ALEXANDRE SOUZA BOSSONI

A cefaleia na fase tardia da trombose venosa cerebral

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Neurologia

Orientadora: Profa. Dra. Adriana Bastos Conforto

SÃO PAULO
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I desired always to stretch the night and fill it fuller and fuller with dreams.

Virginia Woolf
The Waves

To the patients, who shared their fears, their pain and hope, contributing with their lives to make this work real.

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To Professor Adriana Bastos Conforto, in whom I met a professional and a friend I feel I can trust.

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SUMÁRIO

LIST OF ABBREVIATIONS AND ACRONYMS

BMI - Body mass index
CGRP - Calcitonin gene related peptide
CT - Computed tomography
CTA - Computed tomography angiography
CTV- -Computed tomograph venography
CVT - Cerebral venous thrombosis
DSA - Digital subtraction angiography
GAD7 - General Anxiety Disorder 7-questions
HIS - International Headache Society
ICHD - International Classification of Headache Disorders
IHS - International Headache Society
MMSE - Mini-Mental State Examination
MRA - Magnetic resonance angiography
MRI - Magnetic resonance Imaging
mRS - Modified Rankin Scale
MRV - Magnetic Resonance venography
NIHSS - National Institute of Health Stroke Scale
PCH - Post-cerebral venous thrombosis headache
PHC - Post-CVT headache
PHQ9 - Patient Health Questionnaire 9-questions
RH - Remote headache
SIS 3.0 - Stroke Impact Scale 3.0
TTH - Tension-type-headache
YLD - Years of life with disability

LIST OF BOXES

LIST OF FIGURES

LIST OF TABLES

RESUMO

Bossoni AS. A cefaleia na fase tardia da trombose venosa cerebral [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.

Introdução: A Trombose Venosa Cerebral (TVC) é responsável por aproximadamente 0,5% a 1% de todos os eventos cerebrovasculares. Seus principais fatores de risco são a gestação, o puerpério e o uso de contraceptivos hormonais. É considerada uma doença de bom prognóstico, tendo uma mortalidade estimada ao redor de 8% e, na maioria dos casos, os pacientes apresentam pontuação de zero ou 1 na Escala Modificada de Rankin entre seis e 12 meses após o diagnóstico e o tratamento. A cefaleia é o principal sintoma de apresentação da TVC e pode ser o único sintoma em até 25% dos casos. Há poucas informações disponíveis sobre a evolução da dor, dias a meses após a TVC (cefaleia pós-TVC, CPT). **Objetivos**: Os objetivos desse estudo foram descrever a frequência, as características e possíveis preditores clínicos/de imagem da CPT. Adicionalmente, comparamos características da CPT com características de cefaleias relatadas remotamente, antes da TVC. **Métodos**: Nesse estudo transversal foram incluídos 100 pacientes que haviam apresentado TVC confirmada por exame de imagem entre 6 meses e 5 anos antes do momento da inclusão no estudo. Foram avaliadas características demográficas, clínicas e de neuroimagem em todos os pacientes. Foram realizadas entrevistas estruturadas para avaliar detalhadamente características de cefaleias presentes cefaleia antes, no momento do diagnóstico e na fase crônica após a TVC. Humor, qualidade de vida e abuso de analgésicos também foram avaliados. As características dos sujeitos que relataram ($Grupo_{CPT}$) e não relataram ($Grupo_{Controle}$) foram comparadas com testes qui-quadrado, t-Student independente ou teste de Mann-Whitney, de acordo com a natureza e distribuição dos dados. Os tipos de CPT foram comparados com testes do qui-quadrado. Valores de $p < 0,05$ foram considerados estatisticamente significativos.No $Grupo_{CPT}$, testes de Wilcoxon foram usados para comparar: presença de cefaléia (sim ou não) remotamente da TVC e na fase crônica após a TVC; o tipo de cefaleia no momento do diagnóstico de acordo com os critérios da *International Headache Society* e o tipo de cefaleia remota anterior à TVC. **Resultados**: A CPT ocorreu em 59% dos pacientes, foi diferente da cefaleia que levou ao diganóstico de TVC e frequentemente (98,3%) preencheu critérios para

cefaleia primária. O único preditor de CPT foi o antecedente de cefaleia remota, antes do diagnóstico de TVC. Em pacientes com CPT, sintomas de depressão (p=0.002), ansiedade (p=0.028) e abuso de analgésicos (p < 0.001) foram significativamente mais frequentes que em pacientes sem CPT. O tipo mais comum de CPT preencheu critérios de cefaleia tipo tensão. Uma cefaleia secundária foi diagnosticada em 1/59 (1,7%) dos indivíduos com CPT. **Conclusão:** A CPT foi frequente entre os sobreviventes de TVC. O único fator de risco para a CPT foi o antecedente de cefaleia remota. A CPT teve características semelhantes às de cefaleias primárias. Pacientes com CPT frequentemente relataram dor de intensidade moderada ou intensa e apresentaram sintomas de ansiedade, depressão ou uso excessivo de analgésicos. Esses resultados indicam a necessidade de estudos multicêntricos sobre critérios diagnósticos, mecanismos subjacentes, prevenção e tratamento da CPT.

Descritores: Trombose dos seios intracranianos; Cefaleia; Cefaleias vasculares; Transtornos da cefaleia primários; Transtornos da cefaleia secundários; Acidente vascular cerebral.

ABSTRACT

Bossoni AS. *Headache at the chronic phase of cerebral venous thrombosis* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2021.

Background: Cerebral venous thrombosis (CVT) is a rare cause of stroke, being responsible for 0.5% to 1% of all cerebrovascular events. The main risk factors are pregnancy, puerperium and oral contraception. The prognosis of this condition is considered good. The mortality rate in patients with CVT is approximately 8% and scores in the modified Rankin scale range from 0 to 1, six to 12 months after diagnosis and treatment. Headache is the main presenting symptom of this condition and can be the only symptom in up to 25% of the cases. There are no pathognomonic patterns of pain for CVT diagnosis. There is limited information about the progress of pain, weeks to months after CVT (post-CVT headache, PCH). **Objective**: The aims of this study were to describe the frequency, characteristics and potential clinical/imaging predictors of PCH. In addition, we compared characteristics of PCH and headaches reported remotely, prior to CVT. **Methods**: This cross-sectional study included 100 patients within 6 months to 5 years after CVT. Demographic, clinical and neuroimaging characteristics were evaluated in all patients. Structured interviews were conducted to assess in detail the characteristics of headaches present before, at the time of diagnosis and in the chronic phase after CVT. Mood, quality of life and analgesic abuse were also assessed. Characteristics of subjects who reported ($Group_{PCH}$) and did not report ($Group_{Control}$) PCH were compared with chi-square tests, independent t-Student or Mann-Whitney tests, according to the nature and distribution of the data. Types of PCH were compared with chi-square tests. P-values < 0.05 were considered statistically significant. In $Group_{PCH,}$ Wilcoxon tests were used to compare: headache status (yes or no) remotely from CVT and in the chronic phase after CVT; the type of headache at the time of diagnosis according to IHS criteria and the type of remote headache prior to CVT. **Results**: PCH was present in 59% of the patients, was different from the headache that led to CVT diagnosis and often (98.3%) fulfilled criteria for primary headaches. The only predictor of PCH was history of headache prior to CVT ($p=0.002$). Symptoms of depression ($p=0.002$), anxiety ($p=0.028$) and analgesic overuse ($p < 0.001$) were significantly more

common in $Group_{PCH}$ than in $Group_{Control}$. The most common type of PCH fulfilled criteria for tension-type headache. A secondary headache was diagnosed in 1/59 (1.7%) of subjects with PCH. **Conclusion**: PCH was frequent among CVT survivors. The only risk factor for PCH was the history of remote headache. PCH shared characteristics with primary headaches. Secondary headaches were rare. Patients with PCH often reported pain with moderate or severe intensity and presented symptoms of anxiety, depression or analgesic overuse. These results pave the way for future multicenter studies about diagnostic criteria, underlying mechanisms, prevention and treatment of PCH.

Descriptors: Sinus thrombosis, intracranial; Headache; Vascular headaches; Headache disorders, primary; Headache disorders, secondary; Stroke.

1 INTRODUCTION

1.1 Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is a rare cause of stroke, corresponding to about 0.5% to 1% of all cerebrovascular events[1]. CVT is defined by the occlusion of dural sinuses and/or cortical veins that may lead to edema, hemorrhage, infarction and intracranial hypertension[2].

1.1.1 Epidemiology and risk factors

The incidence of CVT ranges from 0.22[3] to 1.57[4] cases/100.000/year, based on studies in high-income countries. Data from the Brazilian population were not yet systematically collected.

In adults, the mean age is around 41 years[5]. CVT affects mainly young females (rate female/male, 3/1). Oral contraceptives, hormonal replacement therapy, pregnancy and puerperium are frequent risk factors and contribute to the greater frequency in women[6-9]. A systematic review described an increase in CVT rates between 1966 and 2014, possibly by improvements in imaging, as well by the increase in use of oral contraceptives and hormonal replacement therapy[10]. Nearly 12.5% of the cases have no identifiable risk factor or any clear mechanism[2]. Box 1 summarizes the most frequent risk factors.

Box 1 - Risk factors for cerebral venous thrombosis

Causes and risk factors
Genetic prothrombotic conditions
Antithrombin deficiency
Protein C and Protein S deficiency
Factor V Leiden mutation
Prothrombin mutation
Genetic Hyperhomocysteinemia
Acquired prothrombotic states
Antiphospholipid antibodies
Acquired Hyperhomocysteinemia
Puerperium
Infections
Meningitis
Systemic infectious disease
Otitis, mastoiditis, sinusitis
Inflammatory disease
Systemic lupus erythematosus
Wegner's granulomatosis
Bechet's syndrome
Hematologic conditions
Polycythemia
Thrombocythemia
Leukemia
Sticky platelet syndrome
Anemia
Drugs
Oral contraceptives
Asparaginase
Mechanical causes
Head injury
Injury to sinuses or jugular vein
Neurosurgical procedures
Endovascular procedures
Lumbar puncture
Miscellaneous
Dehydration
Cancer

1.1.2 Clinical presentation and CVT diagnosis

Headache is the most common symptom in patients with CVT (up to 90% of the patients). In 25% of the subjects, no additional neurological abnormality is observed[1,11] and, in 10%, thunderclap headache may occur. In most cases, headache at the time of CVT diagnosis is described as persistent, progressive, worsening over days, but no pathognomonic pattern has been established[12-15].

Wasay *et al*.[15] described headache related to CVT as acute (1 to 3 days) in 60%, subacute (4 to 14 days) in 24% and chronic (> 14 days) in 10% of the patients. Agostoni [16] described acute (1 to 2 days) in 42%, subacute (3 to 30 days) in 47%, and chronic (> 30 days) in 11% of the subjects with CVT. Headache due to CVT may even resemble primary headaches[16-18].

According to the International Classification of Headache Disorders (ICHD)[19], from the International Headache Society (IHS), headache attributed to CVT must fulfill the following criteria:

I. Any new headache.

II. CVT has been diagnosed.

III. Evidence of causation demonstrated by both of the following:

   a. Headache has developed in close temporal relation to other symptoms and/or clinical signs of CVT, or has led to the discovery of CVT.

   b. Either or both of the following:

      i. Headache has significantly worsened in parallel with clinical or radiological signs of extension of the CVT.

      ii. Headache has significantly improved or resolved after improvement of the CVT.

Neurological deficits, seizures and papilledema are found in up to 40% of the cases[20]. CVT can also present with subarachnoid hemorrhage, acute or subacute diffuse encephalopathy as well as with involvement of multiple cranial nerves[7,21]. Intracranial hypertension, hydrocephalus, brain edema, venous infarction and hemorrhages are also frequently reported[2].

Imaging is the main tool to confirm diagnosis (Figure 1). Enhance Computed tomography (CT) typically reveals venous infarctions in 30% to 40% of the cases. Direct signs, such as the dense triangle, may be observed in 24% to 30% of non-contrast CTs[22] CT with contrast may show the empty delta sign.

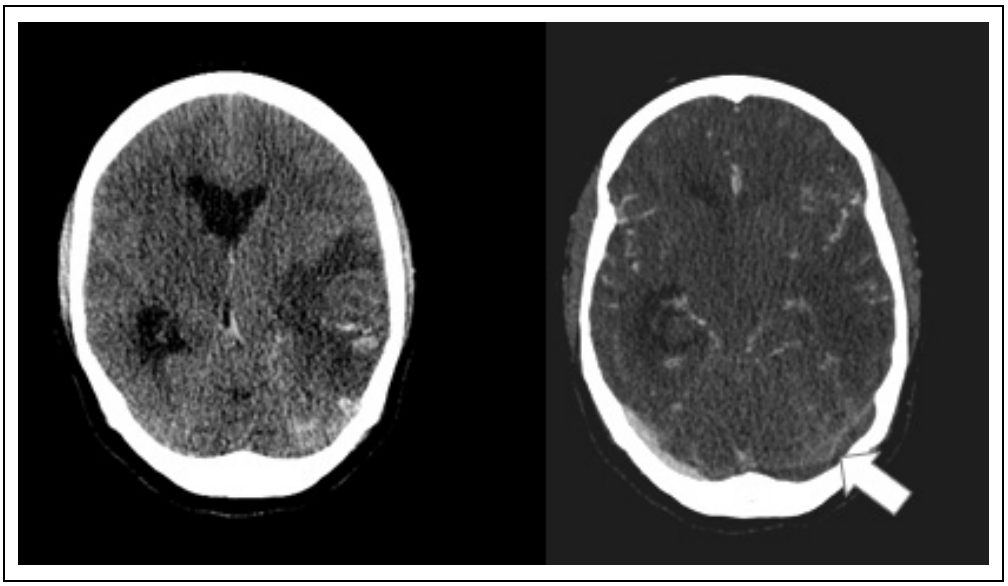
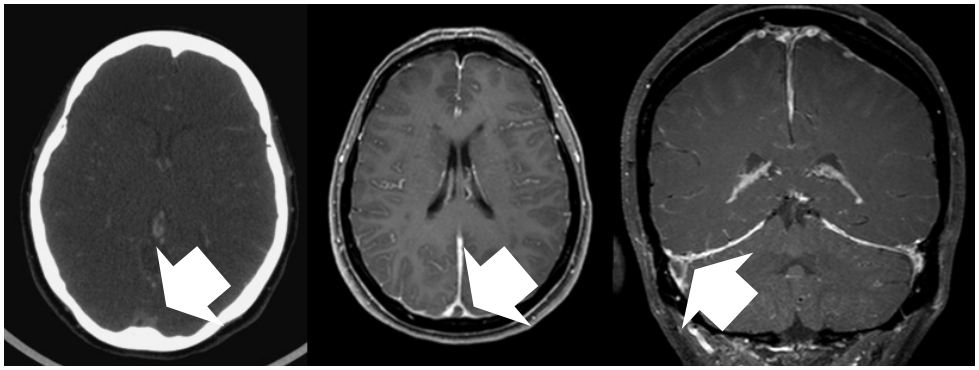


Figure 1 - Enhanced computed tomography scan shows venous infarction due to cerebral venous thrombosis

Magnetic resonance imaging (MRI) has an overall sensitivity of 79.2% and specificity of 89.9% for CVT diagnosis, with moderate inter-rater reliability (k = 0.50)[23]. Enhanced MRA venography has 97% and 99% of sensitivity and specificity, respectively[24]. Better results can be obtained with special protocols, such as 3D-T1 'black blood'[25]. Imaging is strongly recommended to confirm CVT[26,27]. Figure 2 shows examples of CVT diagnosed by Computed tomography venography (CTV) or Magnetic resonance angiography (MRA). Digital subtraction angiography (DSA) is indicated in selected cases, being the gold standard for dural fistula assessment and endovascular treatment[28,29].



Left: Enhanced computed tomography - empty delta sign (arrow).

Middle: Contrast-enhaced MRI. The T1 - weighted image shows contrast around a thrombus in the superior sagittal sinus (arrow).

Right: Contrast-enhaced MRI. The T1 - weighted image contrast around a thrombus in the right lateral sinus (arrow).

Figure 2 - Enhanced computed tomography and enhanced magnetic resonance. Examples of cerebral venous thrombosis

1.1.3 Acute treatment

The main strategy for CVT treatment is anticoagulation in the acute phase[11,30-32]. The optimal duration of oral anticoagulation with warfarin remains controversial and typically ranges from 3 to 12 months[33-35]. Recently, an exploratory, randomized clinical compared dabigatran with warfarin in 120 consecutive patients with CVT. The study reported low risk of recurrence and bleeding rates in patients who fulfilled criteria for the study and were treated with either drug[36].

Thrombosis related with head and neck infections should be treated with antibiotics[11,31,37,38]. Evidence of benefit of endovascular thrombolysis and thrombectomy remains to be demonstrated. The TO-ACT trial – Effect of Endovascular Treatment with Medical Management vs Standard Care on Severe Cerebral Venous Thrombosis - did not show benefit of endovascular procedures but was interrupted for futility after the first interim analysis. The

most commonly used device for thrombectomy was Angiojet and it remains to be determined if the use of stent retrievers, aspiration catheters or other types of devices might lead to better outcomes. Results of the observational DECOMPRESS-2: Decompressive Neurosurgery for Severe Cerebral Venous Sinus Thrombosis Study, presented in international conferences, suggested that decompressive surgery should be considered in patients with focal lesions and severe intracranial hypertension[39].

1.1.4 Prognosis

CVT is described as a condition with an overall good prognosis, based on mortality rates or modified Rankin scales (mRS) at 6 and 12 months. The mortality rate of CVT has been estimated in 8%[3,7,20,40]. In a prospective study, mRS ranged from 0 to 1 in 82% of the patients, but 68% of them reported residual symptoms, like fatigue, neuropsychological impairment, anxiety or depression[41]. Also, 20% to 40% of the patients have been reported not to return to full-time jobs or to work at all[41-43], despite low scores in mRS and in National Institute of Health Stroke Scale (NIHSS) scores.

These data indicate that, despite a low level of neurological impairment and disability assessed by mRS and NIHSS, patients continue to suffer from symptoms or/and conditions that limit their independence and quality of life. There is a need for new methods of assessment and a new concept of outcome that encompasses different aspects of neurological impairments[44].

Headache is the most common symptom after CVT and may be a residual symptom that impacts disability or quality of life in the chronic phase

after diagnosis of this condition. Before detailing the available information about headache in the chronic phase after CVT, we will briefly review key concepts of headache in general.

1.2 Headache

Headache disorders are a major cause of disability around the globe. Migraine and Tension-Type Headache are the most prevalent primary headache disorders. It has been estimated that 1.89 billion and 1.04 billion people have tension-type and migraine, respectively, around the world, leading to 7.2 and 45.1 million of years of life with disability (YLD). Primary headaches are more frequent in women between 15 and 49 years[45,46].

In a cross-sectional population-based Brazilian study, 383 people randomly selected from the “Paraisópolis” area in São Paulo, Brazil, were interviewed. The estimated 1-year prevalence of headache, migraine, chronic migraine, and tension-type headache were 47% (CI 95%: 39.5-52.6%), 20.4% (CI 95%: 16.6-24.9%), 8.4% (CI 95%: 6.1-12.0%), and 6.2% (CI 95%: 3.3-9.8%), respectively[47]. These data confirms the finding of a previous study that assessed the 1-year prevalence of migraine, also using a cross-sectional population-based study strategy. A total of 3.848 people, aged 18-79 year, were interviewed in Brazil. The estimated prevalence of migraine was 15.2% and it was 2.2 times more prevalent in women, and 1.5 times more frequent in subjects with more than 11 years of education[48].

1.2.1 Migraine

Migraine is a common and complex disabling neurological condition, characterized by recurrent episodes of pain. It affects 18% of women, 7% of men[49] and has been ranked as the third cause of disability worldwide in males and females under 50 years. In the United States, migraine and severe headaches are more common among young females (ratio 3:1). This condition is associated with medical and psychiatric comorbidities; it is inversely related to income and education[50,51].

Migraine diagnosis is made according to the following criteria[52]:

I. At least five attacks.

II. Headache attacks lasting 4-72 hours when untreated or unsuccessfully treated.

III. Headache has at least two of the following four characteristics:

   a. Unilateral location.

   b. Pulsating quality.

   c. Moderate or severe pain intensity.

   d. Aggravation by or causing avoidance of routine physical activity.

IV. During headache at least one of the following:

   e. Nausea and/or vomiting.

   f. Photophobia and phonophobia.

V. Not better accounted for by another cause.

Migraine attacks are related to activation of C fibers, especially those localized in deep viscera, meninges, periosteum and cerebral vessels[49].

Structures involved in migraine pathogenesis include the periaqueductal gray matter, hypothalamus, amygdala, pons, medulla and forebrain[53-56]. The pathogenesis is complex and not completely understood, involving trigeminal pathways hyperexcitability, vascular response and neuromodulated inflammation[57]. The calcitonin gene related peptide (CGRP) plays a central role in migraine pathophysiology, being found in high titles during a migraine attack and currently becoming a target to migraine treatment[58-61].

1.2.2 Tension-type-headache (TTH)

Tension-type-headache is the most common primary headache disorder. As in migraine, women are more affected than men[62,63]. Pain episodes are not as disabling as migraine attacks, but 60% of the patients experience considerable disability, decreased work effectiveness, increase absenteeism from work and lower social engagement, especially in the chronic presentation[63,64].

Tension-type-headache may be episodic, frequent episodic TTH or chronic, with or without pericrania muscle tenderness. The diagnosis of TTH is based on the following criterion[52].

At least ten episodes of headache:

I. Lasting from 30 minutes to seven days.

II. At least two of the following:

   a. Bilateral location.

   b. Pressing of tightening (non-pulsating) quality.

   c. Mild to moderate intensity.

III. Not aggravated by routine physical activity such as walking or climbing stairs.

Both of the following:

IV. No nausea or vomiting.

V. Photophobia OR phonophobia[52].

In episodic TTH, headache occurs < 1 day/month and not more than 12 days/year. In frequent TTH, it occurs 1-14 days/month, on average for > 3 months (between 12 to 180 days/year). In chronic TTH, headache is present in 15 or more days/months for three or more months. Costs, disability and psychiatry comorbidities increase with higher headache frequency[45,65].

Tension-type-headache pathogenesis is complex and multifactorial. Environmental issues, genetics, psychogenic components, peripheral nociception from pericrania muscles and central sensitization may play roles in TTH episodes. However, a specific mechanism remains unknown[62,66].

1.2.3 Headache and cranial vascular disorders

The relationship between headache and cranial vascular disorders is recognized by IHS. It is described in part three (secondary headaches), item 6, of ICHD.

Headache is one of the symptoms of many neurovascular conditions. In general, ICHD establishes a relationship between the onset of the headache and the diagnosis of the condition. In some cases, as in ischemic stroke, there are descriptions of headache persisting for more than three months after the acute phase[52]. It is important to note that, according to

ICHD, headaches that persist for more than three months after a vascular event and are due to this event are described as having that same pattern described by the patient in the acute phase.

The International Classification of Headache Disorders does not admit the possibility that a headache different from the pain reported in the acute phase could be attributed to a previous vascular cause. Primary-like headaches were described in 50.6% of 89 subjects in the chronic phase after ischemic stroke[67]. When a structured headache questionnaire was applied, the pain fulfilled criteria for TTH in 28.9% of the patients, and for migraine, in 46.7%. Female sex and pre-ischemic stroke headache were independent headache predictors. Only one subject of this series (n=89) fulfilled the ICHD criteria (item 6.1.1.2.) to headache attributed to a past stroke (cerebral infarction).

1.2.4 Headache and cerebral venous thrombosis

In session 1.1.12 criteria for headache caused by CVT from The International Classification of Headache Disorders were provided. Box 2 provides a summary of headache through published studies.

There are several pathophysiological explanations for headache due to CVT, such as the raise of intracranial pressure, the release of inflammatory mediators, mechanical stimulation of C fibers of meninges, intracerebral hemorrhage and others[1,8]. Late complications of CVT, such as dural fistulae, intracranial hypertension or even CVT recurrence, also have headache as the main presenting symptom, raising concerns about this symptom during follow-up.

Headache weeks to months after CVT has been reported in 20% to 47% of the patients, being severe in up to 14%[3,41,68] (Box 2).

In the VENOPORT Study, Ferro *et al.*[21)]bserved headaches in 47% of 142 patients followed for 1.8 years. The pain was mild in 37%, moderate in 2% and severe in 8%. Details about the characteristics of headaches were not reported. In 2004, Ferro *et al.*[20] described that 14.1% of 624 patients followed for 16 months, on average, reported severe headaches.

Koopman *et al.*[68], in a case-control study, compared 44 patients with CVT with 44 controls. They found out that 43% of the patients presented headache during 12 months of follow-up. In this study, headache was the main residual symptom.

Likewise, Hiltunen *et al*.[41] followed 161 patients up to 39 months after CVT and reported headaches at least once a week as the most frequent late symptom. Headache more than once a week was referred by 20% of the subjects.

In summary, information about the frequency, characteristics or risk factors for headache at the chronic PHASE after CVT diagnosis (post-stroke headache, post-cerebral venous thrombosis headache [PCH]) is scarce.

Box 2 - Summary of studies that followed patients with cerebral venous thrombosis for at least 12 months

Author	Year	Outcomes	Design	N	Follow-up (months)	Results
de Bruijn *et al.*[43]	2000	Mini-mental state examination, 15-word memory test, Warrington Graded Naming Task, Wechsler Adult Intelligence Scale, Rey Complex Figure Test	Double-blinded, randomized trial	47	18.5	Headache was not assessed
Ferro *et al.*[3]	2002	Long-term mortality, functional recovery and long-term complications	Observational Retrospective and prospective	142	12	Headache: 59 patients (47%) Mild: 46 (37%) Moderate: 3 (2%) Severe: 10 (8%)
Ferro *et al.*[20]	2004	Death or dependence (Modified Rankin Scale)	Observational Prospective, multicenter	624	16	Severe headache: 88 patients (14.1%)
Koopman *et al.*[68]	2009	Frequency of headache, fatigue, depression, and cognitive impairment	Case-control	44	63	Headache: 19 (43%) of patients with CVT, 4 (9%) of patients in control group.
Hiltunen *et al.*[41]	2016	Modified Rankin Scale, Employment	Cross-sectional	161	-	Headache more than once week: 33 (20%) patients

2 AIMS

The aims of this study were to describe the frequency, characteristics and potential clinical/imaging predictors of PCH.

In addition, we compared characteristics of PCH and headaches reported remotely (Remote headache [RH]), prior to CVT, and at the time of the diagnosis of CVT.

3 METHODS

3.1 Study Design

This is an observational, cross-sectional study, based on clinical interviews and assessment of medical records in a CVT Clinic at a university hospital.

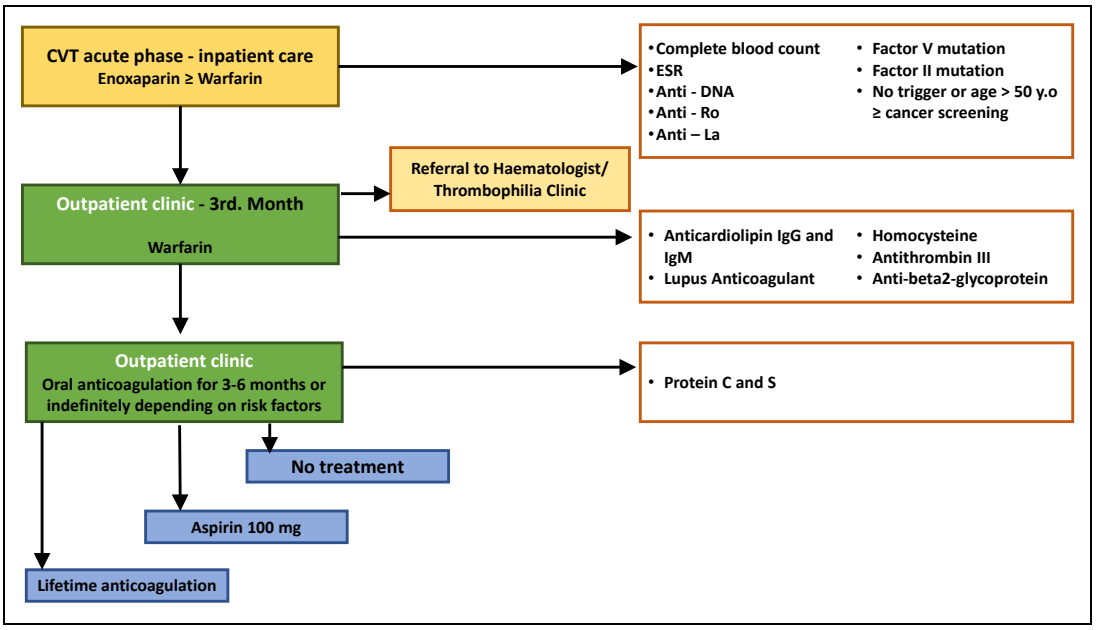
3.2 Eligibility Criteria

Inclusion criteria: Age ≥ 18 years old; CVT within 6 months to 5 years prior to enrollment, confirmed by MRI or magnetic resonance venography (MRV), CTV, or DSA; follow-up in the CVT Clinic; written informed consent to participate in the study (Attachment A).

Exclusion criteria: score of 4 or higher in the Modified Rankin Scale[69]; inability to answer the questions from the interview (for instance, due to aphasia or cognitive impairment).

3.3 Characteristics of the subjects

The protocol routinely performed for assessment and treatment of patients with CVT is shown in Figure 3.



ESR: erythrocyte Sedimentation Rate.

Figure 3 - Institutional protocol for management of cerebral venous thrombosis

The entire protocol was designed to avoid a very long duration (no more than one hour), to avoid cognitive biases[70-72].

The following characteristics were assessed:

- Age at the time of the diagnosis and on the day of the interview.
- Gender.
- Symptoms that led to CVT diagnosis.
- Type and duration of treatment after CVT diagnosis (use of anticoagulation and surgical or endovascular procedures).
- Presence and characteristics of headache at the time of CVT diagnosis according to a structured interview (Attachment B). Headache was defined according to ICHD[19] as any type of

headache in the context of a sinus thrombosis with close temporal relation to that thrombosis and with headache improvement or worsening, in parallel with clinical or radiological improvement or worsening.

- Presence and characteristics of RH before CVT (for instance, migraine tension-type headache, and others) according to a structured interview (Attachment B). Headaches were classified according to ICHD[19].
- Risk factors for CVT.
- Body mass index (BMI).
- Medications on the day of the interview.
- Neurological impairment according to the NIHSS[73] (Appendix A).
- Functional independence according to the mRS[69] (Appendix A).
- Cognitive status according to the Mini-Mental State Examination (MMSE)[74] (Appendix B).
- Quality of life according to the Stroke Impact Scale 3.0[75] (Appendix C).
- Symptoms of depression according to the Patient Health Questionnaire (PHQ9)[76] (Appendix D).
- Symptoms of anxiety according to the General Anxiety Disorder 7 (GAD7)[77] (Appendix E).

Scores in all of these scales were assessed on the day of the interview.

In addition, information from Appendix C was retrieved from medical charts (Appendix C).

Also, an experienced neuroradiologist, blinded to clinical information, assessed head CT, CTV, MRI or MRV performed at the time of CVT diagnosis to ascertain the presence of venous infarcts, intracranial hemorrhage and venous sinus(es) affected by thrombosis. Recanalization was also blindly assessed by the same experienced neuroradiologist in all patients who performed CTV or MRV at least 3 months after CVT.

3.4 Outcomes

3.4.1 Primary outcome

The Primary Outcome was the percentage of patients with PCH.

3.4.2 Secondary outcomes

The secondary outcomes were:

- Characteristics and types of PCH.
- Characteristics and types of headaches reported remotely before CVT - RH.
- Characteristics of headache reported at the time of CVT diagnosis - headache at the time of CVT diagnosis.

3.4.3 Assessment of outcomes

All patients were assessed by ASB, who was blinded to information from medical charts before the interview and physical examination. PCH is routinely evaluated in the CVT clinic, according to the protocol shown in Box 3.

Box 3 - Protocol of assessment of headaches at the chronic phase of cerebral venous thrombosis (CVT)

Protocol of assessment
ROUTINE EVALUATION
• Review medical history • Review Imaging • Review laboratory tests • Define CVT risk factors/need for further investigation
EVALUATION OF HEADACHE AT THE CHRONIC PHASE OF CVT
• New or progressive worsening of headache? • Changes in a previous headache pattern? • New onset visual loss or new onset diplopia? • New or worsening of papilledema? • New onset tinnitus? • Any other focal symptom or progressive worsening in a focal symptom?
IF "YES" TO ANY OF THE ABOVE:
• Repeat CT or MRI + assessment of intracranial venous and arterial systems by CTA, CTV or MRA/MRV • More frequent follow-up medical evaluations • Lumbar puncture if potential benefits outweigh the risks OR clinical evidence of intracranial hypertension OR imaging evidence of intracranial hypertension

CTA: Computed tomography angiography; CTV: Computed tomography venography; CVT: Cerebral venous thrombosis; MRA: Magnetic resonance angiography; MRV: Magnetic resonance venography.

A structured interview[48] was performed to assess (Attachment B) the presence of a current headache, at the chronic phase of CVT (PCH), defined as at least 3 episodes of headache in the 3 months prior the interview. This time frame was chosen to limit recollection bias. The following characteristics were evaluated: frequency, duration, intensity, location, onset, associated symptoms, use of analgesic medications and possible triggers, number of days with pain per month and absence from work due to pain.

We assessed whether PCH fulfilled ICHD for specific types of headaches, such as: probable migraine, probable tension-type, secondary headaches, headache due to CVT and other types[19]. ICHD criteria for the number of attacks for diagnosis of migraine (5, without aura) or tension-type headache (10) were not required – therefore we used the classification of *probable* migraine or tension-type headache if other criteria were fulfilled.

The classification was performed by two different experienced neurologists. When a discrepancy was found, both discussed the case and reviewed all information to define the classification by consensus.

3.5 Sample Size

We planned to include 100 consecutive patients followed in the clinic in order to assess the primary outcome in a representative sample of subjects with CVT, an uncommon type of cerebrovascular disease.

3.6 Statistical Analysis

Means and standard deviations of normally distributed data are presented. Otherwise, medians and ranges are shown. Frequencies of categorical variables were calculated.

Characteristics of subjects who reported ($Group_{PCH}$) and did not report ($Group_{Control}$) PCH were compared with chi-square tests, independent t-Student or Mann-Whitney tests, according to the nature and distribution of the data. Types of PCH were compared with chi-square tests. P-values <

0.05 were considered statistically significant.

In $Group_{PCH,}$ Wilcoxon tests were used to compare: headache status (yes or no) remotely from CVT, and at the chronic phase after CVT.

In $Group_{PCH,}$ Wilcoxon tests were also used to compare whether the same type of headache was present: remotely from CVT and at the time of CVT diagnosis; remotely from CVT and at the chronic stage after CVT. Bonferroni´s corrections for multiple comparisons were performed and p-values < 0.025 were considered statistically significant.

Multivariate regression was planned to evaluate predictors of PCH, if p-values for comparisons of patients´ characteristics in $Group_{PCH}$ and in $Group_{Control}$ were <0.05.

Statistical analysis was performed with JASP®, Version 0.10.2 (Team 2020) and IBM® SPSS ® Statistics, Version 24.

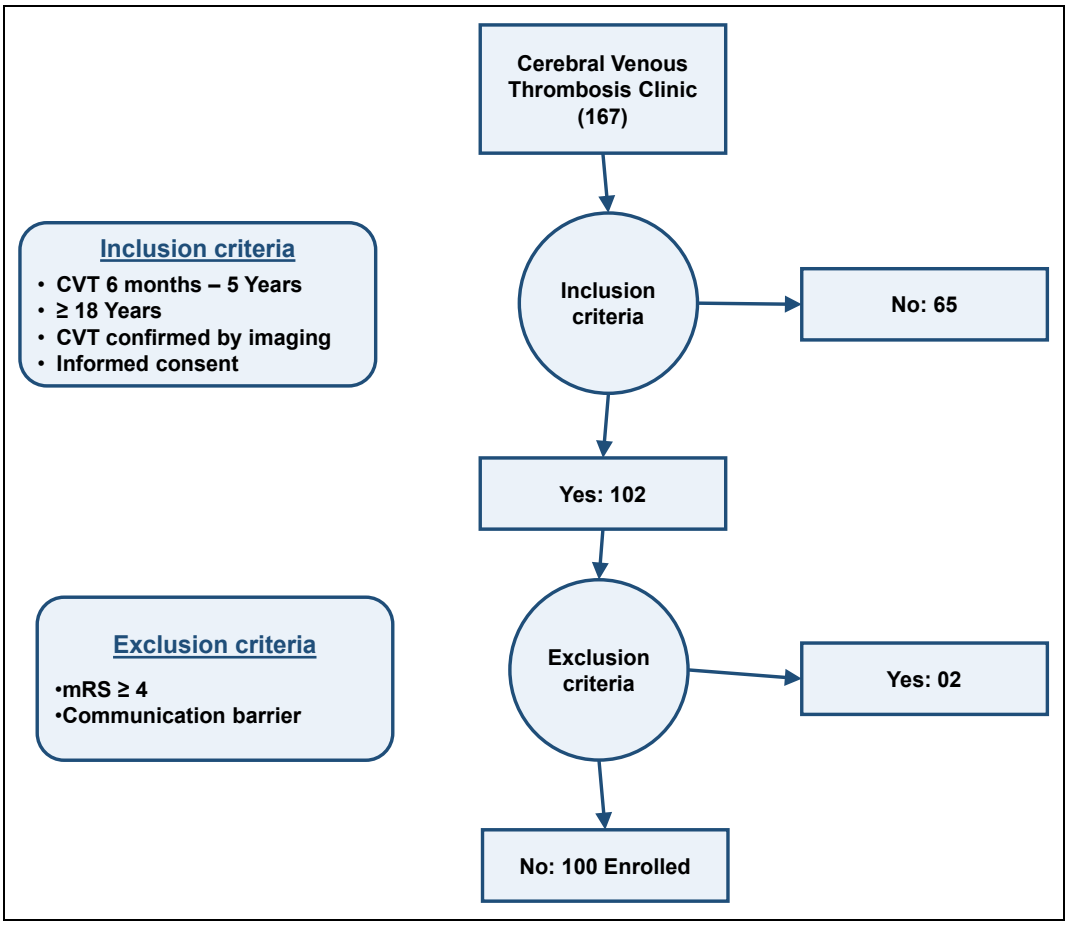
3.7 Ethics

This study received ethical approval from our institutional Research Ethics Committee (number 56307316.70000.0068). All patients provided written informed consent (Attachments A and D).

4 RESULTS

4.1 Subjects

From November, 2016 to October, 2019, 100 patients with CVT were enrolled as described in Figure 4.



CVT: Computed tomography venography; mRS: Modified Rankin Scale.

Figure 4 - Flow of the subjects through the study

Tables 1-4 show patients´ characteristics.

Most patients were women less than 45 years. Slightly more than half of the subjects were White. On average, two visits to medical services were made before CVT diagnosis. The interval between the first symptom and CVT diagnosis was 21 ± 4 days (mean ± standard deviation) Only one subject was not treated with anticoagulation. Slightly more than 20% of the patients had history of RH prior to CVT (Table 1). Presentation was acute (within 0h - 48h) in 21%, subacute in 60% (within 6 - 30 days), and chronic (>30 days) in 19% (p=0.185).

Headache at the time of CVT diagnosis was more often described as pressure-type, progressive over time, bilateral, and associated with nausea, vomiting, or, less frequently, with phono or photophobia. Headache was reported in 93% of all subjects at the time of CVT diagnosis and was the only symptom in 17%.

Other symptoms and signs observed at the time of CVT diagnosis were (considering the entire sample): seizures (39%), hemiparesis (20%), papilledema (19%), decrease in level of consciousness (14%), visual loss (12%), diplopia (11.8%), aphasia (11%), tinnitus (7%), dizziness (6%), behavioral abnormalities (7%), or coma (4%).

The diagnosis of CVT was confirmed by CTV in 89% of subjects. MRI and MRV were performed in 74% of all subjects during hospital admission.

Most patients had NIHSS and MRS scores between 0 and 1 at the time of inclusion in the study (Table 1). Criteria for analgesic overuse were fulfilled in 1/5 of the subjects. Scores in SIS domains, were, on average, greater than 80 (Table 2).

The most frequent risk factor for CVT was oral contraceptive use (Table 3).

The superior sagital sinus was the most frequent site of thrombosis, followed by the left lateral sinus (Table 4). Recanalization was assessed in 92 subjects and was documented in almost 80% of them.

Among all subjects, at the time of the interview, 24 (24%) were in use of antidepressants, 26 (26%) of antiepileptic drugs and 3 (3%), of gabapentinoids. Nine subjects (9%) were in use of antidepressants and anti-epileptic drugs in association; 2 (2%), antidepressants with gabapentinoids. None were in use of the three classes of drugs.

4.2 Post-CVT headache (PCH)

More than half (59%) of the subjects reported headache in the chronic phase after CVT ($Group_{PCH}$).

4.3 Potential predictors of PCH

Tables 1 and 2 show characteristics of the subjects in $Group_{Control}$ and $Group_{PCH,}$ as well as between-group comparisons. History of RH was significantly more frequent in $Group_{PCH}$ than in $Group_{Control}$ (Table 1).

In addition (Table 1), $Group_{PCH}$ presented a higher burden of depressive and anxious symptoms, as well as lower scores in the SIS memory domain (Tables 1 and 2). Analgesic overuse was significantly more frequent in $Group_{PCH}$ than in $Group_{Control}$. There were no other significant

between-group differences in demographic characteristics, NIHSS, MRS, duration of anticoagulation (Table 1) or main risk factors for CVT (Table 3).

Only 3 subjects in $Group_{PCH}$ and 3 subjects in $Group_{Control}$ were treated with surgical or endovascular procedures at the acute phase after the diagnosis of CVT: dural fistula embolization (1), ventriculoperitoneal shunt + optic nerve sheath decompression (1), empyema drainage (1), ventriculoperitoneal shunt (1), optic nerve sheath decompression (1) and intracerebral hemorrhage drainage (1).

There were no significant differences between $Group_{Control}$ and $Group_{PCH}$ in regard to the number of thrombosed sinuses, sites of thromboses, frequencies of venous infarction and hemorrhagic lesions, or rates of recanalization (Table 4). At the time of inclusion in the study, none of the patients had presented CVT recurrence.

Multivariate analysis was not performed because just one variable (history of RH) was significantly more common in $Group_{PCH}$ than in $Group_{Control}$.

Table 1 - Characteristics of all subjects and in the subgroups with (Groupcontrol) and without (Group PCH) recurrent headache within the 3 months prior to the interview

Characteristics	Group control (n = 41)			Group PCH (n = 59)			All Subjects (n = 100)			p-value
Women (%)	31		75.6	51		86.4	82		82.0	0.169[b]
Skin Color										
White	24		58.5	29		49.2	53		53.0	0.448[a]
Non-white	17		41.5	29		49.1	46		46.0	0.503[a]
Age at CVT (years)	40.4	±	16.0	36.7	±	11.8	38.3	±	13.7	0.182[c]
Time from CVT diagnosis (years) until inclusion in the study	1.7	±	1.6	2.1	±	2.0	1.1	±	1.6	0.176[b]
BMI (kg/m^2)	27.4	±	5.3	26.9	±	5.1	27.1	±	5.2	0.672
Education (years)	10.1	±	3.4	11.4	±	4.1	10.8	±	3.8	0.828
Remote Headache (%)	**3**		**7.3**	**20**		**33.9**	**23**		**23.0**	**0.002[a]**
Current Analgesic Overuse (%)	**0**		**0.0**	**20**		**33.9**	**20**		**20.0**	**<.001[a]**
Previous analgesic overuse (%)	1		0.0	7		11.9	8		8.0	0.056[a]
Length of anticoagulation (days)	351.4	±	297.7	370.1	±	317.1	363.0	±	308.3	0.647[b]
PHQ9 total	**6.1**	±	**5.6**	**10.5**	±	**7.2**	**8.72**	±	**6.908**	**0.002[c]**
GAD7 total	**7.0**	±	**6.3**	**9.8**	±	**6.5**	**8.64**	±	**6.542**	**0.028[b]**
SIS memory	**87.7**	±	**16.3**	**77.1**	±	**22.7**	**81.4**	±	**20.9**	**0.017[b]**
NIHSS 0-1 (%)	38		92.7	55		93.2	93		93.0	0.917[a]
NIHSS >1 (%)	3		7.3	4		6.8	7		7.0	0.917[a]
mRS 0-1 (%)	38		92.7	51		86.4	89		89.0	0.326[a]
mRS 2-3 (%)	3		7.3	8		13.6	11		11.0	0.326[a]
Number of visits to hospitals before CVT diagnosis	2	±	1.43	1.9	±	1.1	2	±	1.23	0.324[c]

a: chi-square; b: Mann Whitney test; c: Student-t test.

GAD = Generalized anxious disorder; mRS = Modified rankin scale; NIHSS= National Institute of Health Stroke Scale; PHQ= Patient Health Questionnaire; SIS= Stroke Impact Scale

Table 2 - Scores in Stroke Impact Scale (SIS) scores (means ± standard deviations)

Characteristics	Group control (n = 41)			Group PCH (n = 59)			All Subjects (n = 100)			p-value
SIS recovery	0.9	±	0.2	0.8	±	0.2	0.8	±	0.2	0.055[a]
SIS memory	**88.0**	±	**16.0**	**76.9**	±	**22.7**	**81.4**	±	**20.9**	**0.013[b]**
SIS mood	83.0	±	22.6	74.6	±	25.7	78.1	±	24.7	0.095[a]
SIS communication	93.5	±	14.3	91.5	±	12.9	92.3	±	13.4	0.481[a]
SIS Physical domain	94.9	±	12.8	94.1	±	13.1	94.4	±	12.9	0.753[a]
Strength	95.3	±	12.2	84.1	±	12.8	94.6	±	12.5	0.638[a]
Daily activities	96.0	±	11.3	96.9	±	10.4	96.6	±	10.7	0.677[a]
Mobility	94.0	±	15.9	93.3	±	14.1	93.6	±	14.8	0.817[a]
Hand Function	94.3	±	18.4	91.9	±	21.5	92.9	±	20.2	0.574[a]
SIS social participation	88.3	±	19.6	81.5	±	25.5	84.3	±	23.4	0.153[a]

a: Mann Whitney test; b: Student-t test.

Table 3 - Risk factors for cerebral venous thrombosis (CVT)

Characteristics	Group control (n = 41)		Group PCH (n = 59)		All Subjects (n = 100)		p-value
Pregnancy and Puerperium* (%)	2	4.9	2	3.4	4	4.9*	0.708[a]
Oral Contraceptive* (%)	21	51.2	36	61.0	57	69.5*	0.510[a]
Hiperhomocisteinemia (%)	2	4.9	1	1.7	3	3.0	0.358[a]
Protein C deficiency (%)	1	2.4	0	0.0	1	1.0	0.227[a]
Protein S deficiency (%)	2	4.9	1	1.7	3	3.0	0.358[a]
Antithrombin III deficiency (%)	0	0.0	1	1.7	1	1.0	0.402[a]
Prothrombin gene mutation (%)	2	4.9	9	15.3	11	11.0	0.102[a]
Factor V mutation (%)	0	0.0	1	1.7	1	1.0	0.402[a]
Antiphospholipid Antibody Syndrome (%)	1	2.4	2	3.4	3	3.0	0.783[a]
Behçet Disease (%)	2	4.9	1	1.7	3	3.0	0.358[a]
Probable autoimmune condition (%)	1	2.4	2	3.4	3	3.0	0.783[a]
Sticky Platelet Syndrome (%)	1	2.4	1	1.7	2	2.0	0.793[a]
Cancer (%)	2	4.9	2	3.4	4	4.0	0.693[a]
Undetermined (%)	7	17.1	11	18.6	18	18.0	0.840[a]

a: qui-square; *- % (n=82 women)

Table 4 - Thrombosed sinuses, intracranial lesions and recanalization during follow-up

Sinus and lesions	Group control (n = 41)		Group PCH (n = 59)		All Subjects (n = 100)		p-value
Number of thrombosed sinuses	2.5	± 1.1	2.3	± 10.7	2.4	± 1.1	0.427[b]
Venous Infarction (%)	13	31.7	16	27.1	19	19%	0.618[a]
Hemorrhagic transformation (%)	4	9.8	6	10.2	10	10%	0.945[a]
Subarachnoid Hemorrhage (%)	7	17.1	12	20.3	19	19%	0.682[a]
Intraparenchymal Hemorrhage (%)	10	24.4	12	20.3	22	22%	0.630[a]
Superior Sagittal Sinus (%)	25	61.0	28	47.5	63	63%	0.726[a]
Left Lateral Sinus (%)	22	53.7	21	35.6	43	43%	0.072[a]
Right Lateral Sinus (%)	17	41.5	31	52.5	48	48%	0.275[a]
Deep Venous System and Straight Sinus (%)	6	14.6	7	11.9	13	13%	0.685[a]
Cortical Veins (%)	12	29.3	16	27.1	28	28%	0.754[a]
Internal Jugular Veins (%)	19	46.3	21	35.6	40	40%	0.280[a]
Cavernous Sinus (%)	0	0.0	1	1.7	1	1%	0.402[a]
Any Lateral Sinus (%)	24	58.5	46	77.9	80	80%	0.541[a]
Recanalization*	27	65.8	44	74.6	71	77.2	0.690[a]

a: Chi-square; b: Student-t test

*: Recanalization was assessed in 92 subjects. Eight subjects did not have an available imaging for blind recanalization assessment.

4.4 Characteristics of Post-CVT headache and Remote Headaches

Types of PCH and RH are shown in Table 5. PCH was not classified as a headache attributed to CVT because these subjects presented total or partial recanalization and they presented resolution of acute symptoms of CVT oven the time. In the subgroup of patients with PCH, types of pain resembled primary headaches in 79.7% of the subjects.

Only one patient (1.7%) performed a surgical procedure at the chronic phase. This subject was a male that developed a new headache at the chronic phase. A secondary cause for the headache was investigated according to the Cerebral Venous Thrombosis clinic's protocol (Figure 3) and multiples dural fistulae were diagnosed. Headache ceased after endovascular treatment of the fistulae.

"Other headaches" were identified in 11 (18.6%) patients. One patient had a pain that shared features with trigeminal neuralgia and started after cavernous sinus thrombosis. Ten patients had headaches that did not fulfill criteria for any particular type of headache. The investigation according to the institutional protocol did not reveal secondary causes in these patients.

Characteristics of PCH are shown in Table 7 and associated symptoms, in Table 8.

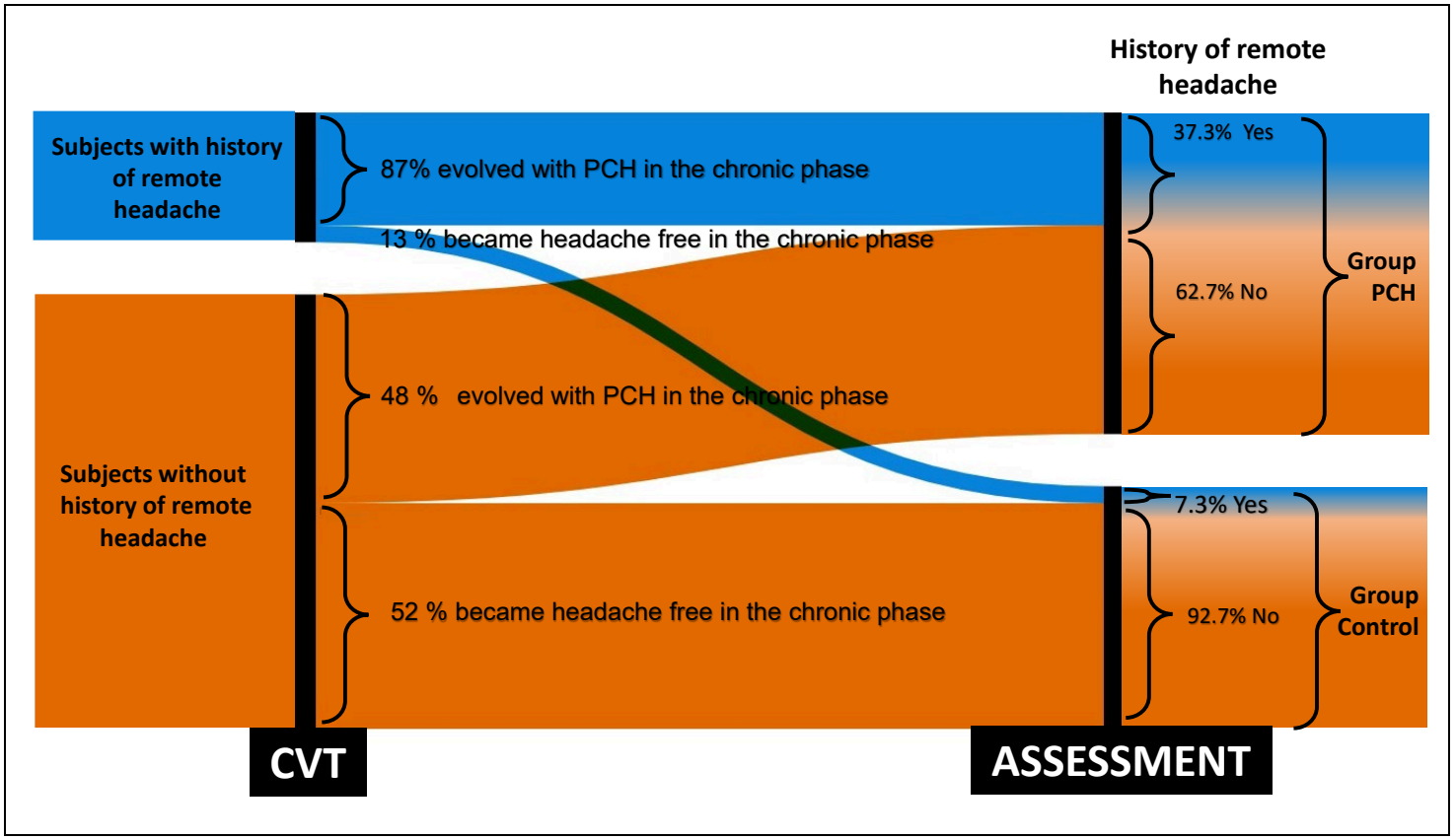
The intensity of PCH was moderate in 28 (47.5%) of the subjects and severe in 14 (23.7%). Overall, the number of days with pain per month (average ± standard deviation) was 13.6 ± 9.9 days and the number of days of absence from work, 2.3 ± 5.1 per month. The burden of disability according to different types of pain, and the intensity of pain according to a

Visual Analog Scale (from zero to 10) are shown in Table 6.

In $Group_{PCH,}$ 16 (27.1%) subjects were in use of antidepressants; (20.3%), of antiepileptic drugs; and 2 (3.4%), of gabapentinoids. There were no significant between-group differences in regard to the frequency of use of these types of medications (p=0.937).

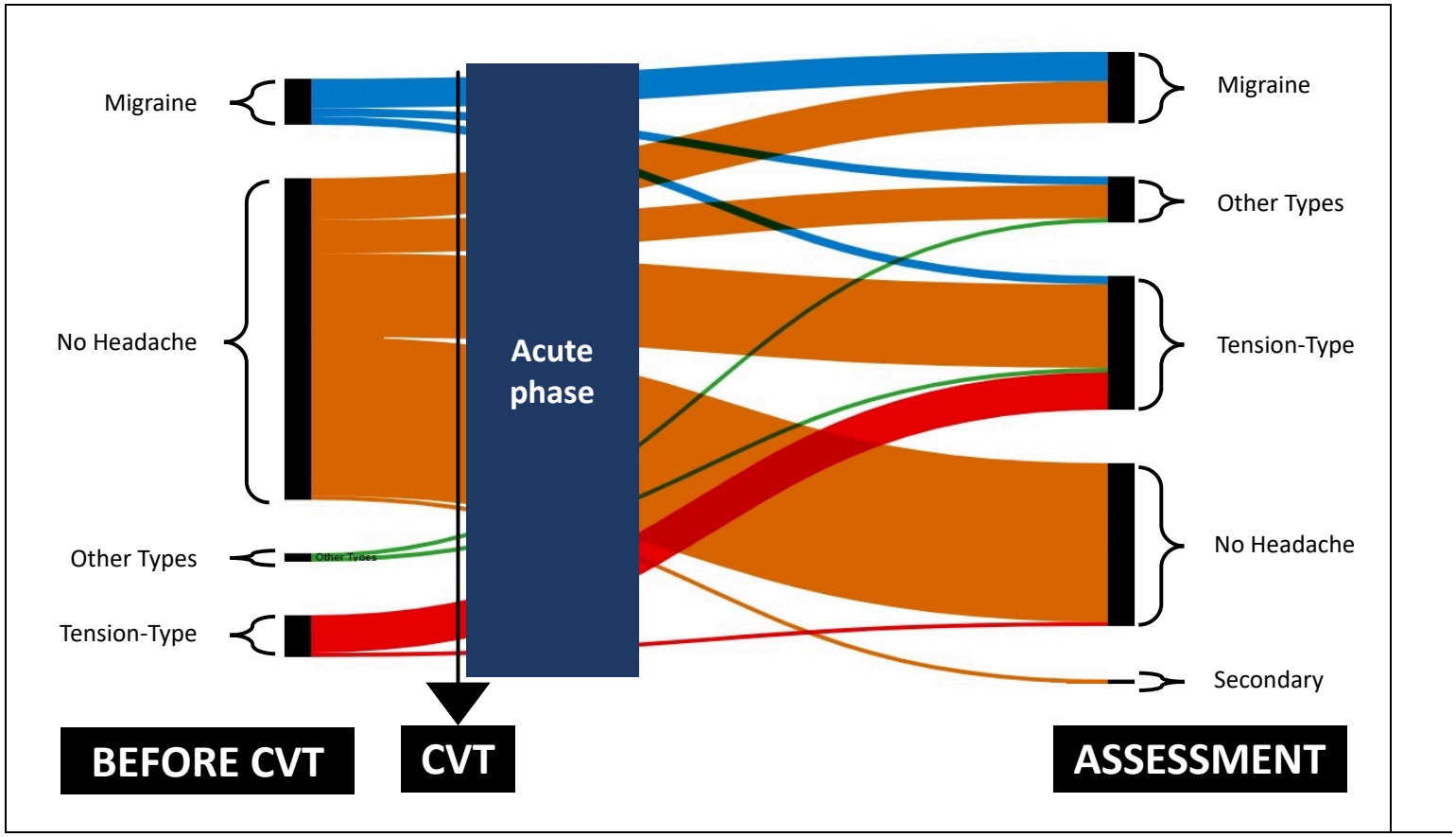
Figure 5 shows the progression of *any headache* in $Group_{PCH}$ and in $Group_{Control,}$ according to prior history, or lack of history, of RH.

Figure 6 shows the progress of different *types of headaches* in $Group_{PCH}$ and in $Group_{Control,}$ according to prior history, or lack of history, of RH.



PCH: Post-CVT headache

Figure 5 - Remote Headache in subjects with (GroupPCH) or without (GroupControl) at the chronic phase after cerebral venous thrombosis



CVT: Cerebral venous thrombosis

Figure 6 - History of headache and type of headache in in subjects with (GroupPCH) or without (GroupControl) at the chronic phase after cerebral venous thrombosis

After CVT, the headache status (yes/no) significantly changed ($p < 0.001$). Most subjects (87%) with history of RH reported PCH, while almost half (48%) of the subjects without history of RH also reported PCH (Figure 5 and Table 1).

Characteristics/types of RH were compared to PCH in Tables 5, 7 and 8. The most common type of RH was migraine, while the most frequent type of PCH fulfilled criteria for probable tension-type headache.

Overall, considering only subjects who reported RH (n=23), almost half reported migraine as their type of RH, and less than one third had PCH with characteristics consistent with probable migraine.

In GroupPCH, in the subgroup of patients with history of RH (n=23), the characteristics of PCH were not significantly different from the characteristics of RH, when within-subject comparisons were performed ($p = 0.9$).

4.5 Comparisons between Post-CVT headaches and headache at the times of CVT diagnosis

Only one patient (1.7%) described PCH with exactly the same characteristics of the headache reported at the time of CVT diagnosis.

Table 5 - Comparison between types of remote headache (RH) and headache in the chronic phase after cerebral venous thrombosis (PCH)

Type of headache	Remote Headache (n = 23)	PCH (n = 59)	p-value
Migraine (n, %)	11 (47.8)	16 (27.1)	0.005[a]
Tension-Type (n, %)	10 (43.5)	31 (52.6)	<.0001[a]
Secondary (n, %)	0	1 (1.7)	-
Other types (n, %)	2 (8.7)	11 (18.6)	.071[a]

[a]: Chi-square
Types of headaches were classified according to International Headache Society criteria (2018), based on characteristics reported by the subjects. For subjects with PCH that fulfilled all criteria except the number of attacks (at least 5, migraine without aura; at least 10, tension-type headache), "migraine" stands for "probable migraine" and "tension-type headache" stands for probable "tension-type headache".

Table 6 - Number of days with pain, days with inability to perform instrumental activities of daily living (per month) and intensity of pain in a Analog Visual Scale from zero to 10, in patients who reported headache in the chronic phase after cerebra venous thrombosis

Variable Mean (SD)	Migraine (n=16)	Tension-type (n=31)	Secondary (n=01)	Other types (n=11)
Number of days with pain per month	15.4 (11.5)	14.2 (9.1)	6	13.4 (10.5)
Number of days with inability to perform instrumental activities of daily living, per month	14.2 (9.1)	0.6 (1.6)	2	1.9 (3.6)
Visual Analog Scale, pain intensity	6.9 (2.4)	3.9 (2.1)	6	6.1 (2.2)

Table 7 - Pain characteristics and associated symptoms

	Remote Headache (n = 23)		Acute CVT Phase Headache (n = 93)		PCH (n = 59)	
Type (%)						
Tightening	2	(8.7)	9.0	(9.7)	6.0	(10.2)
Pressure	6	(26.1)	56.0	(60.2)	27.0	(45.8)
Stabbing	0	(0.0)	6.0	(6.5)	3.0	(5.1)
Throbbing	13	(56.5)	29.0	(31.2)	22.0	(37.3)
Burning	1	(4.3)	3.0	(3.2)	2.0	(3.4)
Shock-like	0	(0.0)	1.0	(1.1)	2.0	(3.4)
Location (%)						
Bilateral	5	(21.7)	46.0	(49.5)	14.0	(23.7)
Left	1	(4.3)	8.0	(8.6)	2.0	(3.4)
Right	1	(4.3)	12.0	(12.9)	13.0	(22.0)
Right or left	10	(43.5)	6.0	(6.5)	18.0	(30.5)
Site of onset (%)						
Forehead	7	(30.4)	13.0	(14.0)	11.0	(18.6)
Eyes	0	(0.0)	3.0	(3.2)	4.0	(6.8)
Temporal†	7	(30.4)	17.0	(18.3)	9.0	(15.3)
Vertex	3	(13.0)	26.0	(28.0)	9.0	(15.3)
Nape¬	3	(13.0)	23.0	(24.7)	9.0	(15.3)
Neck&	0	(0.0)	1.0	(1.1)	1.0	(1.7)
Side of the Head+	4	(17.4)	10.0	(10.8)	13.0	(22.0)

†: Temporal muscle region; ¬: Transition region between the cranium and the neck; &: The whole neck itself; +: The whole lateral of the head, including temporal muscle region plus behind-the-region, without affecting the whole half of the head.

Table 8 - Symptoms associated with remote headache, headache at the time of diagnosis of cerebral venous thrombosis (CVT headache) and post-CVT headache (PCH)

	Remote headache (n = 23)		Acute CVT phase headache (n = 93)		PCH (n = 59)	
Other Symptoms (%)						
Nausea	8	(34.8)	45.0	(48.4)	25.0	(42.4)
Vomiting	1	(4.3)	39.0	(41.9)	5.0	(8.5)
Photophobia	11	(47.8)	18.0	(19.4)	17.0	(38.8)
Phonophobia	10	(43.5)	16.0	(17.2)	20.0	(33.9)
Red eyes	0	(0.0)	2.0	(2.2)	0.0	(0.0)
Tearing	0	(0.0)	3.0	(3.2)	1.0	(1.7)
Nasal Obstruction	0	(0.0)	2.0	(2.2)	1.0	(1.7)
Dizziness	0	(0.0)	7.0	(7.5)	4.0	(6.8)
Aura and other characteristics (%)						
Visual	0	(0.0)	0.0	(0.0)	3.0	(5.1)
Worsening with physical exertion	12	(52.2)	70.0	(75.3)	33.0	(55.9)
Worsening with menses	19	(82.6)	-	-	34.0	(57.6)

CVT: Cerebral venous thrombosis; PCH: Post-CVT headache

5 DISCUSSION

5.1 Frequency of Post-CVT headache (PCH)

The main finding of this study is that almost two-thirds (59%) of the patients presented PCH. This rate is higher than those previously reported: 47% in VENOPORT[3]; 43% according to the 6-item Headache Impact Test[68]; 20% of headache more than once a week[41], and 14% of severe headache in ISCVT[20].

This discrepancy is likely due to different ascertainment criteria because structured headache interviews were not performed in prior studies. Interestingly, a similar rate (51%) of headache was reported by 89 subjects that answered structured interviews 12 months after ischemic stroke[67].

Differences in study design (prospective/retrospective), characteristics of the patients and duration of follow-up may also have contributed to disparities in results between the present study and prior reports of headache at the chronic stage after CVT.

5.2 Characteristics and predictors of PCH

Clinical characteristics at the time of CVT diagnosis, imaging features (site, extent or recanalization of thrombosis), CVT risk factors/etiologies or time since CVT were not significantly different between subjects with or without PCH.

Pain characteristics in PCH and in headaches that led to CVT diagnosis were substantially different. None of the subjects in the present study reported a headache at the chronic phase with similar characteristics to the headache that led to CVT diagnosis. Likewise, in the study from Carvalho Dias *et al.*[67] only 1/89 patients reported headaches at the chronic stage that shared characteristics with the pain reported in the acute phase after ischemic stroke, as described in item 6.1.1.2 of ICHD[19,67].

The descriptions of headache at the time of CVT diagnosis in our patients were consistent with ICHD criteria (no specific pattern of headache attributed to CVT)[19]. Our data are also in line with previous reports that depicted headache as the most frequent presenting symptom of CVT[1,7,8,20,21]. CVT diagnosis was often made just after two or more medical evaluations and, in 73% of the patients, the diagnosis of CVT was only made after a new neurological symptom. These results highlight the concept that new-onset headache may be underestimated in emergency departments, leading to underdiagnosis of CVT.

Approximately one third (33.9%) of the patients with PCH had history of RH. The rate of headaches that fulfilled criteria for primary headaches prior to the diagnosis of CVT was higher in our study than in epidemiological studies in Brazil. The population in our study is mainly composed of young women and is hence not representative of the Brazilian population.

The rate of RH *in subjects with PCH* in the present study was lower than the 77.8% rate of RH, 12 months prior to ischemic stroke, *in subjects with post-ischemic stroke headaches*[67]. The rate of pre-stroke headache was

also substantially higher (57.3%) in the entire series of patients with ischemic stroke than in our entire series of patients with CVT (23%).

Despite having a more than twofold bigger rate of headache prior to the cerebrovascular event, compared to patients with CVT, patients with ischemic stroke had slightly lower rates of post-cerebrovascular event headache than subjects with CVT. These discrepancies may be partially explained by different extents of time for recollection of headache before the cerebrovascular event headache (3 versus 12 months), by different structured interviews used in each of the studies, by different characteristics (such as age or gender) of the patients with ischemic stroke and CVT or by diverse mechanisms of pain at the chronic stage after ischemic stroke and after CVT.

While in our series history of RH prior to CVT was the only factor independently associated with PCH, both history of RH and female sex were independent predictors of headache post-ischemic stroke. This difference may be related to a ceiling effect in our series, that was predominantly composed of women (82%), compared to the series of ischemic stroke (39.3%).

Subjects with PCH had significantly higher rates of analgesic overuse, as well as more symptoms of anxiety or depression than those without PCH. It is not possible to establish a causal relationship between PCH and analgesic overuse or psychiatric conditions in our series, given the design of our study. The associations between pain, decline in cognitive functions and symptoms of depression or anxiety are well recognized in the literature[78-80].

These results highlight the importance of screening patients with CVT for psychiatric symptoms and chronic use of painkillers, despite favorable

mRS and low NIHSS scores. Also, future work is required to assess if treatment with prophylactic drugs early after CVT, particularly in subjects with history of primary headaches prior to CVT, can decrease the burden of PCH.

5.3 Comparisons Between Characteristics of PCH and Remote Headaches

In $Group_{PCH}$, in the subgroup of patients with history of RH, the characteristics of PCH were not significantly different from the characteristics of RH. This result is clinically relevant because it suggests that, in most cases, PCH is not related to feared complications of CVT.

Most subjects with history of RH reported PCH, while almost half of the subjects without history of RH also reported PCH. All together, these findings suggest two main categories of PCH. The first occurs in patients with RH in whom PCH seems to be the reactivation of a previous primary headache, possibly sharing similar underlying mechanisms. On the other hand, in subjects with no history of RH, PCH seems to represents a new category of headache.

PCH might represent a **persistent headache attributed to a past cerebral venous thrombosis**. The criteria for this condition may include: a new-onset headache, *different from the headache that led to the diagnosis of CVT*; the pain may mimic any primary headache, in patients without history of primary headache disorder; secondary headaches associated with complications o CVT (chronic intracranial hypertension, dural fistulae) must be excluded. PCH may also represent a “de novo” primary headache,

triggered by a relevant clinical event and not specifically, to CVT. In order to test these hypotheses about PCH, comparisons between rates of primary headaches in groups with or without history of CVT in prospective or case-control studies are required.

Studies with biomarkers may also contribute to better understand the pathophysiology of headache. For instance, the calcitonin Gene Related Peptide (CGRP) is a 37-amino acid peptide produced by an alternative splice of the calcitonin gene. It is produced by central and peripheral neurons and is a strong vasodilator and increase nociception. Beyond nociception, CGRP plays a whole in cardiovascular homeostasis[58,59]. The main source of CGRP is the trigeminal ganglia. High levels of this substance are described in migraineurs patients and even higher levels during migraine attacks. The block of the CGRP receptors or the reductions in available CGRP are novel tools in preventive and abortive treatment of migraine[61,81-83]. The comparison of CGRP levels and the effect of anti-CGRP treatment in migraineurs without CVT, and in patients with PCH that fulfills criteria for probable migraine may provide clues about whether CVT, possibly by changes in inflammatory biomarkers or in mediators of nociception, could influence mechanisms of pain.

Secondary headache was very rare in our series, diagnosed in only one patient with a dural fistula diagnosed during follow-up. In secondary headaches, pain may be caused by the stimulation of C fibers of the meninges, arterial or venous structures[56, 59, 84-86].

Dural Fistulae are pathological shunts between dural arteries and dural venous sinuses, cortical veins or meningeal veins[87]. The mechanisms

underlying the genesis of arteriovenous fistulae are not completely understood but one of the hypothesis is a progressive increase in venous pressure due to CVT or other causes[88]. In addition, venous stasis within fistulae might predispose to CVT. Therefore, fistulae may be considered risk factors for CVT in some cases and complications of CVT in other patients. The rate of fistulae in our series (1.7%) is consistent with the 1.6% rate reported)[8,88,89] in other series. Pulsatile tinnitus and changes in headache characteristics should be considered red flags and lead to investigation of dural fistulae[90]. The gold standard for diagnosis is digital subtraction angiography but, considering the invasive nature of this imaging test, CTA and CTV or MRA or MRV may be considered for screening when the diagnosis is suspected[88-90].

Others causes of secondary headache at the chronic phase of CVT, such as intracranial hypertension and CVT recurrence, were not identified in our patients. CVT recurrence is infrequent but is a concern of neurologists faced with patients with headache at the chronic stage after CVT. In ISCVT, 14/624 (2.2%) patients presented recurrence over 16 months[20]. Dentali *et al*.[91], in a multicenter retrospective study, observed recurrence in 31/706 (4.4%) over 40 months. In the present study, recurrence was not observed in any of the patients. In RESPECT-CVT[92], in line with our results, no CVT recurrences were observed after a follow-up of 6 months in patients treated with warfarin or dabigatran. The shorter duration of follow-up at the time of inclusion in our study (on average, one year), the systematic assessment of risk factors, duration of anticoagulation (at least 3-6 months in the presence

of reversible risk factors, indefinite for patients with high-risk thrombophilias) may have contributed to the differences between our study and other series.

Chronic intracranial hypertension is a possible complication but was not identified in any of the subjects in our series. CVT and sinuses stenosis are possible causes of increase in intracranial pressure. ICDH establishes intracranial hypertension headache as a progressive, daily, non-pulsating and/or aggravated by coughing or straining[52]. Diagnosis is made by the measurement of cerebrospinal fluid opening pressure and ventriculoperitoneal/lumbar shunts should be considered to treat this condition[93-96]. Sinus angioplasty has also emerged as a potential intervention[93,97,98].

5.4 Comparison Between Characteristics of PCH and headache at the time of CVT diagnosis

Only one patient referred PCH as having the same characteristics of headache at the time of CVT diagnosis PCH, possibly indicating a headache directly attributed to CVT. However ICHD criteria 6.6.1[52] were not fulfilled because it was demonstrated by imaging and clinical observation that thrombosis had improved in this case.

A similar observation was made by Carvalho Dias *et al.*[67] in the series of patients with ischemic stroke: in only 1/89 subject, criteria for *6.1.1.2 persistent headache attributed to a past ischemic stroke – cerebral infarction* according to ICHD[67] – were fulfilled. In combination with our results, these data suggest that the classification of Vascular Headache deserves an update.

5.5 Limitations and Strengths

The main strength of this study is the detailed assessment of headache in a series of patients with CVT, a rare type of cerebrovascular disease. Clinical evaluation, including symptoms of depression or anxiety and analgesic overuse, as well as radiological assessment, were thoroughly performed. Headache data was collected blindly to information about CVT location, extension or treatment.

The main limitations are the retrospective design and the lack of a control group without CVT, matched by sex and age. Accuracy of recollection of headache might have influenced the rates of RH or PCH. Still, we consider recall bias unlikely, because the mean interval between CVT and the interview was not long (average, 1.1 years) and most patients were young. Another limitation is that specific tests for detailed assessment of cognition were not performed.

Not all patients with PCH underwent extensive investigation for secondary headaches. We do not routinely interrupt anticoagulation to perform lumbar puncture, or order lumbar punctures in every single patient with PCH in clinical practice. We opt to order additional tests, including lumbar puncture and CTV or MRV, when there is a suspicion of secondary headache (lack of criteria for a primary headache, lack of response to treatment, signs of intracranial hypertension or other red flags). In the subset of patients with PCH and “other headaches”, a prospective design might have provided more information about the types of pain. A single interview may have missed features that a detailed follow up might add.

Finally, we did not assess return to work or social/economic burden attributed to PCH. Koopman *et al*.[68] reported that 33 (75%) patients with CVT in a mean follow-up of 63 month, versus 10 (23%) in the control group. In a prospective series of 161 patients, Hiltunen *et al*.[41] found that 70 (43%) from 161 patients were unemployed. The main risk factors for unemployment were male sex, age > 38, low educational level, NIHSS > 2, motor and/or sensory deficits, linguistic-self-reported problems, neuropsychological self-reported-problems, and active epilepsy.

5.6 Future Perspectives

CVT is considered a disease with a good prognosis defined mainly by low MRS scores. However, the mRS may not capture the impact of pain, cognitive or mood disorders at the chronic stage after CVT. Future studies are necessary to close this gap, to understand the pathogenesis of residual symptoms at the chronic stage and decrease the burden of a condition that mainly affects young women.

Our results suggest that a critical review about the classification of vascular headaches is deeply needed, because current criteria do not represent the symptoms described by patients. Criteria for PCH should be defined in order to standardize headache classification, increase awareness of this condition, and facilitate multicenter collaborations[44].

Using a more accurate classification, prospective and case-control studies should be performed and pathogenesis of PCH could be investigated with additional functional imaging and laboratory assessment. The relation

between headache and employment or quality of life based on patient-reported outcomes should be thoroughly investigated in order to capture the full impact of CVT.

In summary, this study paves the way for future multicenter prospective or case-control studies about diagnostic criteria, underlying mechanisms, prevention, treatment and disability from PCH.

6 CONCLUSIONS

PCH occurred in 59% of CVT survivors and shared characteristics with primary headaches.

The only risk factor for PCH was the history of RH.

Patients with PCH often reported pain with moderate or severe intensity and presented symptoms of anxiety, depression or analgesic overuse.

7 ATTACHMENTS

Attachment A - Informed Consent

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

****

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1- NOME: ……

DOCUMENTO DE IDENTIDADE No : …… SEXO : M □ F □

DATA NASCIMENTO: ...../...../.....

ENDEREÇO …… No ……

APTO …… BAIRRO: …… CIDADE ……

CEP:..... TEL: (.....) .....

2- RESPONSÁVEL LEGAL .....

NATUREZA (grau de parentesco) …… …DOC. IDENTIDADE :.....

SEXO : M □ F □ DATA NASCIMENTO.: ...../...../.....

ENDEREÇO …… No ……

APTO …… BAIRRO: …… CIDADE ……

CEP:..... TEL: (.....) ……

****

DADOS SOBRE A PESQUISA

1- TÍTULO DO PROTOCOLO DE PESQUISA: CARACTERIZAÇÃO DA CEFALEIA CRÔNICA EM PACIENTES COM TROMBOSE VENOSA CEREBRAL.

PESQUISADORA : Adriana Bastos Conforto

CARGO/FUNÇÃO: Médica INSCRIÇÃO CONSELHO REGIONAL No CRM: 80.298

UNIDADE DO HCFMUSP: Departamento de Neurologia

PESQUISADOR EXECUTANTE: Alexandre Souza Bossoni

CARGO/ FUNÇÃO: Médico INSCRIÇÃO CONSELHO REGIONAL No CRM: 139.466

2- AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MINIMO x RISCO MEDIO □

RISCO BAIXO □ RISCO MAIOR □

3- DURAÇÃO DA PESQUISA: 36 meses

****

Nós convidamos o(a) senhor(a) para participar de uma pesquisa no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. É importante que o(a) senhor(a) leia ou ouça e entenda o que será feito nesta pesquisa. Sua participação depende somente do senhor, então não se apresse em tomar a sua decisão.

Durante o acompanhamento de pacientes com Trombose Venosa Cerebral, os médicos do ambulatório notaram que a Dor de Cabeça, mesmo após anos da trombose, é um sintoma frequente, persistente, que causa incômodo e prejudica a qualidade e vida. Até o momento não sabemos exatamente os motivos que levam ao aparecimento e a manutenção dessa dor. Também não sabemos qual seria o melhor tratamento para essas dores de cabeça após uma trombose venosa cerebral.

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

1- O objetivo do nosso estudo é avaliar a ocorrência de dor de cabeça em pessoas que tiveram Trombose Venosa Cerebral e descrever como é essa dor nos pacientes que acompanhamos. A avaliação será feita com uma entrevista padronizada feita por um médico neurologista da nossa equipe, que também o examinará e coletará informações do seu prontuário médico.

2- Os procedimentos realizados serão os seguintes:

- Você será apresentado(a) a esse presente termo, podendo tirar todas as suas dúvidas.
- Será feita entrevista com médico neurologista e você responderá a perguntas sobre:
  - característica da sua dor de cabeça
  - como essa dor atrapalha seu dia a dia em diversos aspectos
  - perguntas sobre medicações que usa para dor
  - sintomas de depressão e ansiedade
  - qualidade do seu sono
  - você realizará um breve teste para avaliar o funcionamento da mente
  - você será examinado por nosso médico
  - receberá um cartão no qual marcará, durante três meses, os dias em que teve dor de cabeça, devolvendo-o no final desse período, quando retornar ao hospital.

3- Não há quaisquer desconfortos físicos nessa pesquisa. Todas as perguntas feitas são comumente usadas em outras pesquisas e respeitam integralmente sua ética, cultura, moral, religião, crenças e privacidade. O exame médico realizado é uma exame neurológico comum, direcionado para essa pesquisa.

4- Em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. A pesquisadora principal é a Dra. Adriana Bastos Conforto, que pode ser encontrada no endereço: Departamento de Neurologia do Hospital das Clínicas, Rua Ovídio Pires de Campos, 225 – 5o andar – Sala 5080; telefone: 2661-7955. O pesquisador executante é o Dr. Alexandre Souza Bossoni, que pode ser encontrada no mesmo endereço ou pelo telefone (11) 986531232. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – Prédio da Administração - 5o andar – Cerqueira Cesar tel: 2661-7585 – e-mail: cappesq.adm@hc.fm.usp.br, durante o horário de funcionamento: Segunda a Sexta-feira 9h as 16h.

5- A qualquer momento o(a) senhor(a) poderá deixar de participar deste estudo sem nenhum prejuízo à continuidade de seu tratamento no Hospital das Clínicas. Participar desse estudo não altera em nada seu tratamento e a periodicidade das suas consultas e exames no Hospital das Clínicas.

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

6- Todas as informações obtidas durante o estudo serão analisadas em conjunto com as informações de outros pacientes, sendo que não será divulgada a identificação de nenhum paciente.

7- O(a) senhor(a) tem direito de ser mantido atualizado(a) sobre os resultados parciais desta pesquisa.

8- O(a) senhor(a) não receberá nenhum valor referente à sua participação nesse trabalho. No caso do senhor(a) comparer no hospital em dia diferente da sua consulta, exclusivamente para participação nesse trabalho, será oferecida uma ajuda de custo referente ao transporte público atualizado. O valor dessa ajuda de custo é padronizado em duas passagens de ônibus, com o valor atualizado. Não haverá compensação financeira relacionada à sua participação no estudo.

9- Todo o material coletado durante esta pesquisa será usado somente para esta pesquisa.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo **"Caracterização da Cefaleia Crônica em pacientes com Trombose Venosa Cerebral"**

Eu discuti com a Dra. Adriana Bastos Conforto e/ou Dra. Alexandre Souza Bossoni sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

_____
Assinatura do paciente/representante legal Data ...../..... /.....

_____
Assinatura da testemunha Data ...../..... /.....

para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.

(Somente para o responsável do projeto)
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

_____
Assinatura do responsável pelo estudo Data ...../..... /.....

Rubrica do sujeito de pesquisa ou responsável_____
Rubrica do pesquisador_____

Attachment B - Structured Headache Interview

1

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
UNIVERSIDADE DE SÃO PAULO - HCFMUSP

CADERNO DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA E DADOS SÓCIO DEMOGRÁFICOS (ENTREGAR NO FINAL DA ENTREVISTA PARA CADASTRO DO PACIENTE)

NOME: ……

DATA AVALIAÇÃO: ...../...../..... DATA NASCIMENTO: ...../...../..... IDADE …… SEXO : M □ F □

PRONTUÁRIO T.V.C. …… DATA DA TVC ……..

ENDEREÇO …… N ……

APTO ..... BAIRRO: ..... CIDADE ……

CEP:..... TEL: (.....) …….. TEL: (.....) ……..

DOMINÂNCIA 1.( ) DESTRO 2.( ) CANHOTO ESCOLARIDADE _____ ANOS

PESO _____ KG ALTURA _____ CM IMC _____ KG/M2

RENDA MENSAL IBGE CENSO 2010

1.( ) SEM RENDIMENTO 2.( ) ATÉ R$150 3.( ) ENTRE R$150 E R$300

4.( ) ENTRE R$300 E R$600 5.( ) ENTRE R$600 E R$1.200 6.( ) ENTRE R$1.200 E R$1.800

7.( ) ENTRE R$1.800 E R$3.000 8.( ) ACIMA DE R$3.000 9.( ) PREFIRO NÃO RESPONDER

COMO VOCÊ SE CONSIDERA (IBGE CENSO 2010) ?

1. ( ) BRANCO 2. ( ) PRETO 3. ( ) PARDO 4. ( ) AMARELO 5. ( ) INDÍGENA

1

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA

UNIVERSIDADE DE SÃO PAULO-HCFMUSP

CADERNO DE AVALIAÇÃO CLÍNICA DA CEFALEIA, EXAME FÍSICO E ESCALAS DIVERSAS

1- AVALIAÇÃO DA CEFALEIA - CEFALEIA ATUAL

CEFALEIA ( ) 1. SIM ( ) 2. NAO

HÁ QUANTO TEMPO TEM CEFALEIA? _____ ANOS

FREQÜÊNCIA _____ DIAS POR MÊS

FALTAS ESCOLA/ TRABALHO/ ATV DIÁRIA _____ DIAS NO MES

EPISÓDIOS DE DOR POR DIA _____ Nº EPISÓDIOS

DURAÇÃO DA DOR _____ ( ) HORAS ( ) SEG

CONSEGUE REALIZAR ATIVIDADES DIÁRIAS/ TRABALHO MESMO COM A DOR? ( ) 1. SIM ( ) 2. NAO

INTENSIDADE MAXIMA ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Sem Dor — Pior Dor Possível

IMPACTO NAS SUAS ATIVIDADES DO DIA A DIA (EM CASA E NO TRABALHO) ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — Totalmente Incapacitado

IMPACTO DA DOR NO SEU HUMOR ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NO SEU TRABALHO ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — Não consigo trabalhar

IMPACTO DA DOR NO RELACIONAMENTO COM OUTRAS PESSOAS ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NO SEU SONO ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NA SUA CAPACIDADE DE APRECIAR A VIDA ( ) 99. NAO SEI

0 ● ——— ● 10 ☐

Nenhum Impacto — O máximo possível

2

TIPO DA DOR ( ) 1. APERTO ( ) 2. PRESSÃO
( ) 4. FACADA ( ) 5. PULSAÇÃO OU LATEJANTE
( ) 6. ARDÊNCIA ( ) 7. CHOQUE

LOCALIZAÇÃO ( ) 1. TODA A CABEÇA ( ) 2. APENAS A ESQUERDA
( ) 3. APENAS A DIREITA ( ) 4. ORA A DIREITA, ORA A ESQUERDA
( ) 5. DOS DOIS LADOS AO MESMO TEMPO.

APARECIMENTO ( ) 1. TESTA ( ) 2. OLHOS ( ) 3. TEMPORAIS
( ) 4. EM CIMA DA CABEÇA ( ) 5. ATRAS DA CABEÇA/ NUCA
( ) 6. PESCOÇO ( ) 7. LATERAL DA CABEÇA

SINTOMAS ASSOCIADOS ( ) 1.NAUSEA ( ) 2.VOMITO ( ) 3.FONOFOBIA
( ) 4. FOTOFOBIA ( ) 5. HIPEREMIA CONJUNT.
( ) 6. LACRIMEJAMENTO ( ) 7. OBSTRUÇÃO NASAL
( ) 8.HEMIPARESIA ( ) 9. DIPLOPIA
( ) 10.HEMIPARESIA ( ) 11.TONTURA/ VERTIGEM

AURA ( ) 1.VISUAL ( ) 2. SENSITIVA ( ) 3. MOTORA
( ) 4. AURA SEM DOR ( ) 9. AUSENTE

OUTRA AURA _____

DURAÇÃO DA AURA _____

QUAL? _____

PIORA COM ATV. FÍSICA ( ) 1. SIM ( ) 2. NÃO

PIORA NA MENSTRUAÇÃO ( ) 1. SIM ( ) 2. NAO ( ) 3. N.A.

DESENCADEANTE ( ) 1. SIM ( ) 2. NAO
QUAL?_____

MEDICAÇÃO PROFILÁTICA ( ) 1. NAO USA ( ) 2. ANTIDEPRESSIVO
( ) 3. DAE ( ) 4. BETA BLOQ ( ) 5. BLOQ. CANAL CA+
( ) 6. OUTRAS MEDICAÇÕES?
QUAL/ DOSE (MG)? _____

SINTOMÁTICO ( ) 1. NAO USA ( ) 2. ERGOT. ( ) 3. TRIPTANO
( ) 4. AINE ( ) 5. CORTICOIDE ( ) 6. ANALG. COMUM
( ) 7. OPIOIDE FRACO ( ) 8. OPIOIDE FORTE ( ) 9. RELAX. MUSC.
QUAL/ DOSE (MG)?_____

_____

QUANTOS DIAS POR MÊS USA SINTOMÁTICOS? _____ DIAS POR MÊS

QUANTAS VEZES POR DIAS USA SINTOMÁTICOS? _____ VEZES POR DIA

HA QUANTO TEMPO USA ESSES SINTOMÁTICOS NESSA FREQUÊNCIA? _____ MESES

JÁ USOU MED. PROFILÁTICA ANTES? ( ) 1. SIM ( ) 2. NÃO

SE SIM, QUAL O MOTIVO PELO QUAL PAROU?_____

QUAL MEDICAÇÃO ? _____

QUANTO TEMPO? _____

SE JÁ USOU ( ) 1. OBTEVE RESULTADO ( ) 2. PAROU POR CONTA PRÓPRIA

QUAL/ DOSE (MG)? _____

2 - AVALIAÇÃO DA CEFALEIA - CEFALEIA PREVIA - AQUELA QUE ACONTECIA ANTES DA TROMBOSE ACONTECER!

CEFALEIA ( ) 1. SIM ( ) 2. NAO

HÁ QUANTO TEMPO TINHA ESSA CEFALEIA? _____ ANOS

FREQÜÊNCIA _____ DIAS POR MÊS

FALTAS ESCOLA/ TRABALHO/ ATV DIÁRIA _____ DIAS NO MES

EPISÓDIOS DE DOR POR DIA _____ Nº EPISÓDIOS

DURAÇÃO DA DOR _____ ( ) HORAS ( ) SEG

CONSEGUIA REALIZAR ATIVIDADES DIÁRIAS/ TRABALHO MESMO COM A DOR? ( ) 1. SIM ( ) 2. NAO

INTENSIDADE MAXIMA ( ) 99. NAO SEI

0 ——— 10 ☐

Sem Dor — Pior Dor Possível

IMPACTO NAS SUAS ATIVIDADES DO DIA A DIA (EM CASA E NO TRABALHO) ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — Totalmente Incapacitado

IMPACTO DA DOR NO SEU HUMOR ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NO SEU TRABALHO ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — Não consigo trabalhar

IMPACTO DA DOR NO RELACIONAMENTO COM OUTRAS PESSOAS ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NO SEU SONO ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — O máximo possível

IMPACTO DA DOR NA SUA CAPACIDADE DE APRECIAR A VIDA ( ) 99. NAO SEI

0 ——— 10 ☐

Nenhum Impacto — O máximo possível

4

TIPO DA DOR ( ) 1. APERTO ( ) 2. PRESSÃO
( ) 4. FACADA ( ) 5. PULSAÇÃO OU LATEJANTE
( ) 6. ARDÊNCIA ( ) 7. CHOQUE

LOCALIZAÇÃO ( ) 1. TODA A CABEÇA ( ) 2. APENAS A ESQUERDA
( ) 3. APENAS A DIREITA ( ) 4. ORA A DIREITA, ORA A ESQUERDA
( ) 5. DOS DOIS LADOS AO MESMO TEMPO.

APARECIMENTO ( ) 1. TESTA ( ) 2. OLHOS ( ) 3. TEMPORAS
( ) 4. EM CIMA DA CABEÇA ( ) 5. ATRAS DA CABEÇA/ NUCA
( ) 6. PESCOÇO ( ) 7. LATERAL DA CABEÇA

SINTOMAS ASSOCIADOS ( ) 1.NAUSEA ( ) 2.VOMITO ( ) 3.FONOFOBIA
( ) 4. FOTOFOBIA ( ) 5. HIPEREMIA CONJUNT.
( ) 6. LACRIMEJAMENTO ( ) 7. OBSTRUÇAO NASAL
( ) 8.HEMIPARESIA ( ) 9. DIPLOPIA
( ) 10.HEMIPARESIA ( ) 11.TONTURA/ VERTIGEM

AURA ( ) 1. VISUAL ( ) 2. SENSITIVA ( ) 3. MOTORA
( ) 4. AURA SEM DOR ( ) 9. AUSENTE

OUTRA AURA _____

DURAÇÃO DA AURA _____

QUAL? _____

PIORA COM ATV. FÍSICA ( ) 1. SIM ( ) 2. NÃO

PIORA NA MENSTRUAÇÃO ( ) 1. SIM ( ) 2. NAO ( ) 3. N.A.

DESENCADEANTE ( ) 1. SIM ( ) 2. NAO
QUAL?_____

MEDICAÇÃO PROFILÁTICA ( ) 1. NAO USAVA ( ) 2. ANTIDEPRESSIVO
( ) 3. DAE ( ) 4. BETA BLOQ ( ) 5. BLOQ. CANAL CA+
( ) 6. OUTRAS MEDICAÇÕES?
QUAL/ DOSE (MG)? _____

SINTOMÁTICO ( ) 1. NAO USAVA ( ) 2. ERGOT. ( ) 3. TRIPTANO
( ) 4. AINE ( ) 5. CORTICOIDE ( ) 6. ANALG. COMUM
( ) 7. OPIOIDE FRACO ( ) 8. OPIOIDE FORTE ( ) 9. RELAX. MUSC.
QUAL/ DOSE (MG)?_____

_____

QUANTOS DIAS POR MÊS USAVA SINTOMÁTICOS? _____ DIAS POR MÊS

QUANTAS VEZES POR DIAS USAVA SINTOMÁTICOS? _____ VEZES POR DIA

HA QUANTO TEMPO USA ESSES SINTOMÁTICOS NESSA FREQUÊNCIA? _____ MESES

JÁ USOU MED. PROFILÁTICA ANTES? ( ) 1. SIM ( ) 2. NÃO

SE SIM, QUAL O MOTIVO PELO QUAL PAROU?_____

QUAL MEDICAÇÃO ? _____

QUANTO TEMPO? _____

SE JÁ USOU ( ) 1. OBTEVE RESULTADO ( ) 2. PAROU POR CONTA PRÓPRIA

QUAL/ DOSE (MG)? _____

5

3 - AVALIAÇÃO DA CEFALEIA - CEFALEIA AGUDA - ZERO A SEIS MESES DA TVC.

CEFALEIA ( ) 1. SIM ( ) 2. NAO

FREQÜÊNCIA _____ DIAS POR MÊS

FALTAS ESCOLA/ TRABALHO/ ATV DIÁRIA _____ DIAS NO MES

EPISÓDIOS DE DOR POR DIA _____ Nº EPISÓDIOS

DURAÇÃO DA DOR _____ ( ) HORAS ( ) SEG

CONSEGUE REALIZAR ATIVIDADES DIÁRIAS/ TRABALHO MESMO COM A DOR? ( ) 1. SIM ( ) 2. NÃO

TIPO DA DOR ( ) 1. APERTO ( ) 2. PRESSÃO
( ) 4. FACADA ( ) 5. PULSAÇÃO OU LATEJANTE
( ) 6. ARDÊNCIA ( ) 7. CHOQUE

LOCALIZAÇÃO ( ) 1. TODA A CABEÇA ( ) 2. APENAS A ESQUERDA
( ) 3. APENAS A DIREITA ( ) 4. ORA A DIREITA, ORA A ESQUERDA
( ) 5. DOS DOIS LADOS AO MESMO TEMPO.

APARECIMENTO ( ) 1. TESTA ( ) 2. OLHOS ( ) 3. TEMPORAS
( ) 4. EM CIMA DA CABEÇA ( ) 5. ATRAS DA CABEÇA/ NUCA
( ) 6. PESCOÇO ( ) 7. LATERAL DA CABEÇA

SINTOMAS ASSOCIADOS ( ) 1.NAUSEA ( ) 2.VOMITO ( ) 3.FONOFOBIA
( ) 4. FOTOFOBIA ( ) 5. HIPEREMIA CONJUNT.
( ) 6. LACRIMEJAMENTO ( ) 7. OBSTRUÇAO NASAL
( ) 8.HEMIPARESIA ( ) 9. DIPLOPIA
( ) 10.HEMIPARESIA ( ) 11.TONTURA/ VERTIGEM

AURA ( ) 1.VISUAL ( ) 2. SENSITIVA ( ) 3. MOTORA
( ) 4. AURA SEM DOR ( ) 9. AUSENTE

OUTRA AURA _____

DURAÇÃO DA AURA _____

QUAL? _____

PIORA COM ATV. FÍSICA ( ) 1. SIM ( ) 2. NÃO

PIORA NA MENSTRUAÇÃO ( ) 1. SIM ( ) 2. NAO ( ) 3. N.A.

DESENCADEANTE ( ) 1. SIM ( ) 2. NAO
QUAL?_____

MEDICAÇÃO PROFILÁTICA ( ) 1. NAO USA ( ) 2. ANTIDEPRESSIVO
( ) 3. DAE ( ) 4. BETA BLOQ ( ) 5. BLOQ. CANAL CA+
QUAL/ DOSE (MG)? _____
( ) 6. OUTRAS MEDICAÇÕES?

SINTOMÁTICO ( ) 1. NAO USA ( ) 2. ERGOT. ( ) 3. TRIPTANO
( ) 4. AINE ( ) 5. CORTICOIDE ( ) 6. ANALG. COMUM
( ) 7. OPIOIDE FRACO ( ) 8. OPIOIDE FORTE ( ) 9. RELAX. MUSC.
QUAL/ DOSE (MG)?_____

TEMPO TOTAL DA CEFALEIA AGUDA _____

QUANTO TEMPO DEMOROU PARA O PADRAO ATUAL DA CEFALEIA SURGIR _____

6

6 - CLASSIFICAÇÃO DAS CEFALEIAS - CONFORME CÓDIGO NO FINAL DESSE C.R.F. [CASO CLASSIFIQUEM ALGUMA CEFALEIA COMO 8.2.X, NÃO DEIXAR DE CLASSIFICAR QUANTO A 1.X (ENXAQUECA) OU 2.X (TENSIONAL)]

a. CEFALEIA ATUAL ( ) ( )
b. CEFALEIA PRÉVIA ( ) ( )
c. CEFALEIA AGUDA ( ) ( )

7 - AVALIAÇÃO BÁSICA DE SONO

HORA QUE VAI DORMIR _____H
HORA QUE DORME _____H
HORA QUE ACORDA _____H
TEMPO TOTAL DE SONO _____H
DESPERTARES NOTURNO _____ VEZES
QUANTO NÃO TEM COMPROMISSOS, QUANTO TEMPO DORMIRIA? _____H
O SONO É RESTAURADOR? ( ) SIM ( ) NÃO RONCO ( ) SIM ( ) NÃO

5 - NIHSS

1A. NIVEL CONSCIÊNCIA ( ) 0. ALERTA ( ) 1. NAO ALERTA ( ) 2. RESP DOR ( ) 3. REFLEX.
1B. PERGUNTAS ( ) 0. DOIS ACERTOS ( ) 1. UM ACERTO ( ) 2. DOIS ERROS
1C. COMANDO ( ) 0. DOIS ACERTOS ( ) 1. UM ACERTO ( ) 2. DOIS ERROS
2. OLHAR CONJUGADO ( ) 0. NORMAL ( ) 1. PARCIAL ( ) 2. DESVIO FORCADO
3. VISUAL ( ) 0.NORMAL ( ) 1. HEMI PARCIAL ( ) 2. HEMI PARCIAL ( ) 3.CEGO
4. FACIAL ( ) 0. NORMAL ( ) 1. LEVE ( ) 2. EVIDENTE ( ) .3 COMPLETA
5 A ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV
( ) 4. SEM MOV. ( ) 99. AMPUTADO
5 B ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV
( ) 4. SEM MOV. ( ) 99. AMPUTADO
6 A ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV
( ) 4. SEM MOV. ( ) 99. AMPUTADO
6 B ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV
( ) 4. SEM MOV. ( ) 99. AMPUTADO
7. ATAXIA ( ) 0. AUSENTE ( ) 1. EM UM MEMBRO ( ) 2. EM 2 MEMBROS ( ) 99. AMPUT.
8. SENSIBILIDADE ( ) 0. NORMAL ( ) 1. LEVE/ MODERADA ( ) 2. GRAVE/ TOTAL
9. LINGUAGEM ( ) 0. NORMAL ( ) 1. LEVE. MODERADA ( ) 2. GRAVE ( ) 4. MUTISMO
10. DISARTRIA ( ) 0. NORMAL ( ) 1. LEVE. MODERADA ( ) 2. GRAVE ( ) 99. BARREIRA
11. EXTINÇÃO ( ) 0. NORMAL ( ) 1. UMA MODALIDADE ( ) 2. DUAS MODALIDADE

7- ESCALA DE RANKIN MODIFICADA

( ) 0 SEM SINTOMAS
( ) 1 SINTOMAS MENORES (NÃO INTERFERINDO COM O ESTILO DE VIDA)
( ) 2 INCAPACIDADE MENOR (SINTOMAS QUE LEVAM A UMA CERTA RESTRIÇÃO DE ESTILO DE VIDA, MAS O PACIENTE É CAPAZ DE CUIDAR DE SI MESMO)
( ) 3 MODERADA INCAPACIDADE (SINTOMAS QUE RESTRINGEM SIGNIFICATIVAMENTE ESTILO DE VIDA E / OU IMPEDEM TOTALMENTE EXISTÊNCIA INDEPENDENTE, MAS CAPAZ DE ANDAR SEM AJUDA)
( ) 4 INCAPACIDADE MODERADAMENTE GRAVE (SINTOMAS QUE IMPEDEM CLARAMENTE EXISTÊNCIA INDEPENDENTE EMBORA NÃO NECESSITAM DE ATENÇÃO CONSTANTE; INCAPAZ DE ANDAR SEM AJUDA)
( ) 5 INCAPACIDADE MUITO GRAVE (TOTALMENTE DEPENDENTE, EXIGINDO DIA ATENÇÃO CONSTANTE E NOITE)
( ) 6 MORTE

Attachment C - Structured Tool for Medical Chart Information Extraction

15

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA

UNIVERSIDADE DE SÃO PAULO-HCFMUSP

COLETA PARA COLETA DE DADOS SOBRE TROMBOSE VENOSA CEREBRAL (CONSULTA DE PRONTUÁRIO)

COLETA DE DADOS SOBRE TROMBOSE VENOSA CEREBRAL (FEITO SEM O PACIENTE - APENAS COM O PRONTUÁRIO MÉDICO)

A. DIAGNÓSTICO DE TROMBOSE VENOSA CEREBRAL

1. DATA DE INÍCIO DOS SINTOMAS _____/_____/_____
2. DATA DA CONFIRMAÇÃO DO DIAGNÓSTICO POR IMAGEM CVT: _____/_____/_____
3. DIAGNÓSTICO CONFIRMADO POR: ( ) MR ( ) MRV CT ( ) CTV ( ) IA
   ( ) ANGIOGRAFIA ( ) CIRURGIA ( ) AUTOPSY

B. NEUROIMAGEM - NA ALTA.

1. CT ( ) SIM ( ) NÃO
2. EXAME DE RESSONÂNCIA MAGNÉTICA ( ) SIM ( ) NÃO
3. LESÃO DO PARÊNQUIMA ( ) SIM ( ) NÃO
4. LESÃO NÃO-HEMORRÁGICO (EDEMA CEREBRAL FOCAL / INFARTO VENOSO) ( ) SIM ( ) NÃO
5. LESÃO HEMORRÁGICA (INFARTO HEMORRÁGICO / HEMATOMA INTRACEREBRAL)( ) SIM ( ) NÃO

OUTROS, ESPECIFIQUE_____

_____

_____

C. SEIOS ENVOLVIDOS (OCLUÍDO NA ANGIOGRAFIA OU TROMBO VISÍVEL NA RM)

1. SUPERIOR SAGITAL SEIO ( ) SIM ( ) NÃO
2. LATERAL (SIGMÓIDE E / OU TRANSVERSAL) DO SEIO ESQUERDO ( ) SIM ( ) NÃO
3. DIREITO LATERAL (SIGMÓIDE E / OU TRANSVERSAL) DO SEIO ( ) SIM ( ) NÃO
4. SEIO RETO ( ) SIM ( ) NÃO
5. SISTEMA VENOSO PROFUNDA (V. GALENO, V. ROSENTHAL) ( ) SIM ( ) NÃO
6. VEIA CEREBRAL INTERNA, SEIO LONGITUDINAL INFERIOR, TÁLAMO-ESTRIADA OU VEIAS CAUDADO)
   ( ) SIM ( ) NÃO
7. VEIAS CORTICAIS ( ) SIM ( ) NÃO
8. VEIAS DO CEREBELO ( ) SIM ( ) NÃO
9. VEIA JUGULAR (S) ( ) SIM ( ) NÃO
10. SEIO CAVERNOSO ( ) SIM ( ) NÃO

D.EXAME DE IMAGEM FASE TARDIA MOSTRANDO RECANALIZAÇÃO

1.TEMPO DE DOENÇA ATÉ O EXAME

RECANALIZAÇÃO	1. TOTAL	2. PARCIAL	3. NENHUMA
2.SUPERIOR SAGITAL SEIO	( )	( )	( )
3.LATERAL (SIGMÓIDE E / OU TRANSVERSAL) DO SEIO ESQ.	( )	( )	( )
4.DIREITO LATERAL (SIGMÓIDE E / OU TRANSVERSAL) DO SEIO	( )	( )	( )
5.SEIO RETO			
6.SISTEMA VENOSO PROFUNDA (V. GALENO, V. ROSENTHAL)	( )	( )	( )
7.VEIA CEREBRAL INTERNA, SEIO LONGITUDINAL INFERIOR, TÁLAMO-ESTRIADA OU VEIAS CAUDADO)			
8.VEIAS CORTICAIS	( )	( )	( )

16

9.VEIAS DO CEREBELO	( )	( )	( )
10.VEIA JUGULAR (S)	( )	( )	( )
11.SEIO CAVERNOSO	( )	( )	( )

D. COM SINTOMAS / SINAIS (DESDE O INÍCIO ATÉ A DATA DO DIAGNÓSTICO)

MODO DE INÍCIO: ( )AGUDA (<48 H) ( )SUBAGUDA (> 48H A 30 DIAS) ( )CRÔNICA (> 30 DIAS)

SINTOMAS / SINAIS:

( )1. COMA (GCS <9) MONO / HEMIPARESIA
( )2. DIMINUIÇÃO DO ESTADO DE ALERTA (GCS 9-14)
( )3. CRISE EPILÉPTICA
( )4. ALTERAÇÃO COGNITIVA
( )5. DOR DE CABEÇA
( )6. AFASIA
( )7. PERDA VISUAL
( )8. PAPILEDEMA DIPLOPIA, PARALISIA OCULOMOTOR
( )9. OUTRO SINTOMA, ESPECIFIQUE_____

_____

_____

E. TROMBOFILIA - TESTE (VOCÊ PODE SELECIONAR MAIS DE UM, QUANDO FOR O CASO)

	NEGATIVO	POSITIVO	NÃO REALIZADO
Anticoagulante Lúpico			
Anticorpos antifosfolípides			
deficiência de proteína C			
deficiência de proteína S			
deficiência de antitrombina			
Mutação do fator V Leiden			
Mutação de protrombina G20210A			
níveis plasmáticos de homocisteína			
Fator VIII			

F. FATORES DE RISCO / CONDIÇÕES ASSOCIADAS (VOCÊ PODE SELECIONAR MAIS DE UM, QUANDO FOR O CASO)

HISTÓRIA PRÉVIA:

( )1. TROMBOSE VENOSA CEREBRAL
( )2. OUTROS TROMBOSE VENOSA (EXTREMIDADES, PÉLVIS, PULMONARES ...) _____

_____

_____

G. FATOR DE RISCO TRANSITÓRIO (S) (0-3 MESES ANTES CVT):

( )1. GRAVIDEZ

( )2. PUERPÉRIO
INFECÇÃO:
( ) 3. SISTÊMICA, ESPECIFIQUE: _____
( )4. CNS, ESPECIFIQUE: _____
( ) 5. ORELHA, NARIZ, GARGANTA
( ) 6. CRANIO OU A PELE FACIAL
( )7. PRECIPITANTES MECÂNICOS (TRAUMA EG CABEÇA), ESPECIFIQUE: _____
( )8. CIRURGIA, ESPECIFIQUE: _____
( )9. DESIDRATAÇÃO GRAVE
( )10. USO DE CONTRACEPTIVOS ORAIS
( )11. OUTRAS DROGAS COM EFEITO PRÓ-TROMBÓTICO, ESPECIFIQUE:
( )12. OUTROS, ESPECIFIQUE: _____
_____
_____

H. FATOR DE RISCO PERMANENTE (S)

( ) 1. TROMBOFILIA GENÉTICA
( ) 2. TROMBOFILIA ADQUIRIDA (POR EXEMPLO, SÍNDROME ANTIFOSFOLÍPIDE, SÍNDROME NEFRÓTICA), ESPECIFIQUE: _____
( ) 3. MALIGNIDADE (CARCINOMA, SARCOMA, LEUCEMIA, LINFOMA ...), ESPECIFIQUE: _____
_____
_____

( ) 4. POLICITEMIA VERA
( ) 5. TROMBOCITOSE ESSENCIAL
( ) 6. ANEMIA GRAVE (<8 G / DL)
( ) 7. VASCULITE, ESPECIFICAR:
( ) 8. DOENÇA INFLAMATÓRIA INTESTINAL
OUTROS DOENÇA SISTÊMICA INFLAMATÓRIA PRÓ-TROMBÓTICO, ESPECIFIQUE:

( ) 9. OUTROS, ESPECIFIQUE:
( ) 99. NENHUM FATOR DE RISCO IDENTIFICÁVEL (S)

I. TRATAMENTO

TEMPO TOTAL DE ANTICOAGULAÇAO _____

Attachment D - CAPPesq registration

HOSPITAL DAS CLÍNICAS
DA
FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO

DIRETORIA CLÍNICA
COMISSÃO DE ÉTICA PARA ANÁLISE DE PROJETOS DE PESQUISA - CAPPesq

CADASTRO DE PROTOCOLO DE PESQUISA

Registro (uso reservado à Secretaria da CAPPesq)	
Nº do Protocolo:	Tipo: Humanos
Instituto: ICHC	
Registro on-line nº: 14451	Data de Entrada: 26/11/2015

Este projeto envolve:

Pacientes HC	Sim
Médicos ou Funcionários HC (como sujeitos de pesquisa)	Não
Documentos HC(Prontuários e Outros)	Sim
Materiais estocados no HC	Não
Peças anatômicas de cadáveres	Não
Haverá necessidade de recrutamento de pacientes na mídia	Não

1. Título do Protocolo de Pesquisa

Caracterização da Cefaleia Cronica em Paciente com Trombose Venosa Cerebral

2. Palavras-chaves que caracterizam o assunto da Pesquisa

Cefaleia, Trombose Venosa Cerebral, Cefaleia Cronica

3. Resumo do Protocolo de Pesquisa:

Para investigar a existência de relação entre aspectos da Trombose Venosa Cerebral e a ocorrência de cefaleia crônica propomos um estudo observacional, retrospectivo, de sujeitos de pesquisa com trombose venosa cerebral ocorrida há no mínimo 6 meses ou no máximo 5 anos, em acompanhamento atual no ambulatório de Doenças Cerebrovasculares da Divisão de Clínica Neurológica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. O Estudo está composto da aplicação da escala de Rankin Modificada e a National Institutes of Health Stroke Scale (NIHSS), além de exame neurológico com fundoscopia para avaliação de edema de papilla e campimetria por confrontação. Serão aplicadas escalas específicas para avaliação de sintomas depressivos (Patient Heath Questionnaire (PHD-9) versão Brasileira), ansiosos (Generalised Anxiety Disorder Assessment (GAD-7) versão Brasileira e de qualidade do Sono (Escala de Pittsburgh). A avaliação cognitiva será feita por meio do Montreal Cognitive Assessment Teste (MoCA-test) , conforme validação para população brasileira. A qualidade de vida será avaliada por meio da Stroke Impact Scale, versão traduzida e adaptada para o português. O Impacto do estresse na qualidade do vida do sujeito de pesquisa será avaliado por meio do Inventário de Sintomas de Stress de Lipp (ISSL). Serão coletados dados sobre a trombose venosa cerebral ocorrida, interessando sintomas de abertura do quadro, tempo necessário para o diagnóstico, método de tratamento de fase aguda, número de seios acometidos, presença de hipertensão intracraniana, crise epiléptica e rebaixamento do nível de consciência na abertura do quadro, presença de doenças e condições que predisponham a trombose, dentre outras informações.

4. Pesquisador Responsável:

Adriana Bastos Conforto

http://lattes.cnpq.br/4375211591851561

Graduação: 1994

Vínculo: HC, FFM

5. Pesquisador Executante:

Alexandre Souza Bossoni

http://lattes.cnpq.br/9289080406017497

6. Possui co-autores?

Sim

Nome dos co-autores: Mario F. P. Peres

7. Onde a Pesquisa será realizada?

Departamento: Neurologia

Disciplina: Neurologia Clínica

LIM: LIM/15 - Lab Investigação em Neurologia

8. Existe entidade externa envolvida?

Não

9. Possui participação Estrangeira

Não

10. O projeto é multicêntrico

Não

11. Outros serviços/ divisões do HCFMUSP envolvidos na pesquisa

Não

12. Finalidade acadêmica da pesquisa e classificação
Doutorado
Outros:
Orientador: Dra Adriana Bastos Conforto

13. Investigação
Retrospectiva

14. Materiais e métodos
Entrevistas e questionários
Prontuários de pacientes

15. Gênero, classificação da Pesquisa
Clínica

16. Áreas temáticas previstas na Res. 466/12
Nenhuma das alternativas

17. Patrocínio
Recursos próprios
Não há patrocínio

18. Valor do financiamento
3.500,00

19. Cronograma de execução da pesquisa

Prazo: 24 meses

20. Assinaturas

Profa. Dra. Adriana Bastos Conforto
Chefe do Grupo de Doenças Cerebrovasculares
e do Laboratório de Neuroestimulação
Divisão de Clínica Neurológica
Matrícula HC: 42.174 / CRM: 80.298

Adriana Bastos Conforto

Ad referendum

Assinatura e carimbo do Pesquisador

Aprovado em 22 / 12 / 15

_____.

Prof. Dr. Manoel Jacobsen Teixeira
Vice-Chefe do Departamento de Neurologia
CRM: 17.968 / Matr. FMUSP: 2.917.632

Ad referendum

Assinatura e carimbo da Chefia
com data de aprovação
pelo Conselho do Departamento

Aprovado em 22 / 12 / 15

_____.

Attachment E - Plataforma Brasil Registration

MINISTÉRIO DA SAÚDE - Conselho Nacional de Saúde - Comissão Nacional de Ética em Pesquisa – CONEP

FOLHA DE ROSTO PARA PESQUISA ENVOLVENDO SERES HUMANOS

1. Projeto de Pesquisa: Caracterização da cefaleia crônica em pacientes com Trombose Venosa Cerebral	2. Número de Participantes da Pesquisa: 100
3. Área Temática:	
4. Área do Conhecimento: Grande Área 4. Ciências da Saúde	

PESQUISADOR RESPONSÁVEL

5. Nome: Adriana Bastos Conforto			
6. CPF: 173.887.808-23	7. Endereço (Rua, n.º): Rua Galeno de Almeida 207 PINHEIROS ap 23 SAO PAULO SAO PAULO 05410030		
8. Nacionalidade: BRASILEIRO	9. Telefone: (11) 3083-7096	10. Outro Telefone:	11. Email: adriana.conforto@gmail.com

Termo de Compromisso: Declaro que conheço e cumprirei os requisitos da Resolução CNS 466/12 e suas complementares. Comprometo-me a utilizar os materiais e dados coletados exclusivamente para os fins previstos no protocolo e a publicar os resultados sejam eles favoráveis ou não. Aceito as responsabilidades pela condução científica do projeto acima. Tenho ciência que essa folha será anexada ao projeto devidamente assinada por todos os responsáveis e fará parte integrante da documentação do mesmo.

Profa. Dra. Adriana Bastos Conforto
Chefe do Grupo de Doenças Cerebrovasculares
e do Laboratório de Neuroimagem
Divisão de Clínica Neurológica
Matrícula HC: 12.174 / CRM: 80.208

Data: 26 / 11 / 15

Assinatura

INSTITUIÇÃO PROPONENTE

12. Nome: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P	13. CNPJ: 60.448.040/0001-22	14. Unidade/Órgão:
15. Telefone:	16. Outro Telefone:	

Termo de Compromisso (do responsável pela instituição): Declaro que conheço e cumprirei os requisitos da Resolução CNS 466/12 e suas Complementares e como esta instituição tem condições para o desenvolvimento deste projeto, autorizo sua execução.

Responsável: ELOÍSA SILVA DUTRA DE OLIVEIRA BONFÁ CPF: 042.658.928-92

Cargo/Função: Diretora Clínica do HCFMUSP

Data: 29 / 12 / 15

PROFESSORA ELOÍSA BONFÁ
Diretor Clínico do HCFMUSP

PATROCINADOR PRINCIPAL

Não se aplica.

Prof. Dr. Manoel Jacobsen Teixeira
Vice-Chefe do Departamento de Neurologia
CRM: 17.968 - Matr. FMUSP: 2.917.532

8 REFERENCES

1. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol*. 2007;6(2):162-70.

2. Coutinho JM. Cerebral venous thrombosis. *J Thromb Haemost*. 2015;13(Suppl 1):S238-44.

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APPENDICES

Appendix A - National Institute of Health and Modified Rankin Scale

6

6 - CLASSIFICAÇÃO DAS CEFALEIAS - CONFORME CÓDIGO NO FINAL DESSE C.R.F. [CASO CLASSIFIQUEM ALGUMA CEFALEIA COMO 8.2.X, NÃO DEIXAR DE CLASSIFICAR QUANTO A 1.X (ENXAQUECA) OU 2.X (TENSIONAL)]

a. CEFALEIA ATUAL ( ) ( )
b. CEFALEIA PRÉVIA ( ) ( )
c. CEFALEIA AGUDA ( ) ( )

7 - AVALIAÇÃO BÁSICA DE SONO

HORA QUE VAI DORMIR _____H
HORA QUE DORME _____H
HORA QUE ACORDA _____H
TEMPO TOTAL DE SONO _____H
DESPERTARES NOTURNO _____ VEZES
QUANTO NÃO TEM COMPROMISSOS, QUANTO TEMPO DORMIRIA? _____H
O SONO É RESTAURADOR? ( ) SIM ( ) NÃO RONCO ( ) SIM ( ) NÃO

5 - NIHSS

1A. NIVEL CONSCIÊNCIA ( ) 0. ALERTA ( ) 1. NAO ALERTA ( ) 2. RESP DOR ( ) 3. REFLEX.
1B. PERGUNTAS ( ) 0. DOIS ACERTOS ( ) 1. UM ACERTO ( ) 2. DOIS ERROS
1C. COMANDO ( ) 0. DOIS ACERTOS ( ) 1. UM ACERTO ( ) 2. DOIS ERROS
2. OLHAR CONJUGADO ( ) 0. NORMAL ( ) 1. PARCIAL ( ) 2. DESVIO FORCADO
3. VISUAL ( ) 0.NORMAL ( ) 1. HEMI PARCIAL ( ) 2. HEMI PARCIAL ( ) 3.CEGO
4. FACIAL ( ) 0. NORMAL ( ) 1. LEVE ( ) 2. EVIDENTE ( ) .3 COMPLETA
5 A ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV ( ) 4. SEM MOV. ( ) 99. AMPUTADO
5 B ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV ( ) 4. SEM MOV. ( ) 99. AMPUTADO
6 A ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV ( ) 4. SEM MOV. ( ) 99. AMPUTADO
6 B ( ) SEM QUEDA ( ) 1. QUEDA ( ) 2. TOCA CAMA ( ) 3. CONTR. SEM MOV ( ) 4. SEM MOV. ( ) 99. AMPUTADO
7. ATAXIA ( ) 0. AUSENTE ( ) 1. EM UM MEMBRO ( ) 2. EM 2 MEMBROS ( ) 99. AMPUT.
8. SENSIBILIDADE ( ) 0. NORMAL ( ) 1. LEVE/ MODERADA ( ) 2. GRAVE/ TOTAL
9. LINGUAGEM ( ) 0. NORMAL ( ) 1. LEVE. MODERADA ( ) 2. GRAVE ( ) 4. MUTISMO
10. DISARTRIA ( ) 0. NORMAL ( ) 1. LEVE. MODERADA ( ) 2. GRAVE ( ) 99. BARREIRA
11. EXTINÇÃO ( ) 0. NORMAL ( ) 1. UMA MODALIDADE ( ) 2. DUAS MODALIDADE

7- ESCALA DE RANKIN MODIFICADA

( ) 0 SEM SINTOMAS
( ) 1 SINTOMAS MENORES (NÃO INTERFERINDO COM O ESTILO DE VIDA)
( ) 2 INCAPACIDADE MENOR (SINTOMAS QUE LEVAM A UMA CERTA RESTRIÇÃO DE ESTILO DE VIDA, MAS O PACIENTE É CAPAZ DE CUIDAR DE SI MESMO)
( ) 3 MODERADA INCAPACIDADE (SINTOMAS QUE RESTRINGEM SIGNIFICATIVAMENTE ESTILO DE VIDA E / OU IMPEDEM TOTALMENTE EXISTÊNCIA INDEPENDENTE, MAS CAPAZ DE ANDAR SEM AJUDA)
( ) 4 INCAPACIDADE MODERADAMENTE GRAVE (SINTOMAS QUE IMPEDEM CLARAMENTE EXISTÊNCIA INDEPENDENTE EMBORA NÃO NECESSITAM DE ATENÇÃO CONSTANTE; INCAPAZ DE ANDAR SEM AJUDA)
( ) 5 INCAPACIDADE MUITO GRAVE (TOTALMENTE DEPENDENTE, EXIGINDO DIA ATENÇÃO CONSTANTE E NOITE)
( ) 6 MORTE

Appendix B - Mini-Mental State Examination

7

8-MINI EXAME DO ESTADO MENTAL

DIA DA SEMANA ..... DIA DO MES ..... MES ..... ANO ..... HORA .....

LOCAL ESP ..... INSTITUICAO ..... BAIRRO ..... CIDADE ..... ESTADO .....

MEMÓRIA: CANECA ..... TAPETE ..... TIJOLO .....

ATENÇÃO E CALCULO: 100 - 7 = 93 .....- 7 = 86 .....- 7 = 79 .....- 7 = 72 .....- 7 = 65 (M-U-N-D-O)

EVOCAÇÃO: CANECA ..... TAPETE ..... TIJOLO .....

LINGUAGEM: NOMEAÇÃO ..... NEM AQUI NEM ALI NEM LA .....

PEGUE O PAPEL ..... FECHE OS OLHOS .....

FRASE DESENHO ..... TOTAL .....

9- EXAME FÍSICO

ESTALIDO ATM	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT
NEURALGIA N OCCIPITAL MAIOR	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT
PONTO GATILHO CERVICAL	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT
PONTO GATILHO MM TRAPÉZIO	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT
PONTO GATILHO MM TEMPORAL	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT
DOR PERICRANIA	( ) 1. SIM	( ) 2. NÃO	( ) 1. DIR	( ) 2. ESQ	( ) 3. BILAT

Appendix C - Stroke Impact Scale

11 - STROKE IMPACT SCALE

ESTAS QUESTÕES SÃO REFERENTES AOS PROBLEMAS FÍSICOS QUE PODEM TER OCORRIDO COMO RESULTADO DO AVE.

1. Na semana passada, como você classificaria a força do seu....	Muita força	Um pouco de força	Alguma força	Mínima força	Nenhuma força
a. Braço que foi mais afetado?	5	4	3	2	1
b. Preensão da mão que foi mais afetada?	5	4	3	2	1
c. Perna que foi mais afetado?	5	4	3	2	1
d. Pé / tornozelo, que foi mais afetado?	5	4	3	2	1

ESTAS QUESTÕES SÃO SOBRE A SUA MEMÓRIA E PENSAMENTO.

2. Na semana passada, o quão difícil foi para você ...	Nada difícil	Um pouco difícil	Mais ou menos difícil	Muito difícil	Extremamente difícil
a. Lembrar de coisas que as pessoas te disseram?	5	4	3	2	1
b. Lembrar de coisas que aconteceram no dia anterior?	5	4	3	2	1
c. Lembrar de fazer as coisas (por exemplo, manter compromissos agendados ou tomar medicamentos)?	5	4	3	2	1
d. Lembrar o dia da semana?	5	4	3	2	1
e. Concentre-se?	5	4	3	2	1
f. Pensar rapidamente?	5	4	3	2	1
g. Resolver problemas do dia-a-dia?	5	4	3	2	1

ESTAS QUESTÕES SÃO SOBRE COMO VOCÊ SE SENTE, SOBRE ALTERAÇÕES NO SEU HUMOR ES OBRE SUA HABILIDADE DE CONTROLAR SUAS EMOÇÕES DESDE O SEU AVE.

3. Na semana passada, com que freqüência você ...	**Nenhuma vez**	**Poucas vezes**	**Algumas vezes**	**A maioria das vezes**	**Todo o tempo**
a. Sentiu-se triste?	5	4	3	2	1
b. Sentiu que não há ninguém próximo de você?	5	4	3	2	1
c. Sentiu que você é um fardo para os outros?	5	4	3	2	1
d. Sentiu que você não tem nada para olhar para frente (futuro)?	5	4	3	2	1
e. Responsabilizou-se pelos erros que você fez?	5	4	3	2	1
f. Aprecia as coisas mais do que nunca?	5	4	3	2	1
g. Sentiu-se muito nervoso?	5	4	3	2	1
h. Sentiu que a vida vale a pena viver?	5	4	3	2	1
i. Sorriu e riu pelo menos uma vez por dia?	5	4	3	2	1

AS SEGUINTES PERGUNTAS SÃO SOBRE SUA HABILIDADE PARA SE COMUNICAR COM OUTRAS PESSOAS, BEM COMO SUA CAPACIDADE DE ENTENDER O QUE VOCÊ LÊ E O QUE OUVE EM UMA CONVERSA.

4. Na semana passada, o quão difícil foi para ...	**Nada difícil**	**Um pouco difícil**	**Mais ou menos difícil**	**Muito difícil**	**Extremamente difícil**
a. Dizer o nome de alguém que estava na sua frente?	5	4	3	2	1
b. Entender o que estava sendo dito a você em uma conversa?	5	4	3	2	1
c. Responder às perguntas?	5	4	3	2	1
d. Nomear corretamente os objetos?	5	4	3	2	1
e. Participar de uma conversa com um grupo de pessoas?	5	4	3	2	1
f. Ter uma conversa ao telefone?	5	4	3	2	1
g. Conversar com outra pessoa no telefone, incluindo a seleção do número de telefone correto e discagem?	5	4	3	2	1

AS QUESTÕES SEGUINTES PERGUNTAM SOBRE ATIVIDADES QUE VOCÊ PODE FAZER DURANTE UM DIA TÍPICO.

5. Nas duas últimas semanas, o quão difícil foi para ...	Nada difícil	Um pouco difícil	Mais ou menos difícil	Muito difícil	Não conigo realizar
a. Cortar a sua comida com garfo e faca?	5	4	3	2	1
b. Vestir a parte superior do seu corpo?	5	4	3	2	1
c. Banhar-se?	5	4	3	2	1
d. Cortar suas unhas?	5	4	3	2	1
e. Ir ao banheiro a tempo?	5	4	3	2	1
f. Controlar sua bexiga (não ter um acidente)?	5	4	3	2	1
g. Controlar seu intestino (não ter um acidente)?	5	4	3	2	1
h. Fazer tarefas domésticas leves(ex. poeira, arrumar a cama, tirar o lixo, lavar os pratos)?	5	4	3	2	1
i. Ir às compras?	5	4	3	2	1
j. Fazer tarefas domésticas pesadas (por exemplo, lavar roupa, varrer quintal, passar o aspirador de pó?	5	4	3	2	1

AS SEGUINTES PERGUNTAS SÃO SOBRE A SUA CAPACIDADE DE SE MOVIMENTAR (LOCOMOVER), EM CASA E NA COMUNIDADE.

6. Nas duas últimas semanas, o quão difícil foi para ...	Nada difícil	Um pouco difícil	Mais ou menos difícil	Muito difícil	Não conigo realizar
a. Ficar sentado sem perder o equilíbrio?	5	4	3	2	1
b. Ficar em pé sem perder o equilíbrio?	5	4	3	2	1
c. Andar sem perder o equilíbrio?	5	4	3	2	1
d. Passar de uma cama para uma cadeira?	5	4	3	2	1
e. Andar um quarteirão?	5	4	3	2	1
f. Andar rápido?	5	4	3	2	1
g. Subir um lance de escadas?	5	4	3	2	1
h. Subir vários lances de escada?	5	4	3	2	1
i. Entrar e sair de um carro?	5	4	3	2	1

13

AS SEGUINTES PERGUNTAS SÃO SOBRE SUA HABILIDADE DE USAR A MÃO QUE FOI MAIS AFETADA PELO SEU AVE.

7. Nas duas últimas semanas, o quão difícil foi usar a mão que foi mais afetada para ...	**Nada difícil**	**Um pouco difícil**	**Mais ou menos difícil**	**Muito difícil**	**Não conigo realizar**
a. Carregar objetos pesados (por exemplo, sacola de compras)?	5	4	3	2	1
b. Virar uma maçaneta?	5	4	3	2	1
c. Abrir uma lata ou pote?	5	4	3	2	1
d. Amarrar um cordão de sapatos?	5	4	3	2	1
e. Pegar uma moeda de dez centavos?	5	4	3	2	1

AS SEGUINTES QUESTÕES SÃO SOBRE COMO AVE AFETOU A SUA CAPACIDADE DE PARTICIPAR DAS ATIVIDADES QUE VOCÊ COSTUMA FAZER, COISAS QUE SÃO SIGNIFICATIVAS PARA VOCÊ E O AJUDAM A ENCONTRAR UM PROPÓSITO NA VIDA.

8. Durante as últimas 4 semanas, quanto do tempo você tem sido limitado dentro ..	**Nenhum tempo**	**Pouco tempo**	**Algum tempo**	**Na maioria do tempo**	**Todo o tempo**
a. Seu trabalho (pago, voluntária ou outro)	5	4	3	2	1
b. Suas atividades sociais?	5	4	3	2	1
c. Recreação tranquila (artesanato, leitura)?	5	4	3	2	1
d. Recreação ativa (esportes, passeios, viagens)?	5	4	3	2	1
e. Seu papel como um membro da família e / ou amigo?	5	4	3	2	1
f. Sua participação em atividades religiosas ou espirituais?	5	4	3	2	1
g. Sua capacidade de controlar sua vida como você deseja?	5	4	3	2	1
h. Sua capacidade de ajudar os outros?	5	4	3	2	1

14

12. RECUPERAÇÃO DO AVE

EM UMA ESCALA DE 0 A 100, SENDO 100 RECUPERAÇÃO COMPLETA E 0 NENHUMA RECUPERAÇÃO, O QUANTO VOCÊ RECUPEROU APÓS SEU AVE?

_____ 100 RECUPERAÇÃO TOTAL

_____ 90

_____ 80

_____ 70

_____ 60

_____ 50

_____ 40

_____ 30

_____ 20

_____ 10

_____ 0 NENHUMA RECUPERAÇÃO

Appendix D - Patient Health Questionary 9

9 -QUESTIONARIO ANSIEDADE E DEPRESSAO - PHQ9

QUESTIONÁRIO SOBRE A SAÚDE DO/A PACIENTE- (PHQ-9)

Durante as últimas 2 semanas, com que freqüência você foi incomodado/a por qualquer um dos problemas abaixo? *(Marque sua resposta com "✔")*	Nenhuma vez	Vários dias	Mais da metade dos dias	Quase todos os dias
1. Pouco interesse ou pouco prazer em fazer as coisas	0	1	2	3
2. Se sentir "para baixo", deprimido/a ou sem perspectiva	0	1	2	3
3. Dificuldade para pegar no sono ou permanecer dormindo, ou dormir mais do que de costume	0	1	2	3
4. Se sentir cansado/a ou com pouca energia	0	1	2	3
5. Falta de apetite ou comendo demais	0	1	2	3
6. Se sentir mal consigo mesmo/a — ou achar que você é um fracasso ou que decepcionou sua família ou você mesmo/a	0	1	2	3
7. Dificuldade para se concentrar nas coisas, como ler o jornal ou ver televisão	0	1	2	3
8. Lentidão para se movimentar ou falar, a ponto das outras pessoas perceberem? Ou o oposto – estar tão agitado/a ou irrequieto/a que você fica andando de um lado para o outro muito mais do que de costume	0	1	2	3
9. Pensar em se ferir de alguma maneira ou que seria melhor estar morto/a	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

Se você assinalou qualquer um dos problemas, indique o grau de dificuldade que os mesmos lhe causaram para realizar seu trabalho, tomar conta das coisas em casa ou para se relacionar com as pessoas?

Nenhuma dificuldade	Alguma dificuldade	Muita dificuldade	Extrema dificuldade
☐	☐	☐	☐

Appendix E - General Anxiety Disorder 7

9

10 - QUESTIONARIO ANSIEDADE E DEPRESSÃO - GAD7

GAD-7

Durante as <u>últimas 2 semanas</u>, com que freqüência você foi incomodado/a pelos problemas abaixo? *(Marque sua resposta com "✔")*	Nenhuma vez	Vários dias	Mais da metade dos dias	Quase todos os dias
1. Sentir-se nervoso/a, ansioso/a ou muito tenso/a	0	1	2	3
2. Não ser capaz de impedir ou de controlar as preocupações	0	1	2	3
3. Preocupar-se muito com diversas coisas	0	1	2	3
4. Dificuldade para relaxar	0	1	2	3
5. Ficar tão agitado/a que se torna difícil permanecer sentado/a	0	1	2	3
6. Ficar facilmente aborrecido/a ou irritado/a	0	1	2	3
7. Sentir medo como se algo horrível fosse acontecer	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

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