Cerebral Venous Sinus Thrombosis in Adults with Prothrombotic Conditions: A Systematic Review and a Case from Our Institution

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Abstract

Cerebral venous sinus thrombosis (CVST) is a rare condition characterized by elevated intracranial pressure due to impaired cerebral venous drainage, potentially leading to life-threatening consequences. We searched the PubMed electronic database for ‘cerebral venous sinus thrombosis’ and ‘prothrombotic’ cases reported in adults (≥19 years) and conducted a systematic review for the published literature in the English language pooled with a case from our institution. Data were analyzed regarding patient demographics, risk factors, clinical features, treatment modalities, and outcomes when available.

Thirty cases of CVST were identified (29 case reports, of whom two were described in a case series, and the case one from our institution). The patients’ mean age was 39 years (range: 19–65). The male:female ratio was 1.14:1. The majority (75.3%) had at least one preexisting risk factor, with prescription drug use being the most common risk factor (33.3%) shared among all patients. Most patients (83.3%) presented with at least two symptoms. The most common presenting symptoms were headache (70%), gastrointestinal disturbance (50%), and seizures (40%). Focal deficits (36.7%), vision disturbances (30%), and altered consciousness (20%) were the remaining presenting complaints. Twelve cases (40%) commented on papilledema, with 10 (83.3%) having papilledema present. Anticoagulation abnormalities were examined in 26 cases (86.7%), out of which four cases (15.4%) had isolated protein S (PS) deficiency, three cases (11.5%) had isolated antithrombin III (ATIII) deficiency, and one case (3.8%) had isolated protein C (PC) deficiency. The most common initial imaging modality (22 cases, 73.3%), and most commonly used overall (23 cases, 76.7%), was computed tomography (CT). Magnetic resonance imaging (MRI) was the second most common imaging modality for initial use (five cases, 16.7%), diagnosis or confirmation of CVST (eight cases, 26.7%), and overall (21 cases, 70%). Heparin treatment was involved in the treatment of 18 cases (60%), and warfarin treatment was used in 10 cases (33.3%). Heparin-warfarin combination treatment was utilized in eight cases (26.7%). Most patients survived (28 cases, 93.3%), while the two remaining patients died secondary to brain death from the CVST (6.7%).

The findings from this study highlight the clinical characteristics of CVST. Therefore, this study aims to increase awareness of this rare entity. Physicians should maintain a high index of suspicion in order to diagnose patients presenting in the proper clinical context, given this case shares various forms of presentations with other common clinical conditions but requires long-term anticoagulation.

Introduction And Background

Cerebral venous sinus thrombosis (CVST) is a relatively uncommon, but potentially life-threatening condition, that has variable and non-specific forms of clinical presentations [1-2]. Anticoagulants, mainly heparin agents, are used as first-line therapy, with most patients attaining an excellent response [3]. This study’s objective is to review the patient characteristics, risk factors, clinical features, treatment modalities, and outcomes of CVST, a rare and life-threatening condition in patients with prothrombotic states.

Review

Methods

Search Strategy

The present study protocol adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for reporting systematic review protocols. The PubMed database was searched for adults (≥19 years old) and case reports in English using the terms ‘cerebral sinus venous thrombosis’ and ‘prothrombotic’ as keywords. Reference lists were also examined to identify relevant case reports. All full-text published cases were selected, and the authors independently assessed cases for inclusion.

Data Extraction and Analysis

All studies evaluating CVST with prothrombotic abnormalities were screened, with the selection of only those reports containing data on demographic information, clinical features, prothrombotic laboratory results, and diagnostic imaging. Unrelated case reports and those without prothrombotic lab results were excluded (Figure 1). Data are expressed in descriptive statistics using central tendency and dispersion measures.
Results

A total of 42 case reports of CVST with prothrombotic laboratory results were screened, with 28 publications ultimately included [4-31]. One case series described two cases, both of which were included, yielding 29 cases for this systematic review. With the addition of a case from our institution, a total of 30 case reports were analyzed. The demographics, clinical features, and outcomes of the 30 cases are summarized in Table 1.

| Author (Yr) | Age (Yr) | Gender | Medical History | Duration of Symptoms Before Presentation | Presenting Symptoms | Initial Physical Examination Findings | Anticoagulation Abnormality | Diagnostic Imaging | Treatments Provided | Follow-Up Period | Outcome | Complications | Final Diagnosis |
|-------------|----------|--------|-----------------|------------------------------------------|---------------------|--------------------------------------|-----------------------------|---------------------|-------------------|-----------------|---------|---------------|-----------------|
| Heistinger [4] (1992) | 38 | F | Multiple episodes of UE phlebitis and DVT post-delivery, appendectomy, tobacco | NR | Seizure, meningismus, cranial nerve deficits, R corneal reflex, facial palsy, R arm loss | Normal AT III, normal PC, decreased PS | Initial imaging: CT; Additional imaging: b/l carotid angiography (confirmed) | Heparin | NR | Alive | None | CVST d/t hereditary PS deficiency |
| Musio [5] (1993) | 24 | M | UC | NR | Hematochezia, weight loss, fulminant NAs, GCTE | Yes | Initial imaging: CT; Additional imaging: MR (confirmed) | IV methylprednisolone & oral sulfasalazine (for acute UC); phenytoin, anti-platelet therapy , acetazolamide; recanalization of thrombosed venous sinus | NR | Alive | None | CVST associated with UC |
| Tuite [6] (1993) | 24 | M | Chronic LBP | NR | R arm focal motor seizures; HAs, neck pain, photophobia, unilateral sensory loss | Decreased AT III, normal PC, normal PS | Initial imaging: CT; Additional imaging: MR (confirmed) | IV mannitol and dexamethasone, IV furosemide | NR | Brain dead, life support terminated | Elevated ICP, ARF | CVST d/t hereditary AT III deficiency |
| Vayá [7] (1995) | 42 | M | Anemia | 6 days | Anemia | No neurological deficits | Yes | Initial imaging: CT; Additional imaging: MR (confirmed) | LP, leukocytosis, elevated platelets, superior ophthalmal vein thrombosis | NR | Encephalopathy death | Elevated ECP, ARF |

FIGURE 1: The PRISMA flow diagram for the systematic review detailing the association of CVST with prothrombotic abnormalities

CVST: cerebral venous sinus thrombosis; PRISMA: preferred reporting items for systematic reviews and meta-analyses
| Name                         | Age | Gender | Skin Color | Marital Status | Height | Weight | Blood Pressure | Associated Medical Conditions | Medications | Presenting Symptoms | Initial Imaging | Outcome | Follow-up | Additional Notes |
|------------------------------|-----|--------|------------|----------------|--------|--------|----------------|-------------------------------|--------------|---------------------|----------------|----------|-----------|-------------------|
| Rufa [15]                    | 2007 | Rufa   | M          | Female        | 57 / M | None   | 140 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Muthukumar [20]              | 2007 | Muthukumar | M          | Female        | 38 / M | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Akatsu [12]                  | 1999 | Akatsu | M          | Female        | 19 / M | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Lefebvre [9]                 | 2001 | Lefebvre | M          | Female        | 40 / F | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Singhal [9]                  | 1998 | Singhal | M          | Female        | 42 / M | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Bowen [11]                   | 1998 | Bowen  | M          | Female        | 65 / F | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Atluri [12]                  | 2003 | Atluri | M          | Female        | 3 / F  | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Ricoza [12]                  | 2005 | Ricoza | M          | Female        | 3 / F  | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Tiranay [1]                  | 2000 | Tiranay | M          | Female        | 3 / F  | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Multanar [20]                | 2004 | Multanar | M          | Female        | 3 / F  | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Ruus [11]                    | 2005 | Ruus   | M          | Female        | 3 / F  | None   | 160 / 90       | None                          | None         | None                | None           | Alive   | None     | None              |
| Case | Date | Sex | Age | History | Symptoms | Imaging | Treatment | Outcome |
|------|------|-----|-----|---------|----------|---------|-----------|---------|
| Opara [17] (2008) | 53 / M | | | | | | | |
| Verma [20] (2012) | 28 / F | | | | | | | |
| Kolacki [19] (2012) | 65 / M | | | | | | | |
| Sharpe [16] (2011) | 35 / M | | | | | | | |
| Nayak, Kumar [21] (2011) | 23 / M | | | | | | | |
| Shiek [21] (2011) | 23 / F | | | | | | | |
| Kadam [21] (2011) | 30 / F | | | | | | | |
| Iwama [21] (2011) | 30 / M | | | | | | | |

### Clinical Details
- **Opara [17] (2008)**: Single ectopic kidney with UVR.
  - Transplantation: 3 years prior.
  - Immunosuppressive therapy: prednisolone, cyclosporine, azathioprine.
  - Transplantation: kidney with VUR.

- **Verma [20] (2012)**: Sildenafil occurred within 24 hours of thrombosis.
  - 14 days prior to kidney transplantation.

- **Kolacki [19] (2012)**: Pregnant, AT III deficiency.
  - 3rd trimester pregnancy.

- **Sharpe [16] (2011)**: NuvaRing from 2002-2006 without complications.
  - Intermittent use.

- **Nayak, Kumar [21] (2011)**: Known cerebrovascular accident, loss of consciousness.
  - Unsteadiness.

- **Shiek [21] (2011)**: Coughing.
  - Decreased AT III and PC.

- **Kadam [21] (2011)**: Acute kidney failure.
  - Chronic kidney disease.

- **Iwama [21] (2011)**: CVST d/t PS induced by NuvaRing.
  - cvt.

### Symptoms
- **Opara [17] (2008)**: None.
  - Weakness.

- **Verma [20] (2012)**: None.
  - Nystagmus.

- **Kolacki [19] (2012)**: None.
  - Photosensitivity.

- **Sharpe [16] (2011)**: None.
  - Loss of PS.

- **Nayak, Kumar [21] (2011)**: None.
  - Persistent L hemiparesis.

- **Shiek [21] (2011)**: None.
  - Thrombosis.

- **Kadam [21] (2011)**: None.
  - Persistent L hemiparesis.

- **Iwama [21] (2011)**: None.
  - Thrombosis.

### Imaging
- **Opara [17] (2008)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Verma [20] (2012)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Kolacki [19] (2012)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Sharpe [16] (2011)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Nayak, Kumar [21] (2011)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Shiek [21] (2011)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Kadam [21] (2011)**: Initial imaging: CT head.
  - Additional imaging: MRV.

- **Iwama [21] (2011)**: Initial imaging: CT head.
  - Additional imaging: MRV.

### Treatment
- **Opara [17] (2008)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy, thalidomide.

- **Verma [20] (2012)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Kolacki [19] (2012)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Sharpe [16] (2011)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Nayak, Kumar [21] (2011)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Shiek [21] (2011)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Kadam [21] (2011)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.

- **Iwama [21] (2011)**: Enoxaparin, dicoumarol.
  - Steroids, decongestive therapy.
| Name            | Age | Gender | Duration | Symptoms/History | Diagnosis/Imaging | Treatment | Outcome |
|-----------------|-----|--------|----------|-----------------|------------------|-----------|---------|
| **Case 1**      | 50 F | Diabetes, obesity | 8 weeks | None | Unremarkable | | Married |
| **Case 2**      | 25 F | History of thrombophlebitis | 3 days | None | Unremarkable | | Alive |
| **Case 3**      | 70 F | History of stroke | 6 months | None | Unremarkable | | Alive |
| **Case 4**      | 45 F | History of stroke | 1 year | None | Unremarkable | | Alive |
| **Case 5**      | 65 F | History of stroke | 2 years | None | Unremarkable | | Alive |
| **Case 6**      | 55 F | History of stroke | 3 months | None | Unremarkable | | Alive |
| **Case 7**      | 60 F | History of stroke | 1 year | None | Unremarkable | | Alive |

**Note:** *NR* = Not Recorded

**Diagnosis:**
- Diabetes
- Obesity
- Stroke
- Thrombophlebitis
- Thrombosis

**Treatment:**
- Anticoagulants
- Antihypertensives
- Antibiotics
- Corticosteroids

**Outcome:**
- Married
- Alive
- NR

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- Varner M, Ganeshan V, Qadir A, et al. (2014). *Cureus*, 6(9): e422. DOI 10.7759/cureus.422
The mean age at presentation was 39 years old (range: 19 - 65), with 24 (80%) being less than 50 years old. There were 16 male (53.3%) and 14 female (46.7%) patients (Figure 2). The majority (73.3%) had at least one preexisting risk factor (Figure 3). Prescription drugs were the most common risk factor (33.3%) shared among all patients. A history of tobacco smoking was reported in four cases (13.3%).

TABLE 1: Summary of the Clinical Characteristics, Risk Factors, Diagnostic, Management, and Outcomes of CVST Case Reports Included in the Systematic Review

| Study | Present | ET / M | negative cocci ag | 7 days | None | Blurry vision | HTN | Yes | Decreased AT | 3.0, normal, PC, normal PS, negative P | G2O105, gamma | Antiphospholipid antibody | Alive | None | Papiolo | Alive | None | Papiolo |
|-------|---------|--------|-------------------|--------|------|---------------|-----|-----|--------------|-----------------|----------------|--------------------------|--------|------|--------|--------|------|--------|
Among females, 11 (78.6%) reported having gender-specific risk factors. Six (54.5%) were receiving exogenous estrogen hormone therapy (EEHT), four (36.3%) were pregnant or puerperal patients, and one (9.1%) was receiving norethisterone therapy. Three case reports (10%) involved mechanical precipitants. Other disorders, including congenital heart disease, thyroid disease, Evans syndrome, diabetes, and cirrhosis, were reported in three cases (10%). The least common risk factors were a preexisting hematologic condition (two cases, 6.7%) or inflammatory disease (one case, 3.3%).

Of the 20 cases (66.7%) that reported the duration of symptoms, most (55%) had symptoms between two to seven days at presentation. Four patients (20%) presented earlier with symptoms up to one day, while five patients (25%) presented later with symptoms lasting at least eight days. One patient (5%) had symptoms more than two weeks, not presenting until two months after symptom onset (Table 2).

### TABLE 2: The Duration of Symptoms Before the Patients' Presentation

| Duration     | The fraction in each category (%) |
|--------------|-----------------------------------|
| 0 - 1 day    | 4/20 (20.0%)                      |
| 2 - 7 days   | 11/20 (55.0%)                     |
| 8 - 14 days  | 4/20 (20.0%)                      |
| > 2 weeks    | 1/20 (5.0%)                       |

Most patients (83.3%) presented with at least two symptoms (Figure 4). The most common presenting symptoms were headache (70%), gastrointestinal disturbance (50%), and seizures (40%). Focal deficits (36.7%), vision disturbances (30%), and altered consciousness/confusion/disorientation (20%) were the remaining presenting complaints. Twelve cases (40%) commented on papilledema, with 10 patients (83.3%) having papilledema present.
Anticoagulation abnormalities were examined in 26 cases (86.7%). Four cases were excluded as they did not mention at least one of the following levels: antithrombin III (AT III), protein C (PC), or protein S (PS). AT III, PC, and PS were all normal in 11 cases (42.3%). An abnormality in at least two out of the three anticoagulants was reported in six patients (23.1%). Isolated AT III (three cases, 11.5%), PC (one case, 3.8%), or PS (four cases, 15.4%) deficiency was noted in the remaining cases (Figure 5).

Hyperhomocysteinemia (HHcy) was found among three (21.4%) female patients where it was associated with a G20210A prothrombin gene mutation in the first, low PS in second, and normal AT III, PC, and PS in the third patient. Moreover, among females with HHcy, one was puerperal, the second was using EEHT, and one was puerperal and had a two-year history of EEHT use.

The G20210A prothrombin gene mutation was found among three (9.4%) patients overall, out of which one was a male with low AT III and two were females (one with normal AT III, PC, and PS, and the other with no reported data on AT III, PC, and PS testing).

The most common initial imaging modality (22 cases, 73.3%) and most commonly used overall (23 cases, 76.7%) was computed tomography (CT) scan (Figure 6). Magnetic resonance venogram (MRV) was the most common modality that diagnosed or confirmed CVST (10 cases, 33.3%). Magnetic resonance imaging (MRI) was the second most common imaging modality for initial use (five cases, 16.7%), diagnosis or confirmation of CVST (eight cases, 26.7%), and overall (21 cases, 70%).

FIGURE 4: The presenting symptoms of cerebral venous sinus thrombosis (CVST)
*The percentage of papilledema out of 12 cases with available data

FIGURE 5: The prevalence of different prothrombotic conditions in patients with CVST
AT III: antithrombin III; CVST: cerebral sinus venous thrombosis; PC: protein C; PS: protein S
FIGURE 6: Imaging modalities used when evaluating patients with suspected CVST

Initial (blue): first imaging used to evaluate the patients. Diagnosis/Confirmation (orange): the ultimately used imaging to diagnose or confirm the diagnosis of CVST. Overall (grey): the percentage of cases where imaging used at any point in patients’ evaluation.

CVST: cerebral sinus venous thrombosis

Heparin agents were involved in the treatment of 18 cases (60%), and warfarin agents were used in 10 cases (33.3%). A heparin-warfarin combination treatment was utilized in eight cases (26.7%). Ten cases (33.3%) reported using other anticoagulants either with or without the use of heparin and/or warfarin agents (Figure 7). Surgical intervention occurred in three cases (10%).

FIGURE 7: Treatments used for patients with cerebral sinus venous thrombosis (CVST)

Most patients survived (28 cases, 93.3%), while the two remaining patients died secondary to brain death from the CVST (6.7%). The two patients (100%) that died were administered mannitol and corticosteroids during their treatment course, and neither were given warfarin. One other patient who survived and recovered fully was given mannitol (Table 3).

| Outcome | No. of patients/Total (%) |
|---------|--------------------------|
| Alive   | 28/30 (93.3%)            |
| Dead    | 2/30 (6.7%)              |

TABLE 3: Survival outcome among cerebral sinus venous thrombosis (CVST) patients

CVST occurs with similar frequency in males and females, and the symptom presentation often leads to a broad differential diagnosis.
Discussion

In this systematic review of CVST cases, several findings are notable. CVST is a rare condition that represents a unique challenge to physicians. It occurs at a similar frequency in both men and women and has a wide variety of symptoms that are clinically indistinguishable from other common clinical conditions, which most often lead to a broad differential diagnosis [1, 32-33].

Most cases had at least one preexisting risk factor indicating multifactorial etiology with multiple mechanisms involved in its pathogenesis. Prescription drug use was the most common risk factor, including those involved in oral contraceptive use. Among females, 10 (71.4%) reported having gender-specific risk factors. Four (40%) were pregnant or puerperal patients and six (60%) were getting EEHT.

Exogenous hormone therapy, pregnancy, and puerperium were the common risk factors for transient prothrombotic states and present in 78.6% of the female patients [34-36]. Tobacco use being the most common risk factor identified. More than half of the cases had symptoms between two to seven days before the presentation [37-38].

Most patients had symptoms for two to seven days at presentation and had at least two symptoms, with headache, gastrointestinal disturbance, and seizures being the most common presenting symptoms [39]. Normal AT III, PC, and PS were found in 42% of cases. Moreover, at least two of the three anticoagulants were deranged in a quarter of cases with available data [40].

The G20210A prothrombin gene mutation is linked with heightened risk for venous thrombosis, including CVST [40]. In this study, the G20210A prothrombin gene mutation was found in 9.4% of patients overall. Raised serum homocysteine levels are reported in the literature to cause a 4-fold higher risk of CVST [41]. In this study, HHcy was found among three (21.4%) female patients with a mean age of 25 years (range: 21 - 30).

CT scan was the initial modality of choice for most cases and the most commonly used overall, which could be due to its easy accessibility, relatively shorter scan period, and lower cost. MRI and MRV are the second and third most commonly used imaging overall, respectively. MRI and MRV were also the two most common imaging modalities used for diagnosis or confirmation of CVST. Therefore, MRV, in combination with MRI, is a non-invasive, specific modality that has proven reliable in diagnosing CVST [42-43].

Survival rate was 95.3%, and all deceased cases were not given warfarin during their treatment course. Papilledema (optic disc swelling due to high intracranial pressure) was present in 83.3% of the cases with symptomatic cases. Survival rate was 93.3%, and all deceased cases were not given warfarin during their treatment course. Papilledema (optic disc swelling due to high intracranial pressure) was present in 83.3% of the cases with symptomatic cases.

Conclusions

CVST may present with a variety of clinical presentations, which makes it a diagnostic dilemma and could lead to misdiagnosis or delayed diagnosis. Appropriate physical examination by primary care providers combined with a high index of suspicion, especially in the right context, is crucial in diagnosis. We advise for increased utilization of the direct ophthalmoscope to evaluate for papilledema in patients with suspected CVST. Further well-designed studies are warranted to help determine etiologies, as well as diagnostic and management strategies, for identifying CVST cases and to establish trends in patient outcomes.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: 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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