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

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Abstract

Introduction

Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease with an estimated incidence of 1-2/1,000,000 people per year (1). Although accounting for less than 1% of all strokes (2), CVT-related complications (e.g., venous ischemia (VI), intracranial hypertension (IH), parenchymal hemorrhage (PH), subarachnoidal hemorrhage (SAH)) account for important morbidity and mortality rates (about 1.5% (3)). 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 (4,5). Other less common risk factors include genetic or paraneoplastic thrombophilia, infectious or autoimmune diseases, and traumatic head injury (6-8). CVT can present with a wide variety of neurological symptoms depending on many factors such as age and the anatomical location of the thrombus (9,10). Headache is notoriously the most common symptom of CVT (90% of all cases) (11) and can result from either mechanical stretching of trigeminal nerve fibers in the walls of the occluded sinus or from cortical and dural inflammation (12). However, CVT-related headache location and characteristics are extremely heterogeneous, ranging from thundertod headache pain to less specific features (e.g., throbbing pain with nausea, vomiting, photophobia, vertigo, and neck stiffness) (13,14). Few studies attempting to identify recurrent headache patterns have failed to provide univocal data (15-17) so that the clinical suspicion of acute CVT still relies on the concurrence of presence of risk factors and neuroimaging findings (18-20). Furthermore, the relationship between headache and neuroimaging findings has been not univocally characterized, and the only reported associations are with superficial pain and cingulated sinus thrombosis (15,16).

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.O. Malpighi University Hospital of Bologna and discharged between January 1, 2012, and June 30, 2019, with a diagnosis of CVT (study period = 90 months). Additionally, we recruited our hospital database in order to the inclusion of all CVT cases with the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 437.6 (non-episodic thrombosis of intracranial venous sinus), 335 (phlebitis and thrombophlebitis of intracranial venous sinuses), and 653.7 (other phlebitis and thrombosis in pregnancy and puerperium). Overall, patients underwent several neurological evaluations during admission. However, medical records were also recollected from discharge reports and checked by an expert vascular neurologist (MG) to confirm the diagnosis.

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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. Since our hospital ED services covered about 250,000 persons, the estimated CVT incidence resulted to be about four patients/250,000 inhabitants per year (16/1,000,000 per year). The median age of our population was 41 years (IQR 26-49) 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 (hypermethycysteinemia, antiphospholipid antibodies, antithrombin III deficiency, protein S/C deficiency, factor V Leiden mutation, prothrombin mutation, antithrombin C deficiency). Among gender-specific risk factors, the assumption of oral contraceptives was the most prevalent condition (67%), followed by pregnancy (18%). 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 3-11). Neurological signs at presentation favored early ED attendance (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 6% of cases, and in all (100%) cases, it was the presenting symptom of acute CVT. Among patients presenting with a headache, 75% had a prior headache history, but they all experienced unusual pain as the inaugural CVT symptom. Patients presenting with a headache tend to be younger in comparison with subjects without a headache (median 39, IQR 25-46 vs. 61, IQR 53-64 respectively); p<0.001. In most cases, the headache presented with concomitant neurological symptoms (16%), while the remaining seven patients had isolated headaches (26%). No patient presented a thunderclap headache, with the majority (61%) showing a subacute course. The median mRS was 4 (IQR 4-6). 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 subdural fluid collection. Clinical features are displayed in Table 2.

**Statistical analysis**

Patients were stratified into different groups based on clinical variables. Demographics and neuroimaging 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 demography, clinical features, and neuroradiographic 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**

| Demographic characteristics | Age – Median (IQR) | Sex Female – N (%) | Risk factors | Gender-specific (female) | Oral contraceptives | Pregnancy | Non-gender-specific | Hereditary thrombophilia | Factor V Leiden (heterozygous mutation) | Prothrombin G20210A (homozygous mutation) | Malignant tumours | Metastasis | Dental abscesses | Odontogenic meningitis | Malignancy | Lupus anticoagulant (LAC) | Hyperhomocysteinemia | Hyperfibrinogenemia | Thrombocytopenia | Recent dental puncture (<1 month) | Traumatic skull injury |
|-----------------------------|-------------------|--------------------|--------------|--------------------------|----------------------|-----------|-------------------|--------------------------|--------------------------------------|-------------------------------|-----------------|-----------|----------------|------------------------|-------------|-----------------------|-----------------|-----------------------|-----------------|-----------------------------|-------------------|
| Age – Median (IQR)         | 41 (26 – 49)      | 24/32 (77)         | N (%)        | 17 (56)                 | 16 (50)             | 1 (3)     | 21 (66)           | 3 (10)                   | 2 (6)                                | 1 (3)                          | 1 (3)                       | 2 (6)                  | 1 (3)     | 1 (3)                | 2 (6)                  | 1 (3)               | 2 (6)               | 1 (3)                | 2 (6)                |

**TABLE 1: Demographic characteristics and frequency of risk factors**

IQR = interquartile range

§ Malignancy included a patient with pancreatic adenocarcinoma and a patient with a history of essential thrombocythemia (positive genetic testing for JAK V617F mutation)
Clinical presentation with headache
- Unusual headache: 27/32 (85)
- New-onset headache: 18/32 (57)

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: 16/27 (57)
- Severe: 9/27 (33)
- Persistent and refractory to common analgesic: 22/27 (81)

Isolated headache
- Holocranial: 12/27 (57)
- Unilateral: 10/27 (37)
- Ipsilateral to the involved sinus: 9/10 (90)
- Bilateral (“band-like”): 5/27 (19)

Headache location
- Transverse sinus: 26/32 (81)
- Sigmoid sinus: 19/32 (59)
- Sagittal superior sinus: 14/32 (44)
- Sagittal inferior sinus: 3/32 (9)
- Straight sinus: 6/32 (19)
- Cavernous sinus: 2/32 (6)
- Concomitant involvement of ≥1 cortical vein: 2/32 (6)
- Concomitant involvement of ≥1 deep cerebral vein: 6/32 (19)
- Venous ischemia: 10/32 (31)
- Hemorrhagic complications: 6/32 (19)
- Parenchymal hemorrhage: 5/32 (16)
- Subarachnoidal hemorrhage: 1/32 (3)

Neuroimaging findings
All patients underwent an urgent unenhanced head CT scan, which resulted positive for signs suggestive of CVT in 83% of cases. In all cases (100%) the diagnosis of CVT was confirmed by either brain CT (59%) or MR venography (41%). Nine out of thirty-two patients (28%) showed CT signs of VI, while hemorrhagic complications were observed in six patients (19%). The median (IQR) number of involved sinuses was 2 (2–3). Neuroimaging findings are presented in Table 3.

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

| Clinical characteristics | N (%) |
|--------------------------|-------|
| Clinical presentation with headache | 27/32 (85) |
| Unusual headache | 9/27 (33) |
| New-onset headache | 18/32 (57) |
| 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 | 16/27 (57) |
| Severe | 9/27 (33) |
| Persistent and refractory to common analgesic | 22/27 (81) |
| Isolated headache | |
| Holocranial | 12/27 (57) |
| Unilateral | 10/27 (37) |
| Ipsilateral to the involved sinus | 9/10 (90) |
| Bilateral (“band-like”) | 5/27 (19) |
| Headache location | |
| Transverse sinus | 26/32 (81) |
| Sigmoid sinus | 19/32 (59) |
| Sagittal superior sinus | 14/32 (44) |
| Sagittal inferior sinus | 3/32 (9) |
| Straight sinus | 6/32 (19) |
| Cavernous sinus | 2/32 (6) |
| Concomitant involvement of ≥1 cortical vein | 2/32 (6) |
| Concomitant involvement of ≥1 deep cerebral vein | 6/32 (19) |
| Venous ischemia | 10/32 (31) |
| Hemorrhagic complications | 6/32 (19) |
| Parenchymal hemorrhage | 5/32 (16) |
| Subarachnoidal hemorrhage | 1/32 (3) |

TABLE 3: Neuroimaging findings
CVT = cerebral venous thrombosis; IQR = interquartile range

| Number of sinuses involved – Median (IQR) | II (0–3) |
|-----------------------------------------|---------|
| 1 sinus – N (%) | 4/32 (33) |
| ≥2 sinuses – N (%) | 24/32 (75) |
| CVT location | N (%) |
| Transverse sinus | 26/32 (81) |
| Sigmoid sinus | 19/32 (59) |
| Sagittal superior sinus | 14/32 (44) |
| Sagittal inferior sinus | 3/32 (9) |
| Straight sinus | 6/32 (19) |
| Cavernous sinus | 2/32 (6) |
| Concomitant involvement of ≥1 cortical vein | 2/32 (6) |
| Concomitant involvement of ≥1 deep cerebral vein | 6/32 (19) |
| Venous ischemia | 10/32 (31) |
| Hemorrhagic complications – N (%) | 6/32 (19) |
| Parenchymal hemorrhage | 5/32 (16) |
| Subarachnoidal hemorrhage | 1/32 (3) |

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 (65% vs. 15%; p=0.049) and superior sagittal sinus (14%) thrombosis (17% vs. 50%, p=0.045). Finally, patients presenting with vomit showed more frequent involvement of the straight sinus (83% vs. 17% without vomit; p=0.005). All tested associations are reported in Table 4.
TABLE 4: Clinicoradiological associations

| Neurological findings | Sex | Age | Presentation with headache | Isolated headache | Chronic radiological presentation | Headache intensity | Headache location |
|-----------------------|-----|-----|-----------------------------|------------------|---------------------------------|-------------------|------------------|
|                       |     |     |                             |                  |                                 |                   |                  |
|                       |     |     |                             |                  |                                 |                   |                  |

Treatment and outcome

All patients underwent immediate anticoagulation with low-molecular-weight heparin (LMWH, 10 U/kg) or sodium heparin (10%). Therewith, anticoagulation therapy was continued with warfarin (target INR >2) or LMWH (75%) according to current guidelines for CVT treatment. [15-16]. Specifically, 27 out of 30 patients (90%) were treated with anticoagulants for >12 months while 10 patients (33%) underwent anticoagulation for <12 months. Only few patients (10%) with permanent risk factors (genetic thrombophilia, 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 15-54 days). Headache completely resolved after the acute phase in 59% of patients while it persisted during the entire follow-up. In five patients (16%) with permanent risk factors (genetic thrombophilia, malignancies including a case of essential thrombocythemia), complete recanalization was observed in 41% of patients. Two patients (6.7%) and one patient (3.7%) had grade 3 and grade 2 headaches, respectively, at the discharge in the remaining patients. Follow-up (median time 23 months, IQR 15-47 months), a good overall functional outcome (median mRS ≤1) was recorded, and no patients died. CT/MR venography (median time from the first CT/MR venography = 36 months, IQR 21-51 months), complete recanalization was observed in 41% of patients and partial recanalization in 15%. 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 >2) outcome (OR = 1.07, 95% CI 1.00-1.15; p=0.047 and OR = 1.00, 95% CI 0.99-1.01; p=0.55, respectively) at discharge. Women showed a lower degree of poor outcome in comparison to male patients (13.5% vs. 23%), although female sex was not able to predict good prognosis (OR = 1.28, 95% CI 0.37-4.51; p=0.71). Multivariate analysis confirmed that both increasing age (OR = 1.00, 95% CI 0.99-1.01; p=0.90) and VI (OR = 1.10, 95% CI 0.83-1.46; p=0.50) were independently associated with mRS >2.

Discussion

In this study, we analyzed a cohort of consecutive acute CVT patients admitted to one of our hospitals in a period of 90 months. We study outlined some relevant clinicoradiological 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 >10%,) are in line with observations from larger cohort studies (e.g., International Study on Cerebral Vein and Dural Sinus Thrombosis - ISCVT [5], Central Venous Sinuses Thrombosis Study - VENEST [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 [15-16]. However, data from recent research support our results, indicating an incidence of 15-17.5 million cases/year [15-16], perhaps because of more complete ascertainment, suggesting that CVT occurrence could be higher than previously believed.

Remarkably, aneurysmal head CT scan resulted positive for direct (e.g., subdural, dural sinus) or indirect (e.g., venous infarcts, subcortical hemorrhagic infarcts, brain swelling) signs consistent with acute CVT in a great proportion of patients (83%), suggesting great value in the emergency diagnosis of CVT [17-19].

As expected, headache was the most prevalent presenting symptom of acute CVT (58%), 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 atrophy in the elderly, attenuating effects of IH, as well as to diminished pain reactivity [1]. Notably, the clinical-diagnostics 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 headache. Head pain was more often unilateral (52%), new-onset (67%), or with unusual features in comparison to previous episodes of headache (10%), possibly related to the involved sinus when hemispheric (7%), with moderate to severe intensity (7%), persistent and refractory to common analgesics (1%), associated with other neurological signs/syndromes (“Headache plus” – 74%). However, the wide spectrum of CVT presentations observed in our population highlighted 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-III [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 [7], which reported a more frequent involvement of the SSS (>80%). This difference might be explained by the high prevalence (75%) of patients with thrombosis of ≥2 sinuses, probably for the higher rate of genetic/acquired systemic prothrombotic risk factors (>70%) in our population vs. localized brain or in vascual anomalies, central nervous system (CNS) tumors, or meningeal precursors (e.g., infection or trauma, 13%) which are liable to cause focal CVT. Head CT signs of CVT were found in approximately 30% of patients, aligning to the frequency reported by larger studies [3,5]. Interestingly, patients with VTH probably had a higher incidence of holocranial headache (p=0.027). This clinicoradiological association was observed independently from the concomitant presence of ICH or symptoms of IL, suggesting the hypothesis that CVT and IL may contribute to the development of head pain in CVT patients [11] (25%). The most frequent location of ICH/IL was幕loral (p=0.046), likely for the concomitant involvement (25%) of central and/or deep cerebral veins, not allowing the development of adequate collateral outflows [4,25], thus leading to transient dysfunction of eloquent parenchymal areas. The more frequent presence of vomiting in patients with straight sinus thrombosis (p<0.05) is an early finding and may be interpreted as an early sign of IH due to the initial development of impaired cerebrospinal fluid circulation when structures neighboring the III ventricle outlet (e.g., thalamus) are involved [4,26]. ASD was a rare complication of CVT in our population also (only one case, 3%). Our high rate of venous occlusion (partial/complete in 94% of patients) was also in line with observations from prior cohorts reporting neuroangiography [20-22].

Concerning the prognosis, acute CVT was associated with a good overall functional outcome (median mRS 0, IQR 0-1), with cases of death when properly treated. IL and increasing age were associated with poor functional outcomes at discharge (mRS >5), as observed by larger studies [3,5]. 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 interpretability of our findings and maximal otherwise relevant associations. Second, the retrospective design represents a known source of potential 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, 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/MR venography. Prompt and adequate recognition and management led to an excellent functional outcomes at discharge (mRS 2-5), as observed by larger studies [3,5]. ICH was a rare complication of CVT in our population also (only one case, 3%). Our high rate of venous occlusion (partial/complete in 94% of patients) was also in line with observations from prior cohorts reporting neuroangiography [20-22].

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. S. Orsola-Malpighi University Hospital ethics committee issued approved 91/2020, dated November 12, 2019. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payments/compensation: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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