Clinicoradiological Profile and Functional Outcome of Acute Cerebral Venous Thrombosis: A Hospital-Based Cohort Study

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Abstract
Introduction
Acute cerebral venous thrombosis (CVT) may result in a variety of clinical presentations, with headache being the most common. The relationship between clinical and neuroradiological characteristics in acute CVT patients is still not univocally characterized.

Materials and methods
We enrolled 32 consecutive acute CVT patients admitted to our emergency department from January 1, 2012, to June 30, 2013. Clinicoradiological associations and their relationship with the functional outcome at the discharge were tested.

Results
Headache was the presenting symptom in 85% of patients, more frequently subacute (52%), new-onset (47%), with unusual features in respect to prior headache episodes (100%), and associated with persistent neurological symptoms/signs (74%). Patients with facial headache showed more frequent venous ischemia (VI) compared to those with facial and unilateral headache (50% vs. 20% vs. 0%, respectively, p=0.027). Patients with concurrent neurological deficits had a higher prevalence of VI (51% vs. 15.5%, p=0.049) and sigmoid sinus thrombosis (67% vs. 50%; p=0.047) than those without. Vomit was more frequently observed in patients with sigmoid sinus thrombosis (67% vs. 30%; p=0.043). Increasing age and VI were independently associated with poor (modified Rankin scale (mRS) 2-5) functional outcome (odds ratio (OR) 1.015, 95% confidence interval (CI) 1.004-1.035; p=0.015 and OR 1.007, respectively).

Conclusions
Our study confirms and enriches available data on the clinicoradiological profile of patients with acute CVT and suggests that increasing age and venous ischemia are independently associated with poor outcomes.

Categories: Emergency medicine, Neurology
Keywords: outcome, prognosis, neuroradiology, headache, cerebral venous thrombosis

Introduction
Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease with an estimated incidence of 5.1 (850;860) people per year [1]. Although accounting for less than 1% of all strokes [2,3], CVT-related complications (e.g., venous ischemia (VI), intracranial hypertension (IH), parenchymal hemorrhage (PH), subarachnoid hemorrhage (SAH)) account for important morbidity and mortality rates (about 1.5%-5%) [2]. CVT has a three-fold higher incidence in women younger than 50 years old, reflecting sex-specific risk factors such as pregnancy, contraceptive use, and estrogen fluctuations [4-6]. Other less common risk factors include genetic or paraneoplastic thrombophilia, infectious or autoimmune disorders, and traumaticail injury (1-2,4-6). CVT can present with a multitude of neurological symptoms depending on many factors such as age and the anatomical location of the thrombus (1-2). Headache is the most common symptom of CVT (up to 90% of all cases) [2,7] and can result from either mechanical stretching of trigeminal nerve fibers in the walls of the occluded sinus or from cortical and dural inflammation (1,2). However, CVT-related headache location and characteristics are extremely heterogeneous, ranging from thunderrhead pain to less specific features (e.g., throbbing pain with nausea, vomit, photosensitivity, malaise, neck pain, fever) (1-2,4-6). Few studies attempting to identify recurrent headache patterns have failed to provide univocal data (1-2) so that the clinical suspicion of acute CVT still relies on the concurrence of risk factors and neuroradiological findings (1-2,4-6). Furthermore, the relationship between headache and neuroradiological findings has been not univocally characterized, and the only reported association is between occipital pain and sigmoid sinus thrombosis (1-2).

With this background, our study aimed to investigate the clinicoradiological profile and to identify potential associations with the functional outcome in a retrospective cohort of CVT patients.

Materials and Methods
Study design and participants
We retrospectively enrolled all consecutive patients aged >18 years old admitted to the emergency department (ED) of S. Orsola-Malpighi University Hospital of Bologna and discharged between January 1, 2012, and June 30, 2013, with a diagnosis of CVT (study period = 24 months). Additionally, we interrogated our hospital database in order to check the inclusion of all CVT cases with the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 437.6 (non-pyogenic subdural hematoma), 437.6 (non-pyogenic subdural hematoma), and 67.3 (other phlebitis and thrombophlebitis of intracranial venous sinuses), and 67.13 (other phlebitis and thrombosis in pregnancy and puerperium). Overall, patients underwent several neuroradiological evaluations during admission. However, medical records were also reviewed from discharge reports and checked by an expert vascular neurologist (MG) to confirm the diagnosis. Clinical, neuroradiological, and neuroradiological findings were individually compared.

Definitions, classifications, and diagnostic procedures
Headache was classified according to the time from the onset as acute (<48 hours), including thunderhead headache (sudden onset with maximum intensity within 1 min), subacute (1-7 days), and chronic (>1 week). Pain intensity was assessed using the numeric rating scale (NRS) and divided into mild (NRS ≤4), moderate (NRS 5-7), and severe (NRS >8). Pain was defined as refractory to medications when present with moderate-to-severe intensity (NRS 5–10) despite the administration of adequate analgesic treatment. Unenhanced brain CT scan was considered consistent with CVT in the presence of a hyper-attenuating clot in the cerebral vein system, signs of VI (in fact not conforming to a conventional artery territory or spanning
Statistical analysis

Patients were stratified into different groups based on clinical variables. Demographic and neuromonitoring patterns were compared between patients dichotomized according to the presence or absence of the specific clinical feature in each of these groups. Categorical variables were summarized as frequencies and percentages while continuous variables were presented as median (interquartile range – IQR). Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. The student t-test for unpaired samples or the Mann-Whitney U test was used to compare normally or non-normally distributed variables, respectively. Univariate logistic regression analysis was performed to study the association of demographics, clinical features, and neuromonitoring findings with poor functional status. Subsequently, variables showing a statistically significant association with the outcome at univariate analysis were included in a multivariate logistic regression model to establish independent associations with a poor functional outcome at discharge. Results were presented as odds ratio (OR) with a 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS software, version 21.0 (IBM Corp., Armonk, NY).

Data availability

Pseudonymized participant data and results of analyses not included in the article will be made available upon request to the corresponding author.

Results

Thirty-four patients aged >18 years old with a diagnosis of acute CVT were included in the study. Two patients were excluded because of secondary referral to our hospital for CVT complications. Therefore, we included 32 patients in the study. Seventeen patients (53%) were male and 15 (47%) female. The median age was 41 years (IQR 26–49). The median age of our population was 41 years (IQR 36–49) with a clear female predominance (75%). All patients underwent cell blood count, D-dimer, fibrinogen blood levels, and screening for known causes of hereditary thrombophilia (hyperhomocysteinemia, antiphospholipid antibodies, antithrombin III deficiency, protein S/C deficiency, factor V Leiden mutation, prothrombin mutation, activated protein C resistance). Among gender-specific risk factors, the assumption of oral contraceptives was the most prevalent condition (67%), followed by pregnancy (4%). The presence of hereditary thrombophilia was the most frequent non-gender-specific risk factor (9%). For five patients (16%), we could not identify any possible prothrombotic factor. Demographic characteristics and frequency of risk factors are reported in Table 1.

Clinical presentation

The median time between symptoms onset and neurological evaluation in the ED was four days (IQR 2–8). Neurological signs at presentation favored early ED admission (median time 2 days, IQR 2–3). Baseline mRS was 0 for all but a single patient with mRS 1. Headache was present in most of the patients at admission (27/32, 85%), with a de novo presentation in 7% of cases, and in all (100%) cases, it was the presenting symptom of acute CVT. Among patients presenting with a headache, 55% had a prior headache history, but they all experienced an unusual pain as the inaugural CVT symptom. Patients presenting with a headache tended to be younger in comparison with subjects without a headache (median 39, IQR 25–46 vs. 61, IQR 53–64 respectively; p=0.087). In most cases, the headache presented with concurrent neurological symptoms (71%) while the remaining seven patients had isolated headaches (26%). No patient reported a thunderclap headache, with the majority (61%) showing a subacute onset. The median NRS was 6 (IQR 4–9). Besides headache, two cases presented with cavernous sinus syndrome (6%) and two cases with a decreased level of consciousness (6%). Only one patient (3%) presented with retinal focal seizures. Clinical features are displayed in Table 2.
Clinical presentation with headache | N (%) | 27/32 (85)
---|---|---
Unusual headache* | 9/27 (33)
New-onset headache | 18/27 (67)

Chronological presentation
Thunderclap | 0/27 (0)
Acute (<48 hours) | 4/27 (15)
Subacute (48 hours - 1 week) | 22/27 (81)
Chronic (>1 week) | 1/27 (4)

Headache characteristics
Mild | 6/27 (22)
Moderate | 15/27 (56)
Severe | 9/27 (33)
Persistent and refractory to common analgesic | 22/27 (81)
Isolated headache | 1/27 (4)

Headache associated with other neurological signs/symptoms ("headache plus")
+ Focal neurological defects | 10/27 (37)
+ Focal and/or generalized seizures | 1/27 (4)
+ ≥ 1 sign/symptom of IH (visual loss and/or 6th cranial nerve palsy and/or tinnitus) | 7/27 (26)

Headache location
Holocranial | 12/27 (57)
Unilateral | 10/27 (37)
Ipsilateral to the involved sinus | 9/10 (90)
Bilateral ("band-like") | 5/27 (19)

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TABLE 2: Clinical characteristics
IH = intracranial hypertension
*: different features in respect to prior headache episodes

Number of sinuses involved – Median (IQR)

<table>
<thead>
<tr>
<th>Number of sinuses involved</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 sinus – N (%)</td>
<td>6/32 (20)</td>
</tr>
<tr>
<td>≥2 sinuses – N (%)</td>
<td>24/32 (75)</td>
</tr>
</tbody>
</table>

CVT location

<table>
<thead>
<tr>
<th>CVT location</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse sinus</td>
<td>26/32 (81)</td>
</tr>
<tr>
<td>Sigmoid sinus</td>
<td>19/32 (59)</td>
</tr>
<tr>
<td>Sagittal superior sinus</td>
<td>14/32 (44)</td>
</tr>
<tr>
<td>Sagittal inferior sinus</td>
<td>3/32 (9)</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>6/32 (19)</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>2/32 (6)</td>
</tr>
<tr>
<td>Concomitant involvement of ≥1 cortical vein</td>
<td>2/32 (6)</td>
</tr>
<tr>
<td>Concomitant involvement of ≥1 deep cerebral vein</td>
<td>6/32 (19)</td>
</tr>
<tr>
<td>Venous lakeshine – N (%)</td>
<td>16/32 (51)</td>
</tr>
<tr>
<td>Hemorrhagic complications – N (%)</td>
<td>6/32 (19)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>3/32 (10)</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>1/32 (3)</td>
</tr>
</tbody>
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TABLE 3: Neuroimaging findings
CVT = cerebral venous thrombosis; IQR = interquartile range

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Clinicoradiological associations
As the concerned gender, women had a higher number of involved sinuses compared to male patients (median for female 2, IQR 2-3 vs. 1 for male, 1-3; p=0.07). Considering headache characteristics (Table 2), patients with holocranial pain showed a higher prevalence of VI in comparison to those with bilateral ("band-like") and unilateral headache (50% vs. 20% vs. 0%, respectively; p=0.027). Patients with concomitant neurological deficits had more often VI (55% vs. 15%; p=0.048) and superior sagittal sinus (38%) thrombosis (67% vs. 30%; p=0.04). Finally, patients presenting with vomit showed more frequent involvement of the straight sinus (67% vs. 8% without vomit; p=0.053). All tested associations are reported in Table 4.
Treatment and outcome

All patients underwent immediate anticoagulation with low-molecular-weight heparin (LMWH, 1.5%) or sodium heparin (3%). Therefore, anticoagulation therapy was continued with warfarin (73%) or DDAVP (22%) according to current guidelines for CVT treatment [3]. Specifically, 17 out of 32 patients (54%) were treated with anticoagulants for <12 months while 10 patients (31%) underwent anticoagulation for 1-2 years. Only few patients (<10%) with permanent risk factors (genetic thrombophilias, malignancies including a case of essential thrombocythemia) underwent long-term (>2 years) anticoagulation with LMWH. The large majority of patients (87%) showed a favorable functional outcome (mRS=0-1) at the discharge (median time 20 days, IQR 15-34). Headaches completely resolved after the acute phase in 9% of patients while it improved greatly at discharge in the remaining patients. In all follow-up (median time 25 months, IQR 13-47), a good overall functional outcome (median mRS=1, IQR 0-1) was recorded, and no patients died of CVT. CT/MR venography (median time from the first CT/MR venography = 16 months, IQR 9-23) complete recanalization was observed in 41% of patients and partial recanalization in 33%. No case of CVT recurrence was recorded during the entire follow-up.

Associations with functional outcome

Univariate logistic analysis showed that increasing age and the presence of VS were the only two variables significantly associated with poor (mRS 3-5) outcome (OR = 1.074, 95% CI 1.001-1.152, p = 0.047 and OR = 1.048, 95% CI 1.016-1.085, p = 0.035, respectively) at discharge. Women showed a lower frequency of poor outcome in comparison to male patients (11.5% vs. 25%), although female sex was not able to predict good prognosis (OR = 1.23, 95% CI 0.37-1.51; p = 0.63). Multivariate analysis confirmed that both increasing age (OR = 1.001, 95% CI 1.001-1.004; p = 0.001) and VS (OR = 12.019, 95% CI 2.141-70.04; p < 0.001) were independently associated with mRS 2-5.

Discussion

We analyzed a cohort of consecutive acute CVT patients admitted to the ED of our hospital over a period of 90 months. Our study confirms some relevant clinico-radiological associations, especially with regard to acute CVT-related headache characteristics, which, to date, are still not universally defined.

Epidemiologically, the higher prevalence of women (70%) observed in our population, as well as the distribution of risk factors (mostly gender-specific, e.g., oral contraceptives and pregnancy >50%), are in line with observations from large cohort studies (e.g., International Study on Cerebral Venous and Dural Sinus Thrombosis - ISCST [5], Central Venous Stenosis Thrombosis Study - VENOSTET [6]). Our estimated incidence of CVT turned out to be higher (16 cases/year per million) than expected from prior epidemiological studies 15 cases/year per million people [13, 15-16]. However, data from recent research support our results, indicating an incidence of 15-15.7 million per year [13, 15-16], perhaps because of more complete ascertainment, suggesting that CVT occurrence could be higher than previously believed.

Remarkably, unenhanced head CT scan resulted positive for direct (e.g. cord sign, dense triangle sign) or indirect (e.g. venous ischaemia, subarachnoid haemorrhage) brain swelling; signs consistent with acute CVT in a great proportion of patients (83%), suggesting great value in the emergency diagnosis of CVT [10-19].

As expected, headache was the most prevalent presenting symptom of acute CVT (84%), although with heterogeneous intensity and location (either holocranial, “band-like,” or hemispheric). Patients presenting with headache tended to be younger in comparison to patients reporting different onset. This finding may...
be due to cerebral thrombosis in the elderly, attenuating effects of IH, as well as to diminished pain reactivity [4]. Notably, the classical clustering onset was never reported. Therefore, an isolated headache as a CVT inaugural manifestation reasonably delayed the first-aid access of about a week compared with focal neurological defects at onset. Despite the heterogeneous intensity and location, the recurrence of some features seems to indicate a more frequent patient for CVT-related headaches. Head pain was more often unilateral (52%), new-onset (41%), or with unusual features in comparison to previous episodes of headache (33%), likely to the involved sinuses when hemispheric (52%), with moderate to severe intensity (31%), and persistent and refractory to common analgesics (14%), associated with other neurological signs or symptoms (“headache plus” - 74%). However, the wide spectrum of CVT presentations observed in our population highlights that any recent persisting headache should arouse suspicion, particularly in the presence of an underlying prothrombotic condition, as stated by the current international classification for headache disorders – ICHD-3 [25], to avoid possible delay of treatment initiation.

With reference to neuroimaging findings, the distribution of involved sinuses slightly differed from results of the ISCVT cohort [5], which reported a more frequent involvement of the SSS (48%). This difference might be explained by the high prevalence (75%) of patients with thrombosis of V sinuses, probably for the higher rate of genetic/acquired systemic prothrombotic risks factors (78%) in our population vs. isolated brain (e.g. vascular anomalies, central nervous system (CNS) tumors, or other) or craniofacial precipitants (e.g. infection or trauma, 13%) which are likelier to cause focal CVT. Head CT signs of VS were found in approximately 30% of patients, aligning with the frequency reported by larger studies [1,2]. Interestingly, patients with VS had a higher incidence of hemorrhage (p=0.027). This clinicoradiological association was observed independently from the concomitant presence of ESR or symptoms of ESR, supporting the hypothesis that central irritation and inflammation due to VS might consistently contribute to the development of head pain in CVT. [11-23]. SSS thrombosis was more frequently observed in patients with focal neurovascular defects (p=0.045), likely for the concomitant involvement (55%) of cortical and/or deep cerebral veins, not allowing the development of adequate collateral outflows [4,26], thus leading to transient dysfunction of eloquent parietal areas. The more frequent presence of venous in patients with straight sinus thrombosis (p=0.015) is a novel finding and may be interpreted as an early sign of VS due to the initial development of impaired cerebrospinal fluid circulation when structures neighboring the exit venous outlet (e.g. thalamus) are involved [1,2]. SIMD was a rare complication of CVT in our population also (only one case, 3%). Our high rate of venous recanalization (partial/completeness in 94% of patients) was also in line with observations from prior cohorts reporting reperfusion [20-23].

Connecting the prognosis, acute CVT was associated with a good overall functional outcome (median mRS3, IQE 0-5), without cases of death when properly treated. VS and increasing age were associated with poor functional outcomes at discharge (mRS 2-5), as observed by larger studies [1,5]. Remarkably, neither the clinical presentation nor any specific characteristic of headache (e.g. location, intensity, responsiveness to common analgesics) showed an independent association with functional outcome, suggesting the weak prognostic value of pain characteristics at CVT onset.

Our study has several limitations. First, the small number of enrolled subjects (reflecting disease rarity) might have hampered the reliability of our findings and masked otherwise relevant associations. Second, the retrospective design represents a known source of possible information bias. Moreover, clinical data were mainly obtained from neurological visits carried out by expert neurologists during the hospital stay, thus downplaying possible information biases.

Conclusions
Our study suggests that acute CVT, although accounting for a small part of all cerebrovascular accidents, could be more frequent than previously reported. We confirmed and enriched available data on acute CVT clinicoradiological profiles in a consecutive series of patients admitted to our ED. New onset, headache, moderate to severe, and persistent headache represents a major clinical red flag that should prompt urgent investigation for CVT, especially in the presence of concomitant neurological deficits and/or well-known risk factors. Unenhanced head CT scan showed great sensitivity as the first-line ED-diagnostic investigation, followed by CT-MRI venography. Prompt and adequate recognition and management led to an excellent outcome in most of the patients (95%), whereas older age and presence of VS were associated with poor functional outcomes. Given the rarity of CVT, a disease registry should be implemented to achieve better outcome in most of the patients (>85%), whereas older age and presence of VI were associated with poor functional outcomes. Given the rarity of CVT, a disease registry should be implemented to achieve better outcome in most of the patients (>85%), whereas older age and presence of VS were associated with poor functional outcomes. Give...