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Cerebral venous thrombosis: a retrospective multicentre study of 48 patients

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Abstract The objective was to describe the clinical features and management of cerebral venous thrombosis (CVT) in non-selected centres. An observational study in 11 neurological departments in NW Italy was carried out from 1995 through 1999 on 38 female and 10 male patients. Mean age: 44.8 years, SD=14.3. Onset: acute in 21 patients (44%), subacute in 17 (35%) and chronic in 10 (21%). Most frequent onset: with focal deficits and/or seizures, followed by impaired consciousness or confusion, isolated headache, isolated intracranial hypertension and cavernous syndrome. No risk factor was found in 8 patients (17%). The superior sagittal sinus was involved in 27 patients (56%) and the transverse sinus in 29 (60%). Anticoagulants were used in 45 patients (94%). Rankin Scale score at discharge: 0 (27 patients), 1 (four), 2 (five), 3 (five), 4 (none), 5 (one) and six were dead. Thirteen patients had deep CVT: age, risk factors, neurological signs and outcome differed from cortical CVT (35 patients), although not significantly. Clinical features, risk factors and outcome of CVT patients from non-selected centres are similar to those from specialised centres.

Key words Cerebral venous thrombosis • Multicentre studies • Risk factors • Headache • Seizures

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Introduction

Cerebral venous thrombosis (CVT) displays a wide range of symptoms and signs, and runs a variable course. Although a large multicentre study has recently been published [1], most of the reported case series come from tertiary care centres [2–9] and may thus have a selection bias. This paper describes the clinical features, risk factors, course and current ways of diagnosis and care of CVT in 11 non-selected centres from NW Italy. Long-term follow-up data will be described in a subsequent paper.

Subjects and methods

In 2001, we invited the 19 Neurology Departments in Piemonte and Valle d'Aosta Regions (NW Italy) to participate in a study of symptomatic CVT patients admitted to their hospitals from 1/1/1995 to 31/12/1999. Eleven centres agreed to participate: ten are first-referral centres (out of 18) and one is specialised in cerebrovascular diseases. CVT was diagnosed as cerebral sinus or venous occlusion (partial or total) at MRI, magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) according to Bousser and Russel [10].

The following data were retrieved and collected from clinical charts with an ad-hoc form: demographics, dates of onset, admis-

sion and discharge, symptoms and neurological signs at onset and during hospital stay, aetiological factors, neuroimaging findings, EEG, CSF examination, laboratory findings, therapy, clinical progression, and outcome at discharge. Centres were contacted to remedy discrepancies and incompleteness.

Time of onset was categorised according to Bousser [3] as acute (less than 48 hours), subacute (48 hours–30 days) and chronic (more than 30 days). Type of onset was divided into four categories [3, 11]: (1) focal syndrome (focal deficits or seizures), (2) isolated intracranial hypertension syndrome (headache, papilloedema, VIth nerve palsy), (3) impaired consciousness or confusion (defined as "subacute encephalopathy" by Bousser [3]), and (4) cavernous syndrome (painful ophthalmoplegia with chemosis and proptosis), plus a fifth category: isolated headache without any other sign or symptom. Outcome on hospital discharge was categorised with the modified Rankin scale [12]. If the straight sinus or deep veins were involved, patients were classified as deep CVT, irrespective of whether any other sites were involved; all other patients were classified as cortical vein or sinus thrombosis.

The chi-square test and Student's two-tailed test were used, where appropriate. The significance level for the probability of the null hypothesis was set at 0.05.

Results

We recruited 48 consecutive patients with a mean age of 44.8 years (SD=14.3, range 19–77), 38 women (mean 42.8 years, SD=15.1, range 19–77) and 10 men (mean 52.4 years, SD=7.3, range 41–60). Onset was acute in 21 patients (44%), subacute in 17 (35%) and chronic in 10 (21%). Thirteen patients had deep CVT and 35 cortical vein or sinus thrombosis. Table 1 shows the type of onset, clinical features and outcomes of the two categories. Although only type of onset reached statistical significance, age, risk factors, neurological signs and outcome were different in the two categories.

Type of onset was unrelated (p=n.s.) to age, number of sinuses affected and number of risk factors; acute onset was more frequent among women (19/38, 50%; men 2/10, 20%, p=n.s.) and patients presenting with impaired consciousness or confusion (10/14, 71% *vs*. 11/34, 32%, $p<0.05$).

Cranial CT-scan in 44 patients revealed signs suggestive of CVT (empty delta sign, dense sinus sign or cord sign) in nine (21%). In the others it was normal (11 patients, 25%), or showed only haemorrhagic or ischaemic lesions (24, 55%); in 19 patients CT was repeated after 1–25 days and showed signs of CVT in 5. Brain MRI in 42 patients disclosed signs suggestive of CVT alone in 12 (29%) or associated with haemorrhage or ischaemia in 15 (36%). In the others, it was normal (3, 7%), or showed haemorrhagic or ischaemic lesions alone (12, 29%); MRI repeated in 9 patients after 1–49 days showed signs of CVT in 1. Including first and repeated CT or MRI, signs of CVT were still not evident in 12 patients (25%). MRA in 28

Table 1 Characteristics of deep and cortical vein or sinus CVT. Data are n (%), if not otherwise indicated

Feature	Cortical CVT (n=35)	Deep CVT (n=13)	p
Age, years, mean (SD)	43.1 (14.2)	49.1 (14.0)	n.s.
Age >45 years	12 (34.3)	7 (53.9)	n.s.
Female gender	29 (82.9)	9 (69.2)	n.s.
Length of stay, days, mean (SD)	31 (21.0)	39 (26.0)	n.s.
Without identified risk factors	4 (11.4)	4 (30.8)	n.s.
Acute onset	15 (42.9)	6 (46.2)	n.s.
Type of onset			
Focal deficits and/or seizures*	19 (54.3)	4 (30.8)	n.s.
Impaired consciousness or confusion	6 (17.1)	8 (61.5)	<0.01
Isolated intracranial hypertension	1 (2.9)	1 (7.7)	n.s.
Cavernous syndrome	2 (5.7)	0	n.s.
Isolated headache**	7 (20.0)	0	n.s.
Neurological examination at admission			
Impairment of consciousness	10 (28.6)	7 (53.9)	n.s.
Motor deficits	17 (48.6)	5 (38.5)	n.s.
Sensitive signs	3 (8.6)	0	n.s.
Papilloedema	4 (11.4)	2 (15.4)	n.s.
Impairment of cranial nerves	6 (17.1)	2 (15.4)	n.s.
Speech disturbances	8 (22.9)	1 (7.7)	n.s.
Visual deficits	2 (5.7)	1 (7.7)	n.s.
Cerebellar signs	4 (11.4)	0	n.s.
Neck stiffness	3 (8.6)	0	n.s.
Rankin 3–4–5 at discharge	4 (11.4)	2 (15.4)	n.s.
Deceased during hospitalisation	3 (8.6)	3 (23.1)	n.s.

*Seizures were 11 partial and 8 generalised; after admission, five other patients developed seizures

**Headache was associated with the other presenting symptoms in 29 cases, raising its overall number to 36

patients was normal in 2 (7%) and revealed signs of partial or total occlusion of one or more cerebral sinuses or veins in 3 (11%) and 23 (82%) patients. DSA of cerebral arteries in 19 patients always showed signs of total (15, 79%) or partial (4, 21%) sinus occlusion, associated in four cases with dural fistulae. Neuroradiological imaging showed involvement of different sinuses and veins (Table 2): the superior sagittal sinus was involved in 27 patients (56%) and the transverse sinus in 29 (60%). EEG in 18 patients showed diffuse abnormalities in 12 (67%), epileptic focal abnormalities in 2 (11%) and was normal in 4 (22%). Lumbar puncture in 10 patients was normal in 6 and abnormal in 4 (bleeding, increase of proteins or cells).

Three patients were not treated with anticoagulants because of early death, presumed septic CVT and unknown reasons. The others were treated with i.v. heparin (n=23), sc. heparin (n=18) and oral anticoagulants (n=4). In three, therapy was interrupted because of bleeding complications. No patient underwent local or systemic thrombolysis. Different anti-oedema agents were used in 30; all patients with seizures but one were given antiepileptic drugs. At discharge, oral anticoagulants were still used by 33 patients, and sc. heparin by 6; suggested duration of treatment was 6 months for all but 6 patients.

The mean length of stay was 33 days (SD=22; range 1-96). Rankin Scale score at discharge was: 0 (27 patients), 1 (four), 2 (five), 3 (five), 4 (none) and 5 (one). Six patients died during hospitalisation (three from CVT, two from infectious complications and one from cancer).

Table 2 Site of involvement in 48 patients with CVT

	n
One site (22 patients)	
Superior sagittal sinus	9
Transverse	9
Deep cerebral veins	2
Cavernous sinus	1
Sigmoid	1
Two sites (15 patients)	
Superior sagittal+cortical veins	3
Superior sagittal+transverse	7
Straight sinus+deep veins	2
Transverse+sigmoid	3
Three or more sites (11 patients)	
Superior sagittal+transverse+straight+deep veins	3
Superior sagittal+transverse+straight	2
Superior sagittal+transverse+straight+sigmoid	1
Superior sagittal+straight+deep veins	1
Superior sagittal+transverse+sigmoid	1
Transverse+deep veins	1
Transverse+sigmoid+cavernous	1
Transverse+straight+deep veins	1
Total	48

Table 3 Risk factors in 48 patients with CVT

Risk factor	n	%
Personal history of venous thromboembolic disease	8	16.7
Familial history of venous thromboembolic disease	6	12.5
Oral contraceptives*^	18	47.4
Personal history of multiple abortion*	4	10.5
Hormone replacement therapy*#	3	7.9
Puerperium*^	2	5.3
Prothrombotic factors†		
Leiden mutation of factor V	5	19.2
Hyperhomocysteinemia	3	11.5
Protein C deficiency	2	7.7
Protein S deficiency	2	7.7
Antithrombin III deficiency	1	3.8
Antiphospholipid antibodies	1	3.8
At least one of the above factors	10	38.5
Tumours‡	3	6.3
Cranial infections§	3	6.3

*Percentage calculated for women only (n=38)
^The percentage calculated for the 26 women of reproductive age was 69.2 for oral contraceptives and 7.7 for puerperium
#The percentage calculated for the 12 postmenopause women was 25.0
†Percentages calculated for the 26 patients in whom all the factors were investigated
‡Includes 1 laryngeal carcinoma, 1 mediastinic carcinoma, 1 cerebellar tumour
§Includes 1 extracranial septic focus, 1 meningitis, 1 facial infection

Risk factors are listed in Table 3. No factor was found in 8 patients (17%); 21 (44%) patients had one factor, 16 (33%) two and 3 (6%) three or more. Age of onset was significantly lower in those with risk factors (43.1, SD=14.4 *vs*. 51.7, SD=11.8; p=0.05).

Discussion

Our series of 48 consecutive patients with CVT was drawn from 11 hospitals in two Italian regions, with a catchment area of approximately 3 million people; thus it can be considered representative of CVT in ordinary clinical practice. Most of the other series [2, 4–6, 8] come from single hospitals or were collected for clinical trials [8] and may thus carry a selection bias.

As in other studies [1–3, 5, 7, 9, 11], CVT was more frequent in women and lower age groups. We found presentation with focal signs or seizure to be the most common pattern, as in most other series [3, 4, 6, 11, 13]. Headache was frequent at onset, and it was isolated in seven patients. Onset with isolated headache, which is not included in Bousser's classification [3], may well be

added in the future, given the wide use of MRI and earlier diagnosis. Onset was acute in most patients, including some of those with impaired consciousness (defined as "subacute encephalopathy" by Bousser [3]). We did not find any correlation between mode of onset and presenting signs or symptoms, clinical features and site of the lesions. Only female gender and young age were more frequent in patients with acute onset.

CT failed to reveal direct signs of CVT in most cases; sensitivity for the first scan was only 21%, even lower than in other studies [5, 7, 14]; MRI was much more sensitive (65%). Repetition of CT or MRI did not add as much to sensitivity. MRA and DSA were always diagnostic.

The topography and extension of CVT have rarely been investigated: 46% of our patients had only one site involved, whereas others [2, 5, 14–16] have lower percentages; this may depend on the type and timing of neuroimaging.

Isolated deep CVT are rare and have a worse prognosis [1, 5, 11, 17, 18]. Our cases of isolated deep CVT were too few to form a single category; cases with involvement of the straight sinus or deep veins independently of other sinuses were therefore grouped to look for clinical differences linked to deep CVT involvement. Although none of the differences reached statistical significance due to the small sample size, deep CVT was more frequent in patients older than 45 years and without risk factors; they more frequently had impairment of consciousness and a higher intrahospital mortality. The worse outcome of deep CVT may be due to diagnostic delay, involvement of critical structures or shortfall of collateral compensation mechanisms.

Only eight patients (17%) had no risk factor, a percentage similar to Ferro et al. [1] and less than in other series [2–5, 7, 9]. As some risk factors were not systematically evaluated, this must be considered an upper estimate. Known risk factors may result in an earlier onset; patients with one or more factors in fact were younger at onset.

More than one factor was sometimes present in the same patient. Almost half of our female patients were using oral contraceptives at onset of CVT, a percentage lower than other Italian studies [9, 19, 20]. More than one fourth of patients had a personal or family history of thromboembolic disease, and laboratory screening showed prothrombotic factors in 39% of the 26 fully investigated. The prevalence of prothrombotic factors was similar to another Italian study [19], except for hyperhomocysteinaemia and hormone replacement therapy. CVT is a very rare complication of cancer: Raizer et al. [21] found CVT in only 0.3% of cancer patients, most of whom had other predisposing factors. Whether cancer is a risk for CVT must be determined with further case-control studies.

Treatment of CVT ranges from observation to anticoagulation or thrombolysis [3, 22]. All but 3 of our patients were treated with anticoagulants; the different routes of administration reflect uncertainty of opinions among neurologists [23] as to what type of heparin to use.

Six patients died during hospitalisation; this percentage is quite similar in series of patients diagnosed after 1985, ranging from 6 to 15% [1, 2, 7, 11, 14, 15, 18, 24], despite their different origin. By contrast, the percentage of patients with complete recovery at discharge ranges from 35 to 86% [1, 2, 5, 7, 15, 16, 18, 24] (60% in our series). As the use of anticoagulants is widespread, this variability probably depends more on case-ascertainment criteria, length of stay, and criteria for discharge and outcome measures, than modes of treatment.

In conclusion, our study from non-selected centres found the clinical features, risk factors and outcome of CVT described by most series from specialised centres. Deep CVT showed different features and clinical course, although cases were too few for a sufficient sample size; as these differences may have prognostic implications, they need to be confirmed in larger series.

Sommario *Obiettivo di questo studio è stato quello di descrivere le caratteristiche cliniche e la gestione dei pazienti con trombosi venosa cerebrale (TVC) in centri ospedalieri non selezionati. Si tratta di uno studio osservazionale svolto in 11 reparti di Neurologia situati nelle Regioni Piemonte e Valle d'Aosta dal 1995 al 1999. Nello studio sono stati reclutati 48 pazienti (38 femmine e 10 maschi), età media 44,8 anni, DS=14,3. Inizio: acuto in 21 casi (44%), subacuto in 17 (35%), cronico in 10 (21%). Modalità d'inizio più frequente: segni focali e/o crisi epilettiche, seguite da disturbo della coscienza o confusione mentale, cefalea isolata, ipertensione intracranica isolata e sindrome del seno cavernoso. In 8 pazienti (17%) non è stato riscontrato alcun fattore di rischio. Il seno sagittale superiore è risultato interesssato in 27 pazienti (56%) e il trasverso in 29 (60%). In 45 pazienti (94%) furono utilizzati anticoagulanti. Rankin Scale score alla dimissione: 0 (27 pazienti), 1 (quattro), 2 (cinque), 3 (cinque), 4 (nessuno), 5 (uno), 6 deceduti. Tredici pazienti hanno presentato una TVC profonda: l'età, i fattori di rischio, l'obiettività neurologica e l'esito sono risultati diversi dai pazienti con TVC corticale (35 pazienti), sebbene non in modo statisticamente significativo. Si è potuto pertanto concludere che caratteristiche cliniche, fattori di rischio ed esiti dei pazienti con TVC trattati in centri ospedalieri non selezionati sono analoghi a quelli provenienti da centri specializzati.*

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