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Cerebral venous sinus thrombosis; clinical characteristics, risk factors, diagnosis and outcome in a tertiary hospital, Saudi Arabia

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RESEARCH

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ABSTRACT

Background
Cerebral venous sinus thrombosis (CVT) is an uncommon form of stroke that has a highly variable clinical presentation. Data from Middle East and in particular Saudi Arabia are scarce.

Aims
In this study, we evaluated clinical characteristics, risk factors, and outcomes of patients with CVT in a tertiary hospital, Saudi Arabia.

Methods
A retrospective cross-sectional study was performed at a tertiary hospital in Saudi Arabia which included a total of 97 patients admitted with CVT diagnosis between January 2010 to December 2019. Demographic data, clinical information, radiological test, the in-hospital mortality recorded, and a three month outcome were retrieved from the health information system.

Results
Mean age was 42 years with 83.5 per cent female predominance. Headache was the most frequent initial presentation in 79 per cent. During the course of the illness 41 per cent developed seizures and were significantly associated with the presence of intracerebral haemorrhage (p<0.02). Oral contraceptive was a major risk factor in 21 per cent, no underlying risk factor or cause was found in 30 per cent of the patients. Non-contrast CT scan was reported normal in 30 per cent of the cases. In-hospital mortality was low, and prognosis at follow up was good.

Conclusion
Female predominance and headache being the first manifestation were reconfirmed. A non-contrast CT scan can show some abnormalities but was normal in about 30 per cent of cases. Awareness about CVT clinical presentation and diagnostic tests are important to prevent misdiagnosis. These finding may be important to further characterize the condition in this area.

Key Words
Cerebral venous thrombosis, stroke, hypercoagulable

What this study adds:

1. What is known about this subject?
CVT is a rare type of stroke. The clinical presentation is highly variable and requires a high index of suspicion to avoid misdiagnosis.

2. What new information is offered in this study?
This study describes CVT in Middle East and Saudi Arabia. The finding is in concordance with what is reported from other regions.

3. What are the implications for research, policy, or practice?
Vigilance to the possibility of CVT in cases of headache, especially when CT brain is normal which was reported in up to 30 per cent of the cases.

Background

Thrombosis of the cerebral venous sinuses (CVT) is an

uncommon form of stroke, representing less than 1 per cent of all types of stroke.[1] CVT, unlike thrombosis of arteries, occurs more commonly in young adults and children. The estimated annual incidence is three to four cases per 1 million population and up to seven cases per 1 million among children.[2] About 75 percent of the adult patients are women.

A study conducted in Saudi Arabia in 2011 that included adults and children found out that the mean age of presentation was 29 years with female predominance.[3] The sex ratio imbalance may be due to the increased risk of CVT associated with pregnancy, puerperium and the use of oral contraceptives.[4] In an International Study on Cerebral Veins and Dural Sinus Thrombosis (ISCVT), the median age of patients with CVT was 37 years[5] and only 8 per cent patients were older than 65years.[6]

The pathogenesis of CVT is poorly understood. However, two distinguished mechanisms are essential in understanding clinical manifestations of CVT. One is thrombosis of the cerebral veins, with local effects caused by venous obstruction, and another is thrombosis of the major sinuses, which causes intracranial hypertension. In the majority of patients, these two processes occur simultaneously. Occlusion of the cerebral veins causes localized oedema of the brain, venous infarction and petechiae haemorrhage that can merge to form a large hematoma. Intracranial hypertension without hydrocephalus usually develops following obstruction of major venous sinus. About one-fifth of patients with sinus thrombosis have intracranial hypertension only, without signs of cortical vein thrombosis.[5]

Thus, the most frequent but least specific symptom of sinus thrombosis is severe headache, which is present in more than 90 percent of adult patients Seizures, altered level of consciousness and focal neurological deficit can be the presenting feature of CVT.[7] Less common presentation includes subarachnoid haemorrhage.[8] The clinical presentation often varies, and a high index of suspicion is required to make an early diagnosis. The diagnosis of CVT should be considered in young and middle-aged patients with recent unusual headache or with stroke-like symptoms in the absence of the usual vascular risk factors, in patients with intracranial hypertension, in patients with CT evidence of haemorrhagic infarcts, especially if the infarcts are multiple and not confined to the arterial vascular territories, and in patients with new focal neurological deficit without clear explanation, unexplained seizures and altered level of consciousness.

CT scanning is a useful technique for the initial examination, to rule out other acute cerebral disorders and to show venous infarcts or haemorrhages, but its results can also be entirely normal. CVT is a rare type of stroke and thus data from Middle East are scarce.

The purpose of this study was to, in retrospect; describe the clinical presentation, diagnosis and outcomes of patient with CVT at a tertiary center in Saudi Arabia. We also looked at the utility of non-contrast CT scan as the first neuroimaging test at emergency setting in detecting CVT.

Method

A retrospective cross-sectional study was performed at a tertiary hospital in Saudi Arabia which included a total of 97 patients with CVT from January 2010 to December 2019. All cases with CVT diagnosis were consecutively recruited. Inclusion criteria: Age above 18 years. Confirmed CVT diagnosis by radiological imaging. Patients with unknown outcome or less than three months follow up were excluded. Demographic data and clinical information were retrieved from the health information system. Radiological test for each patient was reviewed, the in-hospital mortality recorded and a three-month outcome registered according to the modified Rankin scale. IBM SPSS version 23 was used for statistical analysis of data and $p<0.05$ was considered statistically significant. Limitations of this study include its retrospective analysis, the timing from the symptoms to diagnosis and treatment initiation was not clear.

Results

Socio-demographic characteristics

A total of 97 patients were recruited for this study. The mean age was 42 (+/-15 SD) years with 83.5 per cent female predominance.

Clinical characteristics and neuroimaging

Headache was the most common initial presenting symptom occurring in about 79 per cent of patients. Seizures and focal neurological deficits occurred in about 8 per cent of patients each as initial presenting symptom. Decreased level of consciousness was an initial presenting symptom in only 4 per cent of patients. During the course of the illness, 41 per cent of patients developed seizures and were started on anti-epileptic drugs, 48 per cent developed focal neurological deficits and 16.5 per cent developed altered level of conciseness. Seizures were significantly associated with haemorrhage ($p<0.02$). The initial neuroimaging modality was a plain CT scan of the brain which was reported normal in about 30 per cent of patients. Hyperdensity of the dural sinus was seen in 25 per cent of

patients. Brain parenchymal haemorrhage was observed in 35 per cent of patients. Hypodensity (venous infarction or oedema) was present in 8 per cent of patients. Only 2 per cent of patients had subarachnoid haemorrhage (Table 1). The majority of patients, about 38 per cent, had thrombosis in only one sinus; two sinuses were thrombosed in 32 per cent of patients and 25 per cent of patients had thrombosis in more than two sinuses. Isolated deep cortical vein thrombosis was present in 4 per cent of patients. The most commonly used diagnostic modality was CT venogram in 66 per cent of patients and magnetic resonance venogram MRV was used in 34 per cent of patients.

Risk factors

A major risk factor for CVT was oral contraceptive use which was found in 21 per cent of patients. Another 12 per cent of patients were on oral contraceptive but an underlying cause such as thrombophilia or autoimmune disease was identified, which was considered as the major risk factor. In about 29 per cent of patients, no any risk factor or cause was identified (Table 2).

Management and outcomes

Unfractionated heparin (UFH) was the most common treatment of choice in the acute setting in 88 per cent of patients, and low molecular weight heparin (LMWH) in 12 per cent of patients. Thrombectomy was done in only 2 per cent of patients. In-hospital mortality rate was around 12 per cent. However, majority of patients had a good outcome as the modified Rankin scale (mRS) at three months follow up was 0 (no symptoms) in 71 per cent of patients, 1 in 12 per cent of patients, and more than 3 in only 4 per cent of patients who had significant neurological disability after three months. There was no significant association between age and outcome, and the presence of parenchymal haemorrhage was not associated with a worse outcome.

Discussion

Thrombosis of cerebral vein and sinus is a highly variable clinical condition with an acute, subacute or chronic course. Headache is usually the first symptom of CVT and can be the only symptom[9] or precedes others by days or weeks.[10] In our study, headache was the initial presenting symptom in the majority of patients occurring in about 79 per cent of patients. This finding was almost similar to the International Study on Cerebral Vein and Dural Sinus thrombosis cohort that found headache in 89 per cent of patients.[5] CVT-related headache which is usually variable in character[10] is caused by intracranial hypertension developing from venous sinus occlusion. Isolated intracranial hypertension syndrome accounts for a significant proportional of CVT cases[11] and is more common in patients with a chronic clinical course who may present with papilledema on fundoscopy. However, the detailed description of the characteristics of headache was unreported in our study. Focal or generalized seizures including status epilepticus are more frequent in CVT than in other cerebrovascular disorders. In our study, seizure as a presenting symptom occurred in 8 per cent of patients and 41 per cent of patients developed seizures during the course of the illness. This finding was contrary to the ISCVT which found seizures as a presenting symptom in 39 per cent of patients and only 7 per cent developed seizures during the course of the illness.[12] Supratentorial parenchymal brain lesions, sagittal sinus and cortical vein thrombosis are frequently associated with seizures[12] In our study seizures were significantly associated with the presence of intracranial haemorrhage. Weakness with monoparesis or hemiparesis, sometimes bilateral, is the most frequent focal neurological deficit associated with CVT. Severe cases of CVT can cause a reduced level of consciousness and cognitive dysfunction such as delirium, apathy, frontal lobe syndrome or multifocal neurological deficits. In our study, 48 per cent of patients developed focal neurological deficit and 16.5 per cent had altered level of conciseness. In-depth characterization of focal neurological deficits could not be retrieved.

The majority of patients, about 38 per cent, had thrombosis in only one sinus, two sinuses were thrombosed in 32 per cent of patients and 25 per cent had thrombosis in more than two sinuses. Isolated deep cortical vein thrombosis which was present in 4 per cent of patients usually produces motor or sensory deficits and seizures. The neuroimaging features of CVT include focal areas of oedema or venous infarction, haemorrhagic venous infarction, diffuse brain oedema or rarely, subarachnoid haemorrhage.[13] In patients with CVT, the proportion who presents with parenchymal haemorrhage is 30–40 percent.[14,15] In our study, brain parenchymal haemorrhage was observed in 35 per cent of patients. Small non-traumatic juxtacortical haemorrhages observed on a non-contrast CT scan located just below the cortex in the white matter account up to one-fourth of these haemorrhages in patients with CVT and are associated with superior sagittal sinus occlusion.[16] Subarachnoid haemorrhage was present in 2.1 per cent of patients. The most commonly used diagnostic modality was CT venogram in 66 per cent of patients and magnetic resonance venogram MRV was used in 34 per cent of patients. Brain magnetic resonance imaging in combination with MRV is the most informative technique for demonstrating the presence of dural thrombus, cortical vein thrombosis, and

extent of brain injury.[17] Parenchymal brain lesions such as venous infarction or oedema were present in 8 per cent of patients.

In emergency settings, urgent neuroimaging with brain MRI and MRV or with cranial CT with CT venogram if MRI is not an option is generally recommended.[13] CT venography when combined with head CT, adds considerable information in suspected cases of CVT,[18] with the overall accuracy of head CT combined with CT venography of about 90 to 100 percent depending on the occlusion site.[19] In our study, we found that MRV was used twice less frequently compared to CT venogram as CT is more accessible in emergency cases and requires shorter time to complete the study. CT venography is therefore a useful alternative to MR venography or intra-arterial angiography for the diagnosis of CVT, and was recommended by the 2011 guidelines of the American heart association and American stroke association to be at least equivalent to MR venography in the diagnosis of CVT.[13] Cerebral inter-atrial angiography is recommended mainly when the diagnosis of CTV is uncertain such as in the rare suspected cases of isolated cortical vein thrombosis, or when the clinical suspicion for CVT is high but MR venography or CT venography are inconclusive. CT scan of the brain as the most common initial imaging modality in our study was reported normal in about 30 per cent of the cases. However, CT is useful as an initial investigation in clinical practice to rule out other acute or subacute cerebral disorders. In about one-third of cases, CT scan demonstrates direct signs of CVT; the dense triangle sign seen on non-contrast head CT, and the empty delta sign seen on contrast CT as a triangular pattern of contrast enhancement surrounding a central region lacking contrast in the posterior part of the superior sagittal sinus. Indirect signs are more frequent including intense contrast enhancement, of falx and tentorium, dilated transcerebral veins, small ventricles and parenchyma abnormalities.

A major risk factor for CVT was oral contraceptive use which was found in 21 per cent of patients. In addition, 12 per cent of patients who had other underlying causes of thrombosis were on oral contraceptive. This highlight the fact that oral contraceptive may be just a provoking factor. Often, a precipitating factor, such as a head injury, obstetrical delivery, lumber puncture, jugular catheter placement, surgery, infections or drugs causes CVT in a person with a genetically increased risk. Multiple risk factors are often found in about half of patients with CVT, which warrant for the search of additional causes even when a specific risk factor is already identified.[5] Hereditary thrombophilia disorders such as deficiency of antithrombin III, protein C, protein S, factor V Leiden mutation were found in 13 per cent. Autoimmune diseases; systemic lupus erythematosus and antiphospholipid syndrome were present in 12 per cent of patients. Other acquired prothrombotic conditions such as puerperium, sickle cell anaemia and drug abuse accounted for less than 8 per cent of all cases. Only 4 per cent of patients had an underlying malignant condition and majority of patients. Infectious causes of CVT were frequently reported in the past, they are responsible for only 2-12 per cent of cases in modern-era studies of adults with CVT.[5,20] This concurred with our finding infections; sinusitis, otitis media, and pneumonia, were present in 13 per cent of patients. About 29 per cent, presented without any clear underlying cause for CVT. This was not unusual but slightly higher than reviewed literature, as no underlying aetiology or risk factor for CVT is found in less than 10 per cent of children and 13 per cent of adults with CVT.[6,21,22]

While the overall aim of treatment of CVT is to improve outcome, the immediate goals are to reanalyse the occluded sinus or vein, prevent the propagation of the thrombus into the bridging cerebral veins and treat the underlying prothrombotic state to prevent pulmonary embolism and CVT recurrence. Although definitive evidence for effectiveness is lacking, there is a general consensus that anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) is effective in the acute management of CVT.[23] Limited evidence suggest than early anticoagulation with subcutaneous LMWH is more effective than UFH and is at least safe for adults with CVT without contraindications.[23,24] However, UFH was the most commonly treatment of choice in the acute setting in about 88 per cent of patients, and LMWH in 12 per cent of patients. Anticoagulation with UFH or LMWH also appear to be safe in adult patients with CVT who have intracranial haemorrhages;[25] intracerebral haemorrhage such as haemorrhagic venous infarction that was found in less than 8 per cent of our patients or subarachnoid haemorrhage that found in 2.1 per cent of patients. Although limited available evidence suggests no benefits,[26-28] adults and children with CVT who develop progressive neurological worsening despite adequate anticoagulation subcutaneous LMWH or intravenous heparin, endovascular thrombolysis or mechanical thrombectomy are treatment options. In our study, thrombectomy was done in only 2 per cent patients. Early deterioration and death occur in approximately 5 per cent of patients with the acute CVT. In our study, the mortality rate was around 12 per cent. Although we did not evaluate the immediate causes of deaths, early death in CVT

is caused by transtentorial herniation secondary to brain oedema a large haemorrhagic lesion.[29]

Majority of the patients had a good outcome as the modified Rankin Scale (mRS) for patients who had neurological disability at three months follow up was 0 (no symptoms) in 71 per cent of patients, 1 in 12 per cent of patients, and more than 3 in only 4 per cent of patients who had significant neurological disability after three months. There was also no significant association between age and outcome, and the presence of parenchymal haemorrhage was not associated with a worse outcome but increased seizure incidence significantly. However, in the ISCVT cohort, old age, male gender, thrombosis of deep cerebral venous system or of the lateral sinus and a motor deficit were predictors of poor outcome in patients with early intracerebral haemorrhage.[15]

Conclusion

In general, CVT is a serious diagnosis that requires a high index of suspicion. Headache was the most common initial presenting symptom. Although initial brain CT scan at the emergency unit can help in the diagnosis of CVT, a normal finding on CT scan of the brain in patients with only headache could lead to delayed diagnosis of CVT. In our study 30 per cent of the CT images were normal and dedicated CTV or MRV was required to confirm the diagnosis of CVT. Seizures were higher in patient with haemorrhage but it did not affect the long term prognosis. The overall outcome was good as 77 per cent of patients had a good outcome. However, mortality rate was up to 12 per cent. Early identification and prompt treatment to decrease the mortality and improves the outcome is essential. Finding of this study will help in better understanding of the clinical characteristics and outcome of CVT in the Middle East and in particular Saudi Arabia. Limitation of this study includes the retrospective nature and absence of certain details such as the characteristic of CVT-related headache or the duration of the presenting symptoms.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table 1: Non-contrast CT findings

CT finding	Frequency (%)
Normal	30
Hyperdense sinus	25
Haemorrhage	35
Hypodensity (oedema, infarction)	8
Subarachnoid haemorrhage	2

Table 2: Risk factors

Risk factor	Prevalence (%)
Oral contraceptives	21
Infections (sinusitis, otitis media, pneumonia)	13
Thrombophilia (factor V Leiden, Protein C and S deficiency)	13
Autoimmune diseases (SLE, Antiphospholipid syndrome)	12
Malignancy	4
Other aetiologies (Sickle cell anaemia, drug abuse, puerperium)	8
No clear underlying cause	29