

Cerebral venous sinus thrombosis in Saudi Arabia

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ABSTRACT

الأهداف: تحليل الأعراض السريرية لتجلط الجيوب الوريدية في الدماغ، ومعرفة الأسباب، والمضاعفات، ومدى استجابة المرضى للعلاج وذلك في مدينتي جدة وأبها.

الطريقة: أُجريت هذه الدراسة الإسترجاعية التي شملت الملفات الطبية لحوالي 111 مريضاً ممن شُخصوا بمرض التجلط الوريدي الدماغية في كل من مدينة الملك عبد العزيز الطبية بجدة ومستشفى الملك فهد بالباحة، المملكة العربية السعودية وذلك خلال الفترة من يناير 1990م إلى نوفمبر 2010م. لقد قمنا بدراسة بيانات المرضى، وتحليل المعلومات ومقارنتها بالدراسات التي عملت محلياً وعالمياً.

النتائج: تكونت عينة الدراسات من 92 بالغ و19 طفل، وكان عدد النساء البالغات يفوق عدد الذكور البالغين، بينما كان الذكور هم غالبية الأطفال المشاركين في الدراسة. وكان متوسط العمر الذي بدأت فيه الأعراض 29.5 عاماً والتي كان أكثرها شيوفاً كلاً من: الصداع، والعلامات العصبية البؤرية، والتشنجات، ووذمة الحليمية البصرية، وانخفاض مستوى الوعي. فيما شملت عوامل الخطر التي تم التعرف عليها كلا من الحمل والنفاس، ومتلازمة أضداد الفوسفولبيد، وحبوب منع الحمل، والأورام الخبيثة، والالتهابات. ولقد أصيب 51 مريضاً (45.9%) بالتجلطات في جيوب متعددة، وعندما كانت الإصابة في جيب واحد (24.3%) فقد كان الجيب السهمي العلوي هو أكثر الجيوب المتأثرة بهذا التجلط. وأشارت نتائج الدراسة إلى شفاء 74 حالة من الأعراض تماماً، وشفاء 23 حالة جزئياً، بالإضافة إلى وفاة 10 مرضى. شملت العوامل المسببة للوفاة أو عدم الاستجابة للعلاج وجود أمراض مصاحبة لا يرجي برؤها مثل الأورام، والحضور المتأخر لتلقي العلاج، وحالة الصرع المستمر.

خاتمة: أثبتت الدراسة بأن الحمل والنفاس كانا من أكثر الأسباب المؤدية لتجلط الوريدي الدماغية في هذه السلسلة التي قمنا بدراستها، وقد كانت الأعراض السريرية متطابقة مع ما تم نشره عالمياً، ولم يكن مرض بهجت من العوامل المسببة للمرض في دراستنا. بالإضافة إلى ذلك فقد كان معظم المرضى مصابين بهذا التجلط في جيوب متعددة. ولقد أدى العلاج السريع باستخدام مضادات التجلط إلى الشفاء الكامل أو الجزئي من المرض وذلك في 87.4% من المرضى.

Objectives: To analyze the clinical patterns, etiologies, treatment, and outcome of cerebral venous sinus thrombosis (CVST) in 2 major cities of Saudi Arabia, Jeddah and Al-Baha.

Methods: One hundred and eleven patients diagnosed as CVST were identified from the medical records at King Abdulaziz Medical City, Jeddah, and King Fahad Hospital, Al-Baha, Saudi Arabia, from January 1990 through November 2010. We retrospectively analyzed the data, compared it with local and international studies, and reviewed the literature.

Results: There were 92 adults and 19 children. Among adults, females predominated, while more boys were affected than girls. The mean age of onset was 29.5 years. The most common clinical presentations were headache, focal neurologic deficits, seizures, papilledema, and decreased level of consciousness. The main risk factors identified were pregnancy/ puerperium, antiphospholipid antibody syndrome, oral contraceptive pills, malignancy, and infections. Multiple sinuses were affected in 51 patients (45.9%). When a single sinus was involved, the superior sagittal sinus (24.3%) was the most common. Seventy-four patients recovered completely, 23 patients recovered partially, and 10 patients died. Bad prognostic factors included incurable co-morbid conditions, late presentation, and status epilepticus.

Conclusions: Pregnancy/puerperium was the most common etiological factor in our series. Clinical features were similar to international series. Behçet's disease was not a major etiological factor in our series. Most patients had involvement of multiple sinuses. Prompt treatment with anticoagulation resulted in complete or partial recovery in 87.4% of patients.

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Cerebral venous sinus thrombosis (CVST) is a distinct cerebrovascular disorder with highly variable clinical presentation. It often affects young adults and children.¹ The estimated annual incidence is 3 to 4 cases per million population, with female preponderance in adults. The prognosis has improved significantly due to increased awareness of the disease, availability of more sophisticated neuroimaging techniques, and more effective treatment.² The objective of our study was to analyze the etiology, clinical presentation, and the outcome of CVST in Saudi Arabia. There are 2 studies reported from Saudi Arabia. In 1995, Daif et al³ reported 40 patients seen over 9 years in 2 hospitals in Riyadh, and a more recent study by Kajtazi et al⁴ was published in October 2009.

Methods. Using the International Classification of Diseases (ICD 10),⁵ we retrospectively studied the medical records of 111 patients with CVST admitted to King Abdulaziz Medical City, Jeddah, and King Fahad Hospital, Al-Baha between January 1990 and November 2010. The research and ethics committee of both institutes approved the study. Patients included in the study were diagnosed clinically and confirmed by neuroimaging, using CT, MRI, and/or 4-vessel cerebral angiography (only in selected patients). All patients who failed to show up for a minimum of a single follow-up visit and those who could not meet the radiological criteria for the diagnosis of CVST were excluded. We recorded the following information: demographic data, clinical presentation, etiology, risk factors, location of the thrombus and number of sinuses/veins occluded, treatment, and outcome. All patients had complete blood count, coagulation profile, and blood biochemistry. Screening for hypercoagulable states (protein C, protein S, antithrombin III, factor V Leiden, homocysteine, prothrombin gene mutation, anticardiolipin antibodies, antinuclear antibodies, and anti double stranded DNA) was carried out in most cases. Selected patients presenting with suspected CNS infection, and those patients with leukemia or lymphoma had CSF examination. All patients' data were analyzed using standard software (Excel, Microsoft Corporation).

Results. There were a total of 111 patients, 33 males, and 78 females with a mean age of 29.5 years (range 8 months to 80 years). Ninety-two patients were adults (73 females and 19 males) and 19 patients

were children, defined as patients below the age of 18 years (14 boys and 5 girls). Most adults were females (79.3%) but among children, males predominated (73.7%) (**Figure 1**). Frequently observed symptoms and signs were: headache, focal neurological deficit, seizures, papilledema, vomiting, and altered level of consciousness (**Table 1**). Other abnormalities reported were visual defects (blurred vision, diplopia, visual field defects), vertigo, behavioral changes, Parkinsonism, catatonia, locked in syndrome, and cerebellar signs. Seventy-nine patients had a CT of the brain. Normal brain CT was seen in 12 cases and hemorrhagic infarction was noted in 10 cases (**Figure 2**). A brain MRI was carried out in 93 patients (**Figure 3**), while cerebral angiography was carried out in only 2 cases. Multiple sinuses were involved in 45.9% of cases. The most common sinus involved, whether alone (24.3%) or in combination (53.2%), was the superior sagittal sinus (SSS) (**Figure 4**).

The CSF studies were performed in 22 patients, 10 were under high pressure, 2 had high protein, 4 had polymorphonuclear pleocytosis due to meningitis, and 4 had abnormal cytology (malignancy). The most common etiological factors were pregnancy/puerperium (15.3%), and antiphospholipid syndrome (13.5%). In males, infection, malignancy, and trauma were the major causes. Twenty-one patients had more than one risk factor (**Figure 5**). One hundred and four patients (93.7%) were treated with anticoagulation, while 7 patients received treatment of the underlying conditions

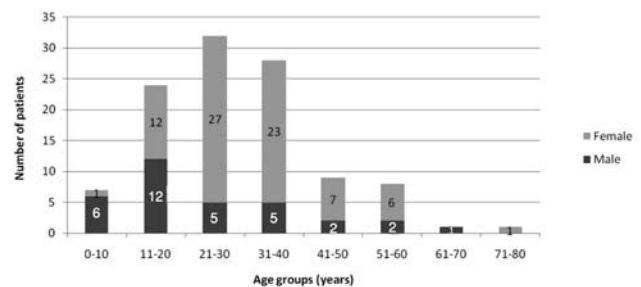


Figure 1 - Distribution of cases by age and gender.

Table 1 - Common symptoms and signs in 111 CVST patients.

Symptoms/signs	Number of patients	(%)
Headache	77	(69.4)
Focal neurological deficit	29	(44.1)
Seizure	45	(40.5)
Papilledema	39	(35.1)
Vomiting	37	(33.3)
Altered sensorium, coma	30	(27.0)
Visual defects (DV, VF defects)	12	(10.8)
Asymptomatic	4	(3.6)

DV - Diminution of vision, VF - visual field,
CVST - cerebral venous sinus thrombosis

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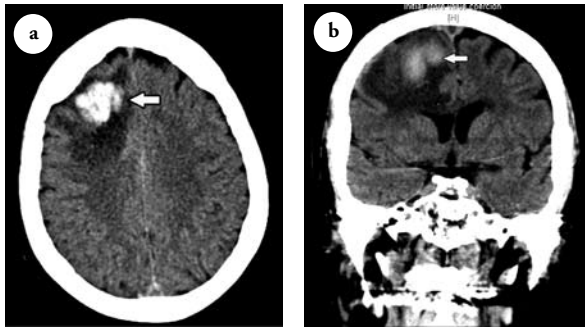


Figure 2 - Neuroimaging of a 55-year-old woman with hemorrhagic infarction, showing a) Axial CT with no contrast is showing a hemorrhagic infarction in the right frontal lobe with surrounding edema. b) Coronal CT with contrast is showing the same abnormality with delta signs demonstrated.

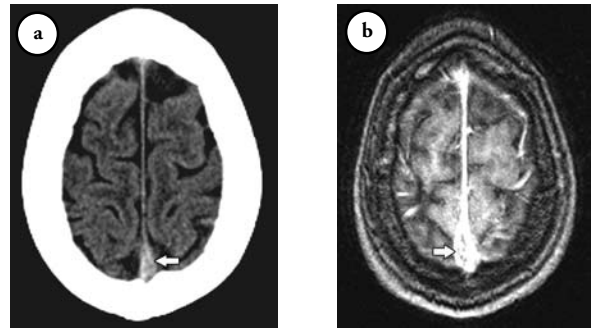


Figure 4 - Neuroimaging of a superior sagittal sinus thrombosis in a 35-year-old woman with CVST, showing a) Non enhanced axial CT scan showing dense superior sagittal sinus due to sinus thrombosis. b) MRI post contrast axial plane demonstrating classical filling defect, limited by the enhancing dural layer, producing "delta sign."

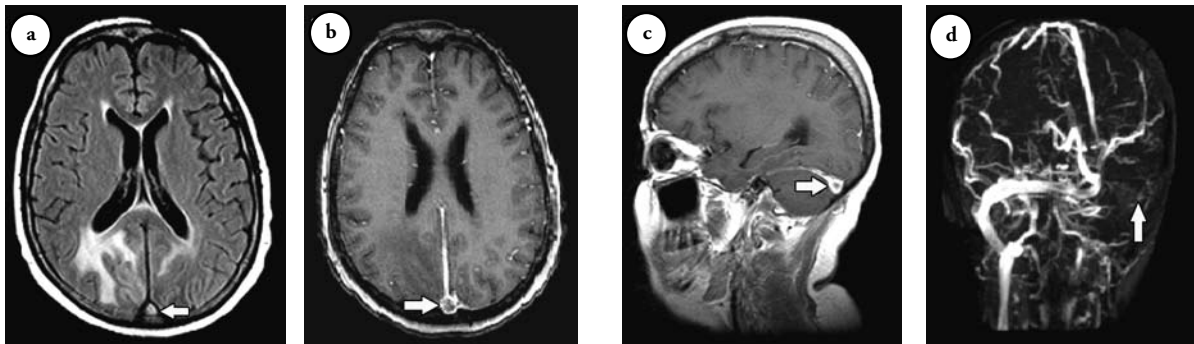


Figure 3 - Neuroimaging of 2 other ladies with CVST, showing a & b) Axial plane FLAIR and post contrast MRI images demonstrating superior sagittal sinus thrombosis, as bright signal in the FLAIR, and the classical delta sign in the post contrast. c) Post contrast sagittal section showing similar delta sign in the left lateral sinus. d) Magnetic resonance venography 2D ToF MIP showing absence of flow in the distal superior sagittal sinus, left lateral sinus, and sigmoid sinus as well as internal jugular vein. ToF - time of flight technique, MIP - maximum intensity projection

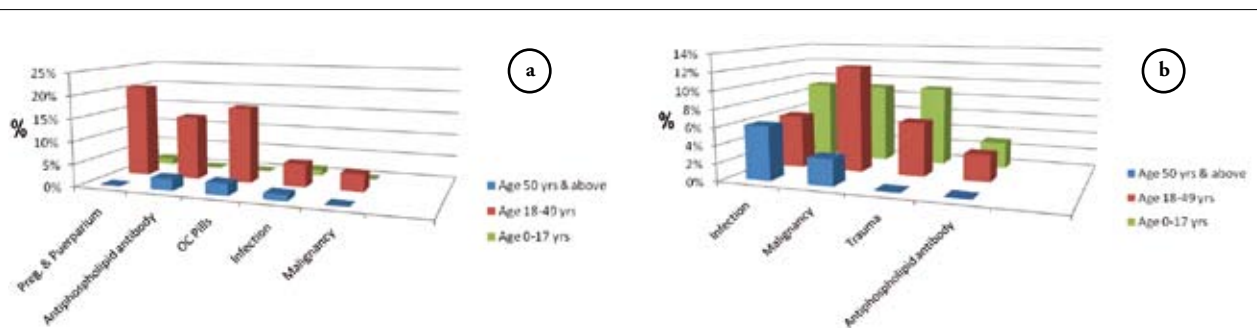


Figure 5 - Graph showing etiological factors among different age groups a) in females and b) in males. Preg - pregnancy, OC - Oral contraceptive.

only (3 patients had cavernous sinus thrombosis, 2 patients had road traffic accident [RTA] with a cerebral contusion, one patient had subdural hematoma, and one patient had arteriovenous malformation). Those patients who were treated with anticoagulation received either intravenous unfractionated heparin with a target partial thromboplastin time of 1.5 to 2 times the normal (85 patients), or low molecular weight heparin (19 patients). This was followed by warfarin with a target international normalized ratio of 2 to 3. The patients who had an underlying hypercoagulable state were advised to continue anticoagulation indefinitely, while patients with no identifiable risk factor were treated for a period of 6 months. Complete recovery was established in 74 patients, and partial recovery with some neurological deficit was seen in 23 patients. Unfortunately, 10 patients died either due to co-morbid condition (malignancy, severe infection, severe head injury, human immunodeficiency virus [HIV] infection, and diabetic ketoacidosis), status epilepticus, or delay in diagnosis. Those who had partial recovery presented late during their illness. Only 4 patients failed to show up for long term follow up visits.

Discussion. Cerebral venous sinus thrombosis has been recognized since 1825 when Ribes⁶ described the clinical history and postmortem examination of a 45-year-old man who died after a 6-month history of headache, seizures, and delirium. An autopsy revealed widespread malignancy and thrombosis of multiple sinuses. The true incidence of CVST is unknown since specific epidemiological studies are lacking. Kalbag and Wolf⁷ indicated that CVST was the principal cause of death in only one per 2 million persons per year in England and Wales between 1952 and 1961. On the other hand, a study carried out by Towbin⁸ found CVST in 9% of 182 consecutive autopsies. The currently accepted annual incidence is 3 to 4 cases per one million population, and up to 7 cases per one million among children.¹ The incidence of CVST is possibly higher than previously thought. This is mainly due to increased awareness of the disease and availability of more sophisticated neuroimaging techniques. In adults, the incidence is higher in females (75% of cases), which is consistent with our findings. For unknown reasons, female preponderance is lacking in children. In our study, 73.7% of children were males, consistent with other international reported series.^{9,10} The mean age in most large studies was between 37-39 years, though all ages can be affected.^{2,11} In our study, the mean age was 29.5 years. Our series included the youngest patient reported in the literature from Saudi Arabia. This 8 month old female patient suffered from orbital cellulitis, which was complicated by cavernous

sinus thrombosis. She was treated with antibiotics and anticoagulation with full recovery.

Cerebral venous sinus thrombosis is remarkable for its extremely diverse clinical presentations. Headache is the most predominant symptom in many studies (70-95%),^{1-4,6} In our study, 69.4% of patients presented with headache. Other associated features included seizures, focal neurological deficit, and altered level of consciousness (Table 1). No specific character or site of headache was noted among our patients. Focal neurological deficits were the presenting feature in 44.1%. They included hemiparesis, monoparesis, paraparesis, and cranial neuropathies. This figure is close to those found in the International Study on Cerebral Vein and Dural Sinus Thrombosis – ISCVT¹¹ (37%) and the Dutch-European study¹² (43%). Papilledema was found in 35.1% of patients. Headache associated with papilledema, suggesting a clinical picture of intracranial hypertension, were seen 16.2%. This is less than the figure reported by Kajtazi et al⁴ (36.3%). Seizures, focal or generalized, are more frequent in CVST than in other stroke types. In the ISCVT, seizure occurred in 39% of patients.¹¹ This finding is similar to our results.

In our series, 27% of patients presented with altered sensorium (not seizing) and 12.6% were in coma. This result is similar to the series reported by Breteu et al¹³ and Ferro et al¹¹ and lower than the results reported by Kajtazi et al,⁴ Kalbag & Wolf,⁷ and Ameri.¹⁴ Among patients who presented in coma, 3 died. One was a 16-year-old boy, a victim of RTA with multiple injuries, including head trauma. He had thrombosis of the lateral sinus without associated venous infarction. Another patient was an 80-year-old lady who presented in status epilepticus and coma. The third was a 35-year-old lady who had diabetic ketoacidosis and sepsis. Coma and altered level of consciousness was described as a bad prognostic factor for survival,¹¹ which is consistent with our study. Status epilepticus was the presenting feature in 13 of our patients, of whom 3 died. We concluded that status epilepticus should be considered a bad prognostic factor.

The literature describes 75-85% of cases with known etiological factors.^{1,2,11} In our study, 80.2% were found to have underlying risk factors which is different from Daif et al findings (25%).³ Among our patients, 61.3% had only a single risk factor, while 17.1% had 2, and only 1.8% had 3, or more risk factors, contributing to their disease. In our study, 19.8% were found to have an underlying hypercoagulable state, which is significantly less than the figure described (34%) in the ISCVT study.¹¹ We assume that the discrepancy reflects the failure to investigate all patients for underlying prothrombotic state. We found pregnancy/puerperium as the most common risk factor. This is different from

the figure reported by Kajtazi et al⁴ (4.5%). Malignancy is another common risk factor in our series (9.9%). This is higher than those reported by Daif et al,³ and Kajtazi et al.⁴ These findings suggest that a thorough work up for hypercoagulable state and underlying malignancy is warranted while investigating patients with CVST. Oral contraceptive pills (OCP) were the cause in 12.6% of our patients. This is lower than most of the studies reported in the literature,¹⁵ including those published from Saudi Arabia.⁴ This could be either due to social phobia from using OCP, or the use of other modalities of contraception. Infection was the cause of CVST in 9.9%, which is similar to the results of the studies carried out by Bouser et al,¹⁶ and Schell and Rathe.¹⁷ Infections included meningitis (3 cases), ear infection (7 cases), facial infection (3 cases), HIV (one case), acute lymphoblastic leukemia with febrile neutropenia (one case) and *Escherichia coli* bacteriemia (one case). Only one case of Behçet's disease was identified in our study. This is different to the study carried out by Daif et al,³ who found that 25% of their cases were caused by this disorder.

In our series, the most commonly involved sinuses (whether alone or in combination) were the SSS (53.2%), and lateral sinuses (44.1%). These results are close to figures described by Ferro et al¹¹ and Breteu et al.¹³ Cortical vein thrombosis was seen in only one patient. This is definitely lower than the reported incidence in Kajtazi et al's study⁴ (45.4%), but close to that reported by Terrazi et al¹⁸ (6.2%) and Stolz et al¹⁹ (6.3%). The site of sinus involved does not play a role in prognosis. Multiple sinuses are involved in more than half of the cases. Other hypercoagulable states that predisposed to CVST in our series included protein S deficiency (5 cases), antithrombin III deficiency (one case), protein C deficiency (one case) and factor V Leiden mutation (one case). This is consistent with the incidence reported by Stolz et al.¹⁹ In CVST, mode of onset is highly variable. In most of our patients (46.8%), presentation was sub acute (later than 48 hours but less than 30 days). Acute (within 48 hours) presentation was noticed in 37.8% of patients, and 13.5% patients presented with chronic symptoms. These results are similar to the figures from other international series.¹¹

There are several limiting factors, which include the type of our study (retrospective rather than prospective), lack of uniform guidelines for diagnosis and treatment, and the study being not representative of the whole population. Despite previously mentioned limitations, this study opens new ideas of research needed in our community and highlights the need for pathways for management.

In conclusion, although CVST is considered a rare disease, the incidence is possibly higher than previously

thought. This is mainly due to increased awareness of the disease and availability of more sophisticated neuroimaging techniques. In our study, pregnancy/ puerperium was the most common cause for CVST. In contrast to a previous study, we found that Behçet's disease is not a major cause of CVST in Saudi Arabia. In 80.2% of our patients one or more etiological factors could be identified. Most of the patients (93.7%) received anticoagulation and recovery was noted in 87.4% of patients. A more rigorous search for the underlying etiology is encouraged since multiple risk factors have been observed in our study as well as other international reports. Clinical features were comparable with international series. Bad prognostic factors observed in our study were grave underlying conditions, late presentation, coma, and status epilepticus. More epidemiological multi-center studies, or a registry is recommended since the current statistics are lacking.

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STATISTICS

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