology as regards the stroke and cerebrovascular disease sciences. The techniques should be novel and extensively described.

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Every issue will be introduced by a section in which Guest Editors will comment on papers in the current Journal. These articles will be summarized, highlighting items of special interest. The commentary will discuss the importance of the paper and its relevance to the field. Controversial aspects of the selected articles will be emphasized.