Cerebral venous thrombosis

Clinical presentation and outcome in a prospective series from Sudan

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ABSTRACT

الأهداف: متابعة مرضى يعانون من تخثر الأوردة الدماغية (CVT) وذلك لوصف الأعراض السريرية عند حضورهم ومعرفة مصير الحالة المرضية في مرضى من السودان كمثال لبلد من البلدان النامية.

الطريقة: أجريت دراسة ومتابعة آنية تم فيها وصف الأعراض السريرية لتخثر الأوردة الدماغية (CVT)، والعوامل المسببة، ومصير المرض في المرضى الذين حجزوا للتطبيب بالمركز القومي التخصصي لأمراض الجهاز العصبي – الخرطوم – السودان، خلال الفترة من فبراير 2001م وحتى أكتوبر 2006م. كان المرضى الوافدين للمستشفى من المقيمين في مدينة الخرطوم، أو تم تحويلهم من المستشفيات الطرفية المجاورة لولاية الخرطوم.

النتائج: شملت الدراسة 15 مريض (12–أنثى و 3–ذكور) من البالغين والمراهقين الذين بلغت أعمارهم 15 عاماً فأكثر، معدل متوسط العمر 33.9±11.8 عاماً. كانت أكثر الأعراض شيوعا هي: الصداع (15 مريض)، يليه وزمة العصب البصري (13 مريض)، شلل الأطراف (3 مرضى)، التشنجات الصرعية العامة (3 مرضى)، تبين وجود عامل مساعد لتخثر الدم في معظم الـ(12) حالة. أظهرت بيانات المتابعة بعد 12 أسبوعاً من خروج المرضى من المستشفى أن: (7 مرضى) (46.7%) قد تماثلوا إلى الشفاء الكامل، و (4 مرضى) (26.7%) أصيبوا بضمور في العصب البصري، بينما توفى (مريضين) (13.3%) وذلك نتيجة لانسداد الشريان الرئوي بواسطة جلطة دموية.

خاتمة: الأعراض السريرية لمرض تخثر الدم في أوعية الدماغ الوريدية (CVT) عند المرضى في السودان لا تختلف كثيراً عنها في البلدان الأخرى، إلا أن مصير المرض يبدو أكثر سوءاً. بعض القصور في سرعة الحصول على خدمات الرعاية الصحية المثالية وقلة المعدات التقنية اللازمة للتشخيص الدقيق قد يؤثر سلباً على تطور ومصير الحالة المرضية في البلدان النامية.

Objectives: To describe the presentation and outcome of treatment of cerebral venous thrombosis (CVT) in patients from Sudan, an example of a developing country.

Methods: In a prospective study, we described the clinical features, risk factors, and outcome of CVT in patients admitted to the National Center for Neurological Diseases, Khartoum, Sudan, the only specialized neurological hospital in the country, during the period from February 2001-October 2006. Patients were referred from other hospitals in the town or from nearby hospitals in Khartoum state.

Results: We recruited only adult and adolescent patients aging ≥15 years. We reviewed 15 patients (12 females and 3 males) with a mean (±SD) age of 33.9±11.8 years. Headache (n=15), papilledema (n=13), paresis (n=3), and generalized seizures (n=3) were the most common symptoms, and signs encountered. A prothrombotic risk factor was often identified (n=12). At the time of the first visit namely, 12 weeks after discharge, 7 patients (46.7%) attained complete neurological recovery, 4 (26.7%) developed optic atrophy, and 2 (13.3%) died of pulmonary embolism.

Conclusion: The clinical features and risk factors of CVT in Sudan are not different from elsewhere, but the outcome is less favorable. Places with less privileged health service resources, late presentation or delayed accessibility to appropriate diagnostic tools may negatively influence the final outcome.

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Cerebral venous thrombosis (CVT) is an uncommon condition that often afflicts young people.[1-3] The diagnosis is often delayed or overlooked due to the

extreme diversity of clinical presentations especially in the early stages of the disease. Fortunately, nowadays MRI gives a simplified quick and accurate diagnosis of CVT, albeit the facility is often not easily accessible, especially in low-income developing countries. The objective of this study was to describe the clinical presentation, risk conditions and outcome of patients with CVT admitted to the hospital in a low-income developing country.

Methods. This prospective study was conducted in the National Center for Neurological Diseases in Khartoum, the capital city of Sudan, during the period from February 2001 to October 2006. Adult and adolescent patients aging ≥15 years who were admitted with the diagnosis of CVT during the study period were included. The patients presented to the emergency department or were referred from other hospitals in the town or from other nearby hospitals in Khartoum state. They were admitted and treated in the general neurology hospital wards. Demographic characteristics, presenting complaints, duration of symptoms from onset to diagnosis, relevant medical history with emphasis on potential risk factors, findings on physical examination, and progress of the clinical course during stay in hospital, and at follow-up visits after discharge was noted. We confirmed the diagnosis of CVT by MRI and MR venography (MRV). We performed MRI, T1-, T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. The MRV was carried out using intravenous gadolinium injection. In each study, we reported the on sites and number of involved sinuses or veins, associated edema, infarction, and hemorrhage. Diagnostic lumbar puncture, and measurement of CSF pressure were not routinely performed in all patients since the clinical and imaging features were usually sufficient for a reasonably accurate diagnosis. Other laboratory investigations were blood counts, prothrombin time, activated partial thromboplastin time (aPTT), IgG, and IgM antiphospholipid antibodies, protein S, protein C, antithrombin III levels, Factor V Leiden, antinuclear antibodies, anti-dsDNA antibodies and red blood cell sickling test. Prothrombin mutation was not tested. Subcutaneous unfractionated heparin was given to all patients as soon as the diagnosis was made. The dose of heparin was adjusted to aPTT between 2 and 3 times the control value. Warfarin was started simultaneously and the dose was adjusted to an INR between 2.5 and 3.5. Heparin was discontinued after 5 days, and oral anticoagulation by warfarin was continued after discharge for at least 12 months in surviving patients. Patients with intracranial hypertension causing papilledema were also given an oral acetazolamide. None of the patient needed any form of neurosurgical intervention. After discharge, the patients were periodically seen and assessed by the neurologist at the neurology outpatient clinic. Informed consent for inclusion in the study was directly obtained from the patient if he was mentally oriented or from a significant relative if consciousness was impaired. The study was approved by the Ethical Committee of the Graduate Studies Board of the Medical Faculty of the University of Khartoum, Sudan.

Results. *Clinical presentation.* Fifteen patients (12 females and 3 males) with CVT were seen and included in the study. Mean age was 33.9 ± 11.8 years (mean±SD) with a range of 16-65 years. Female patients tended to be younger with a mean age of 29.6 ± 6.2 years and a range from 16-36 years. Patients' characteristics, signs and symptoms, and their duration at presentation are summarized in **Table 1.** Headache was the most common presenting symptom encountered in all patients (n=15), and was commonly associated with papilledema (n=13). Convulsions (n=3) and focal weakness (n=3) were the second most commonly observed symptoms. Isolated thrombosis frequently involved the superior sagittal (n=6) or lateral/sigmoid sinus (n=5). Multiple sinus thrombosis spreading to small cortical and deep veins was seen in 3 patients, and it was associated with poor prognosis. A possible risk factor or an underlying cause was identified in 12 patients. The predisposing risk factor was more often in a prothrombotic state such as antiphospholipid syndrome, intake of oral contraceptive, infection, or inflammatory disease.

Follow up and outcome. After discharge, the patients were seen for follow-up in the outpatient neurology clinic, frequently as necessary, and then approximately every 12 weeks. By the end of the study, the length of follow-up period in survivors ranged from 12-208 weeks. Two patients died with pulmonary embolism (PE). Both of them had multiple sinus thrombosis including the superior sagittal sinus. Of the remaining 13 survivors, 4 developed permanent visual impairment due to secondary optic atrophy. In 3 patients with hemiparesis motor function, recovery was complete in 2 and in the third the weakness was mild, and he was independent at the time of his visit in week 12. Seven patients attained complete recovery.

Discussion. In this hospital-based prospective study, we described the clinical features, MR findings and outcome in patients with CVT in an understudied geographic area. The availability of MRI and MRA facilities in our hospital vicinity helped us to establish the diagnosis of CVT with adequate certainty, a privilege that is not readily available in many developing countries. To date, MRI and MRA remain the mainstay and the best tool for diagnosing sinus thrombosis, but, the technique

Table 1 - Demographic, clinical and imaging features, risk factors, and outcome in 15 patients with CVT.

No	Age/ Gender	Presenting symptoms/signs	Symptoms duration (W)	Risk Factor	MRV (site of thrombosis)	Conventional MRI	Follow-up (W)	Outcome
1	31/F	Headache, neck pain, blindness, papilledema	3	SLE	Right SgS	Normal	52	OA, impaired vision
2	34/M	Headache, seizures, papilledema	4	Not known	SSS, DVS	Right & left temporal lobes HI	16	PE, died
3	32/F	Headache, papilledema, left arm numbness and drift	1	Oral contraceptive	SSS	Normal	52	CNR
4	65/M	Headache, left proptosis, chemosis, papilledema	1	ESRD, infection	Left CS	Left proptosis, orbital abscess	40	Blind left eye
5	55/M	Headache, left proptosis, papilledema	1	ESRD, infection	Left CS	Left proptosis	32	CNR
6	22/F	Headache, papilledema	2	APS	Left SgS	Left temporal lobe HI	180	CNR, left leg DVT
7	27/F	Headache, papilledema, seizures, confusion	4	APS	Right SgS	Right temporoparietal HI	208	Left leg DVT Recurrent seizures
8	36/F	Headache, papilledema	4	Behcet's disease	Left SgS	Cerebral vasculitis	48	CNR
9	32/F	Headache	1	Puerperium	SSS	Normal	52	CNR
10	36/F	Headache, papilledema	2	Not known	SSS	Normal	52	CNR
11	31/F	Headache, neck pain, blurred vision, papilledema	2	Not known	Right SS	Normal	24	OA, impaired vision
12	34/F	Headache, seizures, left hemiparesis	1	Oral contraceptive	SSS	R parasagittal HI	30	CNR
13	36/F	Headache, papilledema, right hemiparesis	1	Oral contraceptive, paranasal sinusitis	SSS DVS	Left parasagittal HI, multiple small HI	12	Mild right HP
14	22/F	Headache, loss of vision	6	APS	MST, DVS	Multiple small HI	46	OA, blind
15	16/F	Headache, papilledema, dyspnea	1	APS	MST,	Normal	3	PE, died

SLE - systemic lupus erythematosus, ESRD - end-stage renal disease, APS - antiphospholipid syndrome, SSS - superior sagittal sinus, SgS - sigmoid sinus, CS - cavernous sinus, MST - multiple sinus thrombosis, HI - hemorrhagic infarction, DVS - deep venous system, OA - bilateral optic atrophy, CNR - complete neurological recovery, PE - pulmonary embolism, MRV - magnetic resonance venography, DVT - deep venous thrombosis, PE - pulmonary embolism, CVT - cerebral venous thrombosis

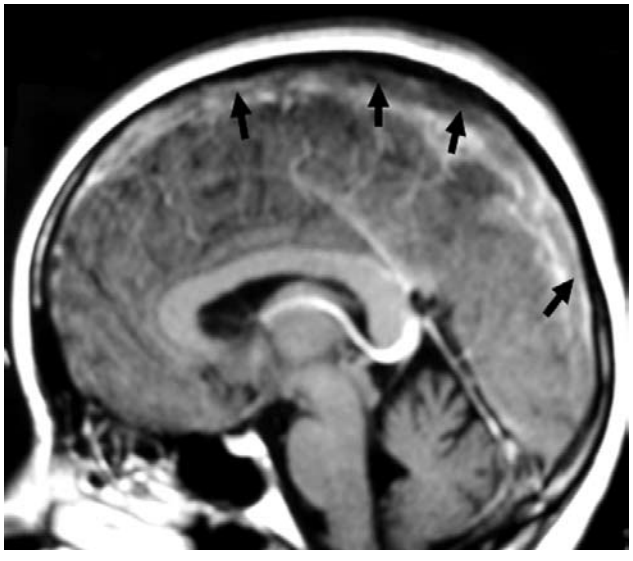

Figure 1 - Post-contrast T1-weighted MRI of the brain in patient no. 2 showing a filling defect along the entire superior sagittal sinus indicating extensive thrombosis (arrows).

is not absolutely without limitations.[4] A promising future tool for more accurate identification of CVT is the newly developing technique of molecular MRI using a novel fibrin-targeted contrast.[5] Consistent with several large studies, the female gender predominated in our series.[3,6] This is usually related to gender associated risk factors such as the use of oral contraceptives, pregnancy and puerperium. Moreover, all of our female patients were in their active reproductive age. Increased risk of cerebral, and extracerebral venous thrombosis in the peripartum period is well recognized especially in developing countries.[7-9] The mean age in men appeared to be much higher than in women due to the study sample, a small number of males (n=3), and that 2 of them were in the sixth and seventh age decade. The presentation of CVT can be extremely varied, and the clinical events can evolve over hours to a few weeks. In our patients, manifestation of intracranial hypertension, namely, headache and papilledema, was the most common clinical presentation followed by limb paresis. The similar mode of presentation was seen in many other

studies.[3,6,10,11] A prothrombotic risk factor was identified in approximately 75% of patients with CVT, and often the risk is multifactorial, for example, puerperal sepsis or congenital thrombophilia and pregnancy.[6,7,12] In our patients, antiphospholipid syndrome, infection, and oral contraceptives were the prevailing risk factors. This contrasts with other reports from the region where Behcet disease was the most common predisposing factor in Saudi Arabia,[10] and contraceptive pills intake in Iran.[13] The MRI revealed that single vessel thrombosis occurred more often than multiple involvements (**Figure 1**). The most common site in isolated involvement was the superior sagittal sinus followed by the transverse sinus. Multiple sinus and deep venous system thrombosis were associated with incomplete neurological recovery and mortality. Of the 2 patients who died, one had multiple sinus and deep venous system thrombosis, and the other had multiple sinus involvement and antiphospholipid syndrome (patients 2 and 15, **Table 1**). In both cases, the cause of deaths was massive PE. This is a recognized fatal complication of CVT especially in the presence of a prothrombotic risk factor.[14,15]

Several controlled trials and meta-analyses have shown that the use of heparin and continuing anticoagulant therapy is associated with significant reduction in the risk of death or dependency even in the presence of hemorrhagic infarction.[11,16,17] The overall prognosis of treated CVT is fairly good and complete functional recovery occurs in more than two-thirds of patients. A recent European guideline on treatment of CVT advocates the use of heparin as first-line and oral anticoagulant as a continuation therapy for a variable duration according to the etiology.[18]

In contrast to the above-cited studies, the functional status in our patients after treatment was less favorable since complete neurological recovery occurred in approximately 47%. The relatively high incidence of permanent visual complications indicated delayed attendance to the appropriate medical care with subsequent delay in diagnosis and intervention. It is well recognized that, independent of the anticoagulant therapy, the final outcome is significantly influenced by the condition of the patient at the time of diagnosis.[3,6]

The study needs to be expanded over a longer period of time to include a larger number of patients for analysis and more accurate epidemiological extrapolation. As prognosis with appropriate intervention is more favorable, the condition should always be considered in the differential diagnosis of unexplained headache, particularly when associated with features of intracranial hypertension or any of the predisposing risk factors.

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