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Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome

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Summary

Neuroimaging and management advances require review of indications for excluding cerebral venous sinus (sinovenous) thrombosis (CSVT) in children. Our goals were to examine (i) clinical presentations of CSVT, (ii) prothrombotic risk factors and other predisposing events, (iii) clinical and radiological features of brain lesions in CSVT compared with arterial stroke, and (iv) predictors of outcome. We studied 42 children with CSVT from five European paediatric neurology stroke registries. Patients aged from 3 weeks to 13 (median 5.75) years (27 boys; 64%) presented with lethargy, anorexia, headache, vomiting, seizures, focal signs or coma and with CSVT on neuroimaging. Seventeen had prior chronic conditions; of the 25 previously well patients, 23 had recent infections, eight became dehydrated and six had both. Two children had a history compatible with prior CSVT. Anaemia and/or microcytosis (21 probable iron deficiency, five haemolytic, including two with sickle cell disease and one with β-thalassaemia) was as common (62%) as prothrombotic disorder (13/21 screened). High factor VIII and homozygosity for the thermolabile methylene tetrahydrofolate reductase polymorphism were the commonest prothrombotic disorders. The superficial venous system was involved in 32 patients, the deep in six, and both in four. Data on the 13 children with bland infarction and the 12 with haemorrhage in the context of CSVT were compared with those from 88 children with ischaemic (AIS) and 24 with haemorrhagic (AHS) arterial stroke. In multiple logistic regression, iron deficiency, parietal infarction and lack of caudate involvement independently predicted CSVT rather than arterial disease. Five patients died, three acutely, one after recurrence and one after 6 months being quadriparetic and blind. Follow-up ranged from 0.5 to 10 (median 1) years. Twenty-six patients (62%) had sequelae: pseudotumour cerebri in 12 and cognitive and/or behavioural disabilities in 14, associated with epilepsy in three, hemiparesis in two and visual problems in two. Eighteen patients, including six with haemorrhage, were anticoagulated. Older age [odds ratio (OR) 1.54, 95% confidence limits (CI) 1.12, 2.13, $P = 0.008$], lack of parenchymal abnormality (OR 0.17, 95% CI 0.02, 1.56, $P = 0.1$), anticoagulation (OR 24.2, 95% CI 1.96, 299) and lateral and/or sigmoid sinus involvement (OR 16.2, 95% CI 1.62, 161, $P = 0.02$) were independent predictors of good cognitive outcome, although the last predicted pseudotumour cerebri. Death was associated with coma at presentation. Of 19 patients with follow-up magnetic resonance (MR) venography, three had persistent occlusion, associated with anaemia and longer prodrome. A low threshold for CT or MR venography in children with acute neurological symptoms is essential. Nutritional deficiencies may be modifiable risk factors. A paediatric anticoagulation trial may be required, after the natural history has been further established from registries of cases with and without treatment.

Keywords: venous sinus thrombosis; anaemia; magnetic resonance; anticoagulation

Abbreviations: CSVT = cerebral venous sinus (sinovenous) thrombosis; MRV = magnetic resonance venography; SCD = sickle cell disease; tMTHFR = thermolabile variant of the methylene tetrahydrofolate reductase gene; SLE = systemic lupus erythematosus

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Introduction

The incidence of cerebral venous sinus (sinovenous) thrombosis (CSVT) is at least 0.67 per 100 000 children per year (de Veber *et al*., 2001), although there is concern that cases of this potentially treatable condition are missed. The clinical manifestations can be life-threatening and cause long-term neurological deficits (Barron *et al*., 1992; Carvalho *et al*., 2000). However, as the symptoms and signs are non-specific, diagnosis is often delayed and may be missed altogether. Although the incidence may be declining, as some of the conditions historically associated with CSVT in children are now rare or treatable, e.g. cyanotic congenital heart disease or mastoiditis, the diagnosis is made more commonly in life because of advances in neuroimaging. The onus is on the clinician to request the appropriate investigations but many have never diagnosed a case. CT may not be adequate to exclude CSVT and indications for MRI and magnetic resonance (MR) venography in acute neurological presentations have not been established, as there are few data from which evidence-based guidelines for investigation could be developed.

The importance of genetic and acquired prothrombotic disorders has been emphasized in recent series of paediatric CSVT (de Veber *et al*., 1998*a*; Bonduel *et al*., 1999; Heller *et al*., 2003). However, although single cases of homocystinuria (Buoni *et al*., 2001; Vorstman *et al*., 2002) and severe anaemia (Belman *et al*., 1990; Hartfield *et al*., 1997; Meena *et al*., 2000; Swann and Kendra, 2000; Keane *et al*., 2002) have been reported as associations, there are few data on the relative importance of milder anaemia or genetic determinants of hyperhomocysteinaemia (Martinelli *et al*., 2003; Boncoraglio *et al*., 2004), both of which might be modified with low risk by nutritional supplementation. High factor VIII levels appear to be associated with CSVT in adults (Cakmak *et al*., 2003), but factor VIII is not commonly performed in children (Kurecki *et al*., 2003).

In order to explore the variety of clinical and neuroradiological presentation and the frequency of associated haematological risk factors, as well as to determine predictors of outcome, we describe our experience with consecutive children with CSVT in five centres. In addition, we compare the clinical presentation of children with infarction or haemorrhage secondary to CSVT with those with arterial ischaemic (Ganesan *et al.*, 2003) or haemorrhagic stroke. We emphasize the need for increased awareness of this entity in children.

Methods

Data review was conducted of consecutive patients personally known to three of the authors (G.S., A.N.W. and F.J.K.) and investigated prospectively at one of five European paediatric neurology centres with a paediatric stroke registry: Hôpital Kremlin-Bicêtre, France (1997); Cliniques Universitaires Saint-Luc, Belgium (1997–2002); The Princess of Wales Children's Hospital, Birmingham (1993–1998); Great Ormond Street Hospital, London (1990–2000); and Southampton General Hospital (1999–2001). Appropriate ethical permission was obtained. Patients were included if a diagnosis of definite CSVT had been made by a neuroradiologist either on CT after contrast enhancement showing the dense-triangle sign, or MR based on classical neuroradiological features (Sébire *et al*., 2004). Patients presenting to neonatal paediatricians were not included. Patients underwent the following laboratory investigations, which increased in number over the study period as possible prothrombotic associations were reported: blood count, cholesterol, triglycerides, lipoprotein (a), fibrinogen, protein C, protein S, antithrombin, plasminogen, heparin cofactor II, prothrombin 20210, factor V Leiden, homozygosity for the thermolabile variant of the methylene tetrahydrofolate reductase gene (tMTHFR), factor VIII, factor XII, anticardiolipin IgG and lupus anticoagulant. Details of the clinical presentation, laboratory and radiological investigations and long term clinical and radiological follow-up were obtained from the databases and were supplemented by return to the medical notes. All patients were seen at least once for a follow-up with a paediatric neurologist and an interview with the parents about function in nursery or school, ongoing headache and epilepsy was conducted, as well as a neurological examination. Outcome was classified as death, cognitive sequelae, motor sequelae, visual sequelae, pseudotumour cerebri or none of these. Pseudotumour cerebri was diagnosed using classical criteria, including cerebrospinal fluid pressure measurement (Balcer *et al*., 1999). 'Cognitive sequelae' refers to children being placed at least one school grade below their expected class for age or requiring a statement of special educational needs or—for preschool children—formal testing suggesting that the developmental speed was less than 75% of normal. Follow-up neuroimaging was undertaken at the discretion of the paediatric neurologist. Parenchymal changes were compared with the previous imaging and were classified as normal, improved or persistent. Venous sinus patency was assessed as normal, improved or persistent. We looked for distinctive features between venous and arterial strokes, in order to examine whether there were clues to the differential diagnosis. Comparison of the clinical, radiological and laboratory features of the patients with bland and haemorrhagic CSVT were made with a consecutive cohort of children with arterial stroke prospectively studied at Great Ormond Street Hospital between January 1994 and April 2000.

Statistical analysis was performed using χ^2 (statxact version 4.0.1), Kruskall–Wallis analysis of variance, Fisher's exact test and logistic regression (SPSS version 11.0).

Results

Forty-two children were included, one from Paris, four from Brussels, nine from Birmingham, nine from Southampton,

Table 1 *Previous medical history in 42 children with CSVT*

	Frequency (%)
Male	24/42 (57%)
Underlying illness	17/42 (40%)
Cardiac disease	2/42 (4%)
Inflammatory bowel disease	1/42 (2%)
Nephrotic syndrome	3/42 (6%)
Systemic lupus erythematosus	2/42 (4%)
Sickle cell disease	2/42 (4%)
Thalassaemia	1/42 (2%)
Hydrocephalus (recent shunt)	2/42 (4%)
Brain tumour	2/42 (4%)
Leukaemia	2/42 (4%)
Previously well	25/42 (59%)
Previous CSVT history	2/42 (4%)
Recent triggering event	42/42 (100%)
Ear infection (mastoiditis)	20/42 (47%)
Sinusitis	1/42 (2%)
Other infection	10/42 (24%)
Diarrhoea	5/42 (12%)
Other dehydration	9/42 (21%)
Recent head trauma	2/42 (4%)
Recent surgery	4/42 (9%)

Table 2 *Clinical features of CSVT in 42 children*

	Frequency (%)
Onset	
Acute	35/42 (83%)
Subacute	7/42 (17%)
Symptoms	
Seizures (generalized tonic-clonic)	17/42 (40%)
Headache	25/37 (68%)
Vomiting	12/42 (28%)
Drowsiness	18/42 (43%)
Anorexia/poor feeding	5/42 (12%)
Lethargy	19/42 (45%)
Irritability	5/42 (12%)
Confusion	5/37 (13%)
Numbness	1/37 (3%)
Signs	
Fever	19/42 (45%)
Coma	12/42 (28%)
Hemiparesis	14/42 (33%)
Ataxia	1/37 (3%)
Cranial nerve abnormality	14/42 (33%)
Visual deficit	4/37 (11%)

and the remainder from Great Ormond Street. Age ranged from 3 weeks to 13 years (median 5.75 years); 27 (64%) of the patients were boys.

Pre-existing diagnosis and triggers (Table 1)

Patients with previous chronic illness

Seventeen patients were known to have chronic illness (Table 1), including four who had CSVT diagnosed immediately after surgical procedures, namely modified Fontan for hypoplastic left heart syndrome, ventriculoperitoneal shunt, brain tumour resection, and colectomy for ulcerative colitis. Eight of the patients with chronic illness had recent infections (three involving the ear, none with mastoiditis) and four were dehydrated. Comparison using Fisher's exact test of the occurrence of underlying illnesses and of triggering events between the three different age groups (<1 year, $n = 5$; 1–6 years, $n = 17$; >6 years, $n = 20$) did not show any significant differences (Table 1).

Previously well children

Twenty-five patients were previously well, all of whom had triggers: 23 had recent infections (17 involving the ear, 11 with mastoiditis), eight became dehydrated and six were both infected and dehydrated.

There were no significant associations between age group and pre-existing diagnosis or any of the triggers (Table 1). Patients without pre-existing chronic illness were more likely to have had a recent infection, an ear infection or mastoiditis (Fisher's exact test, $P = 0.003$, $P = 0.002$, $P = 0.006$ respectively) but were not more likely to be dehydrated (Fisher's exact test, $P = 0.73$).

Clinical presentation (Table 2)

All patients had symptomatic CSVT (Table 2). The median duration of symptoms was 5 days (range 12 h to 120 days). The majority of children presented acutely with seizures, focal signs and symptoms of raised intracranial pressure, such as headache and decreased level of consciousness (Table 2). Subacute presentation, with chronic headache, vomiting, lethargy, anorexia or drowsiness for 3 weeks or more, occurred in six children. Nineteen children were febrile at presentation. Using Fisher's exact test, there was no significant difference in the type of clinical manifestations between the three different age groups (<1 year, $n = 5$; 1–6 years, $n = 17$; >6 years, $n = 20$).

Previous neurological history

Two children had a prior neurological history compatible with previous CSVT. One child with haemoglobin SC disease born at 36 weeks gestation had presented at the age of 2 weeks with a left-sided focal seizure in the context of a chest infection. Head ultrasound revealed bilateral intraventricular haemorrhage and lumbar cerebrospinal fluid was uniformly bloodstained but cerebral venous sinus thrombosis was not excluded. He required a shunt for communicating hydrocephalus and represented at the age of 9 years with severe headache secondary to venous sinus thrombosis (Fig. 1). Another patient, who was chronically iron-deficient, had developed a transient hemiparesis at the age of 18 months.

Laboratory findings

Routine haematology

Twenty-two children (52%) were anaemic (Z score for haemoglobin <2 SDs below the mean for age), two secondary

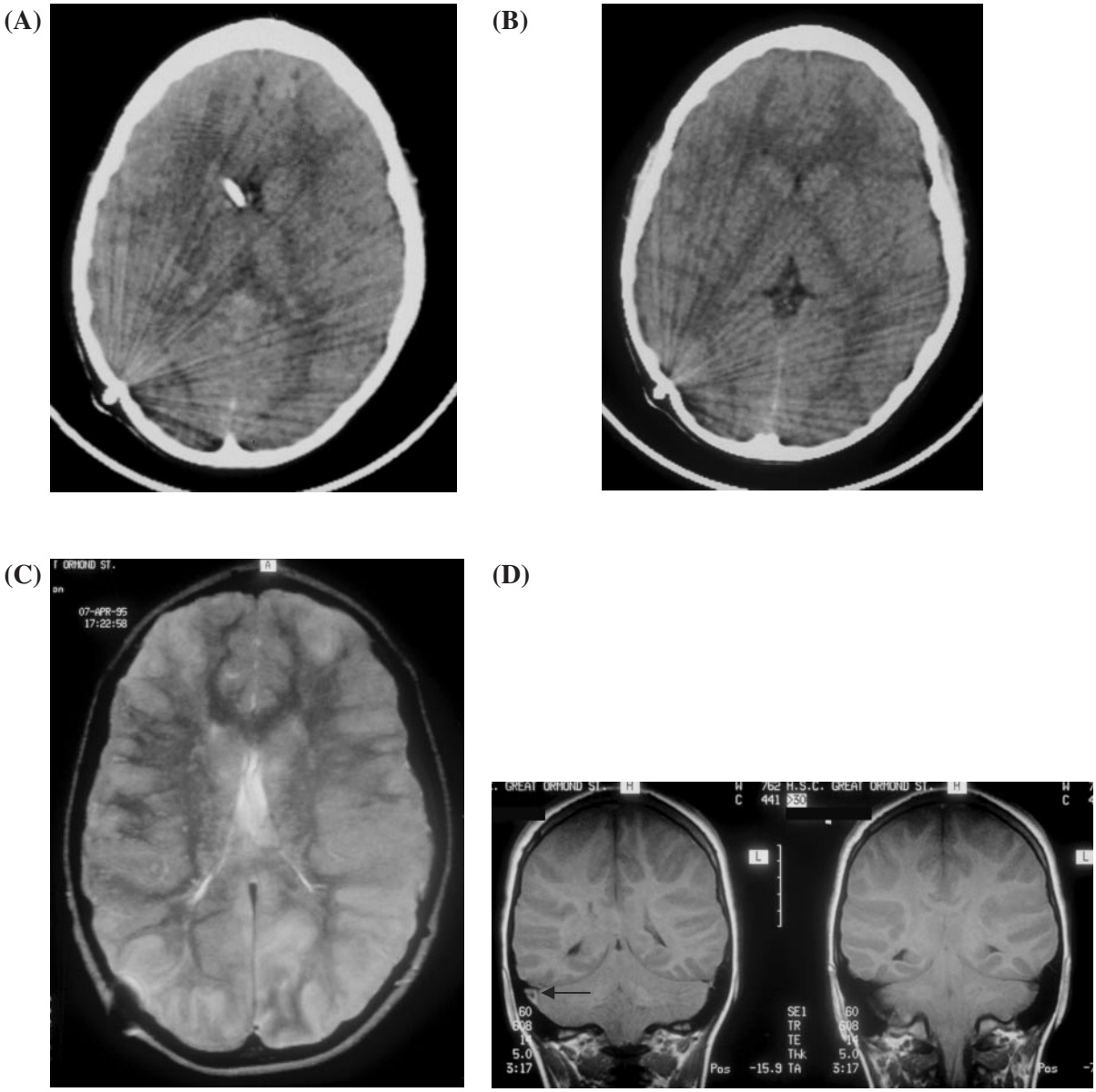

Fig. 1 (**A**) This child with haemoglobin SC disease had presented in infancy with seizures and had required a shunt for hydrocephalus. He represented at the age of 9 with severe chronic headache and 3 weeks later developed generalized seizures. There are no visible sulci and the ventricles are small on the initial CT scan, indicative of cerebral oedema. A right-sided shunt and intracranial pressure monitor are noted. (**B**) The CT scan at 10 days shows definite cerebral oedema and the dense straight sinus raises the possibility of CSVT, but is not diagnostic. (**C**) Two days later there is widespread cortical and basal ganglia high signal on T2-weighted axial MRI. (**D**) Marked swelling of the cerebral hemispheres and posterior fossa, which has led to tonsillar descent, is seen on the T1-weighted coronal images High signal is seen in the right transverse sinus (delta sign) due to either slow flow or thrombus (arrow).

to SC disease (one haemoglobin SC, one homozygous SS), one with β-thalassaemia and two others with haemolytic anaemia in the context of systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma. Seventeen anaemic children, including one treated for acute lymphoblastic leukaemia, and an additional four children with haemoglobin within the normal range, had microcytosis (haematocrit and/or mean cell volume <2 SDs below the mean for age) compatible with iron deficiency. Anaemia and/or microcytosis were seen in all age groups (60, 53, 75% amongst children aged <1 year, 1–6 years and >6 years respectively, χ^2, $P = 0.15$). There was a trend for microcytosis to be commoner in previously well children (Fisher's exact test, $P = 0.07$).

Screening for thrombophilia

A risk factor for thrombophilia was found in 18 of the 29 (62%) screened (Table 3). Although only 13 patients were tested, more than half had high factor VIII. Of 14 patients tested, four (29%) were homozygous for the thermolabile

variant of the methylene tetrahydrofolate reductase (tMTHFR) gene; comparison with 78 unselected controls admitted to Great Ormond Street hospital (Prengler *et al*., 2001), nine (12%) of whom were homozygous for the tMTHFR mutation, shows a trend for an excess of homozygotes for the tMTHFR mutation in children with CSVT (Fisher's exact test, $P = 0.1$). Low protein C, factor V Leiden and prothrombin 20210 mutations were not found in this series.

Table 3 *Laboratory features of 42 children with CSVT*

Laboratory features (normal values)	Tested	Abnormal	%
Anaemia	42	23	55
Microcytosis	42	22	52
High cholesterol	6	1	
High triglycerides	6	1	
High lipoprotein (a)	2	0	
High fibrinogen (1.7–4 g/l)	13	3	23
Low protein S (72–130 IU/l)	22	4	18
Low free protein S (70–140 IU/dl)	5	1	20
Low protein C (37–130 IU/dl)	22	0	0
Low antithrombin (79–131 IU/dl)	20	3	15
Low plasminogen (39–83 IU/dl)	9	0	0
Low heparin cofactor II (50–150 IU/dl)	5	0	0
High factor VIII (50–150 IU/dl)	13	7	54
Low factor XII (50–150 IU/dl)	9	2	22
Factor V Leiden mutation	20	0	0
Prothrombin 20210 mutation	15	0	0
tMTHFR homozygosity	14	4	29
High anticardiolipin IgG (>12 IU/dl)	15	3	20
Lupus anticoagulant	9	1	11
One prothrombotic abnormality	29	13	45
Two prothrombotic abnormalities	29	2	7
Three prothrombotic abnormalities	29	1	3
Four prothrombotic abnormalities	29	2	7

Of two patients with nephrotic syndrome who were tested, one had low protein S and another had slightly low antithrombin and high fibrinogen acutely; the antithrombin was normal on repeat testing but the fibrinogen remained high. Raised IgM anticardiolipin antibodies were found in one of the patients with SLE and IgG anticardiolipin was raised in two other patients, both with familial history of SLE; the other 11 children tested were normal.

Radiological findings

Parenchymal imaging (Table 4)

All 42 children had CT and the diagnosis was made using parenchymal images with contrast enhancement in nine. MRI was performed in addition in 33, of whom 31 had MR venography. Of the 25 patients with parenchymal abnormalities, 24 had cortical involvement. Four children had bilateral haemorrhagic infarcts, seven had bilateral bland infarcts (Fig. 2) and 13 had unilateral infarcts (Fig. 3), eight of which were haemorrhagic. The anatomical regions involved were cortex of the frontal ($n = 8$), temporal ($n = 4$), parietal ($n = 15$) and occipital ($n = 5$) regions, thalamus ($n = 3$), putamen ($n = 2$), caudate ($n = 1$), internal capsule ($n = 1$), hippocampus ($n = 2$), deep white matter ($n = 2$) and cerebellum ($n = 1$). Clinical signs were related to the location of parenchymal lesions as classically expected in strokes. Seventeen patients had no visible infarction but one of these had a temporal abscess in association with mastoiditis and another had an arteriovenous fistula in the middle temporal fossa.

Patients with parenchymal lesions (haemorrhage or infarction) were more likely to present with hemiplegia (Fisher's exact test, $P = 0.01$) but not with seizures ($P = 0.2$) or Glasgow

Table 4 *Comparison of radiological and haematological features of venous and arterial stroke*

	Infarct and haemorrhage				Infarct only			
	Venous ($n = 25$)	Arterial ($n = 112$)	Odds ratio (95% confidence limits)	*P*	Venous ($n = 13$)	Arterial ($n = 88$)	Odds ratio (95% confidence limits)	*P*
Site								
Frontal	32%	48%	0.51 (0.2, 1.27)	0.15	38%	52%	0.57 (0.17, 1.88)	0.36
Temporal	16%	16%	1.0 (0.31, 3.24)	0.99	23%	18%	1.35 (0.33, 5.47)	0.67
Parietal	60%	21%	5.8 (2.31, 15.6)	0.0001	46%	24%	2.74 (0.83, 9.04)	0.10
Occipital	20%	10%	2.3 (0.72, 7.33)	0.16	31%	11%	3.47 (0.90, 13.4)	0.07
Thalamus	12%	6%	2.05 (0.49, 8.53)	0.33	15%	3%	5.15 (0.77, 34.3)	0.09
Putamen	8%	26%	0.25 (0.06, 1.12)	0.07	15%	33%	0.37 (0.08, 1.78)	0.22
Caudate	4%	38%	0.07 (0.009, 0.51)	0.009	8%	49%	0.08 (0.01, 0.70)	0.02
Insula	0%	13%	–	0.76	0%	16%	–	0.78
Internal capsule	4%	14%	0.25 (0.03, 1.98)	0.19	8%	18%	0.38 (0.05, 3.10)	0.36
Corpus striatum	0%	4%	–	0.75	0%	3%	–	0.86
Deep white matter	8%	19%	0.38 (0.08, 1.72)	0.21	0%	24%	–	0.81
Cerebellum	4%	6%	0.63 (0.07, 5.32)	0.67	0%	6%	–	0.81
Pons	0%	4%	–	0.75	0%	2%	–	0.84
Z score for haemoglobin	−3.07 (−6.8, 0.27)	−1.73 (−11.4, 3.87)	0.87 (0.74, 1.03)	0.1	−3.6 (−6.8, 0.13)	−1.87 (−11.4, 3.87)	0.86 (0.71, 1.05)	0.14
Microcytosis	56%	21%	4.93 (1.98, 12.3)	0.001	69%	18%	10.1 (2.77, 37)	0.0001
Platelet count	423 (36, 777)	290 (38, 637)	1.005 (1.001, 1.008)	0.014	475 (272, 717)	290 (38, 637)	1.007 (1.002, 1.012)	0.009

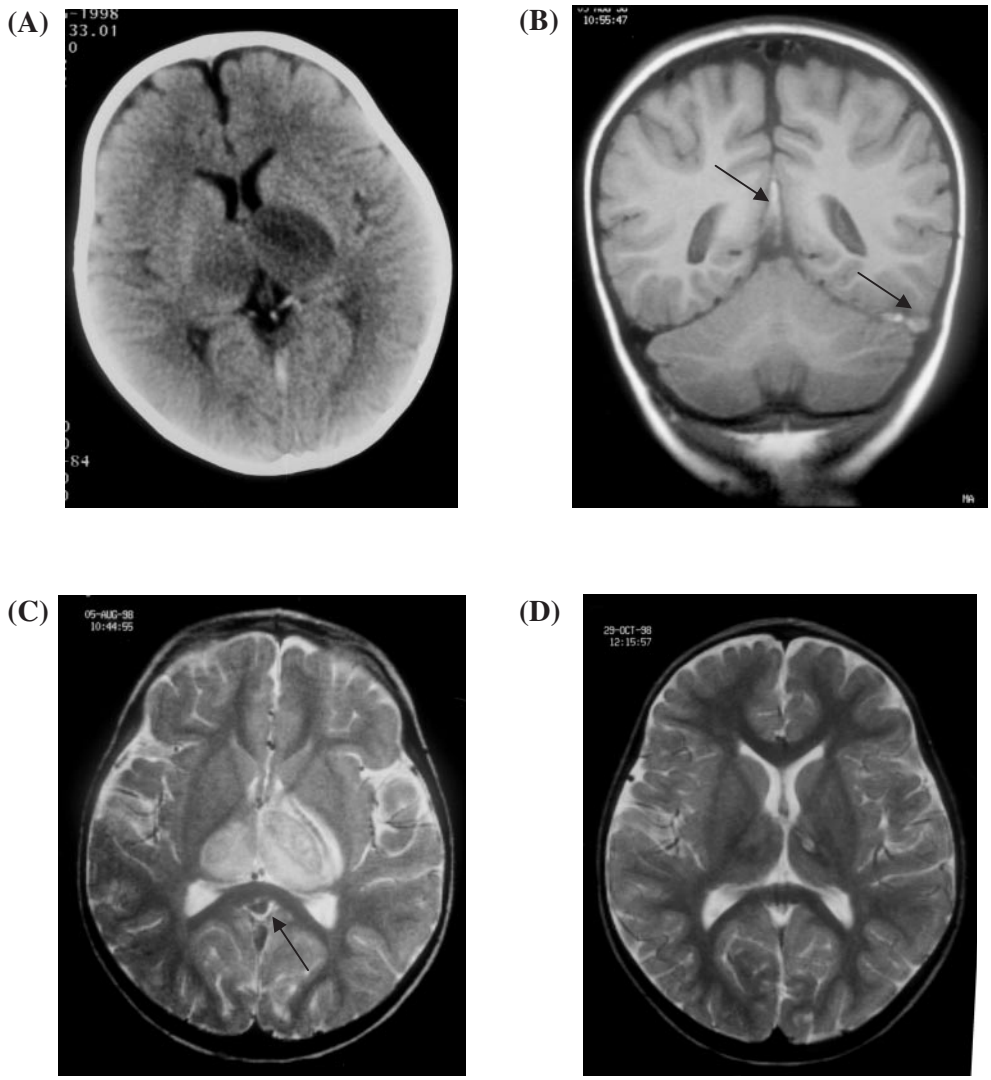

Fig. 2 Neuroimaging from a 20-month-old girl with iron deficiency anaemia. (**A**) Bilateral thalamic hypodensity and thrombus in the straight sinus and deep cerebral veins are demonstrated on the CT scan. (**B**) Thrombus in the straight and left transverse sinuses is seen as high signal on the coronal T1-weighted MRI (arrows). (**C**) The axial T2-weighted MRI shows bilateral thalamic high signal involving the posterior limb of the internal capsule and the posterior putamen. The vein of Galen and straight sinus are dark due to the iron products of haemoglobin (arrow). (**D**) Follow-up T2-weighted MRI 3 months later demonstrates almost complete reversal of the thalamic infarction, with only a small residual scar, and restored flow in the vein of Galen and straight sinus.

coma score <12 ($P = 0.5$). Patients with normal parenchymal imaging were more likely to present with cranial nerve signs ($P = 0.01$) but not with headache ($P = 0.3$).

Venous sinuses involved

The superficial (sagittal, transverse or sigmoid sinuses) and deep venous systems (deep cerebral veins and straight sinus) were involved in 32 and six patients respectively, with both involved in four. Sinuses involved were sagittal ($n = 16$), sigmoid ($n = 11$), transverse or lateral ($n = 20$), cavernous ($n = 4$) and straight ($n = 4$). The jugular vein was involved in three patients. In two patients there was cortical venous sinus thrombosis alone and in another thrombosis of the cortical veins was seen extending into the occluded superior sagittal sinus. Two and three vessels were involved in 14 and three patients respectively.

Comparison with arterial stroke (Table 4)

The data on the 25 children with infarction in the context of CSVT were compared with those from a consecutive cohort of 112 children with clinical stroke and cerebral arterial disease prospectively recruited at Great Ormond Street hospital between 1993 and 2000 and also imaged acutely. There were 82 children with ischaemic stroke and arteriopathy on conventional or MR angiography (11 dissection, 17 occlusion, 42 stenosis, four vasculitis, eight moyamoya) and 24 with haemorrhagic stroke and definite arterial pathology (13 arteriovenous malformation, five cavernomas and six aneurysms).

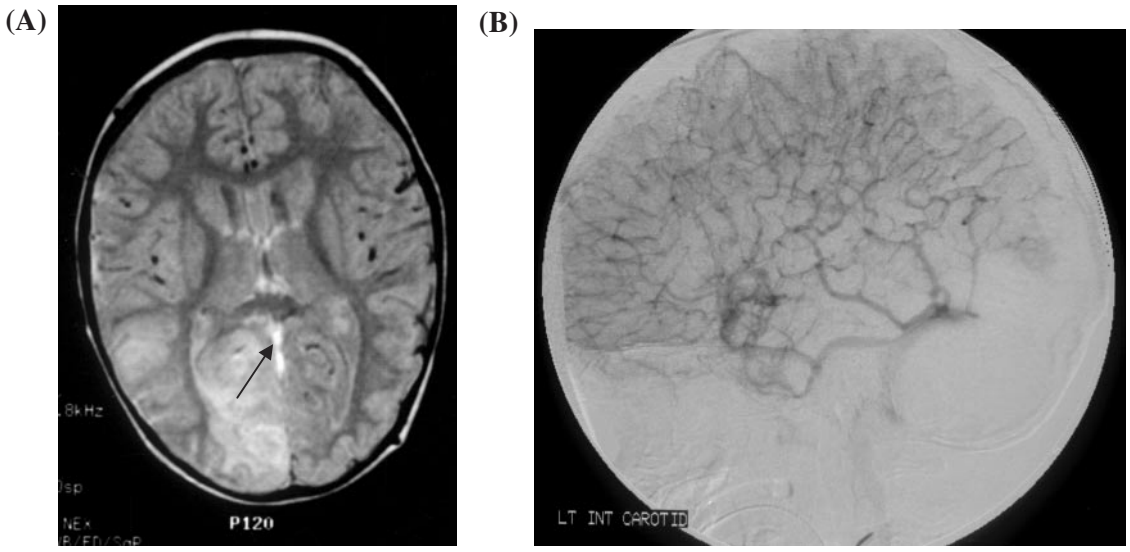

Fig. 3 Neuroimaging from a 22-month-old boy with iron deficiency anaemia. (**A**) MRI showing that the abnormal high signal involves predominantly the right occipital lobe. The straight sinus is occluded; subacute thrombus is seen as high signal on proton density images (arrow). (**B**) Five months later the venous phase of the cerebral angiogram demonstrates absence of flow in the occluded superior sagittal and straight sinus. Multiple collateral vessels drain the hemisphere towards the cavernous sinus.

In univariate analysis, CSVT was significantly commoner in those with parenchymal abnormality in a parietal distribution, and less common in those with involvement of the caudate nucleus. There was a trend for anaemia to be commoner in CSVT, microcytosis was commoner and platelet count was higher (Table 4). In multiple logistic regression, microcytosis [adjusted odds ratio (OR) 7.15, 95% confidence interval (CI) 2.31, 22.1, $P = 0.01$], parietal involvement (adjusted OR 6.8, 95% CV 2.25, 20.6, $P = 0.001$) and lack of caudate involvement (adjusted OR 0.05, 95% CV 0.006, 0.42, $P = 0.006$) independently predicted CSVT rather than arterial disease. Results were similar when infarcts were considered alone; in addition there were trends for occipital and thalamic infarction to be commoner in CSVT.

Outcome

Five patients died, three acutely and two later; one during a recurrent episode of CSVT and one with severe neurological sequelae, respectively 3 and 6 months after the initial event. For the 37 survivors, follow-up ranged from 6 months to 10 years (median 1 year). Eleven children had no neurological or cognitive difficulties at follow-up. Twelve had symptoms and signs compatible with chronic pseudotumour cerebri and 14 had cognitive difficulties (of whom two had a permanent hemiparesis, three had reduced visual acuity and two developed epilepsy). None of the patients with cognitive difficulties was diagnosed with pseudotumour cerebri.

Acute management and relationship with outcome

All of the children with sepsis were treated with antibiotics and three also had a mastoidectomy. Iron supplementation was given to those in whom severe iron deficiency was diagnosed. Three children required ventilatory support and four (including the two with sickle cell disease and one with β-thalassaemia) were transfused. The patient with SLE was immunosuppressed.

Eighteen of the patients in whom the diagnosis was made acutely were anticoagulated immediately with heparin (unfractionated in 15 and low molecular weight in three) and then warfarin or low molecular weight heparin for up to 6 months. Two children were treated with aspirin and one with haemoglobin SC disease was given tissue plasminogen activator but not until after he became deeply unconscious with an MRI showing widespread oedema (Fig. 1C). He died soon after without imaging evidence of haemorrhage.

Six of the anticoagulated patients had haemorrhage at presentation; none had an extension of the haemorrhage and all survived the index episode, although one with congenital nephrotic syndrome died after recurrent haemorrhagic CSVT treated with heparin. Of the six children who were not anticoagulated because of haemorrhage on neuroimaging, one died 16 h after presentation, three had cognitive difficulties (one with seizures, Fig. 3B) and only one had no sequelae.

Anticoagulated patients were more likely to have good cognitive outcome, with a statistical trend of borderline significance, and a reduction in mortality which was not statistically significant (Table 5). In some cases, a therapeutic dose of heparin appeared to have an immediately beneficial effect. One boy with haemorrhage, in whom activated partial thromboplastin time (APTT) was less than 2.5 for the first 24 h, remained unconscious (minimum Glasgow coma score 10) and continued to seize. Repeat CT showed no extension of the haemorrhage and he improved within an hour when the heparin dose was increased to achieve an activated partial

Table 5 *Associations with outcome*

	Odds ratio for death (5/42)	*P*	Odds ratio for good cognitive outcome (19/42)	*P*
Age	0.95 (0.74, 1.22)	0.7	1.26 (1.04, 1.52)	0.02
Duration of prodrome (days)	0.99 (0.94, 1.06)	0.8	1.01 (0.96, 1.04)	0.7
Pre-existing illness	0.98 (0.15, 6.58)	0.9	0.59 (0.17, 2.06)	0.4
Infective trigger	0.48 (0.07, 3.36)	0.5	1.64 (0.40, 6.76)	0.5
Seizures at presentation	2.42 (0.34, 17.0)	0.4	0.59 (0.17, 2.06)	0.4
Glasgow coma score <12 on admission	14.5 (1.42, 149)	0.02	0.29 (0.07, 1.19)	0.08
Parenchymal abnormality	1.14 (0.17, 7.67)	0.9	0.17 (0.04, 0.69)	0.01
Haemorrhage	1.80 (0.26, 12.4)	0.6	0.29 (0.07, 1.19)	0.09
Multiple sinus involvement	0.33 (0.03, 3.23)	0.3	3.06 (0.83, 11.3)	0.09
Involvement of lateral and/or straight sinuses	0.57 (0.09, 3.80)	0.6	0.20 (0.05, 0.75)	0.01
Involvement of deep sinuses	2.42 (0.34, 17.0)	0.4	0.46 (0.11, 1.94)	0.3
Involvement of straight sinus	0.35 (0.03, 4.25)	0.4	0.24 (0.02, 2.55)	0.2
Anticoagulation	0.29 (0.03, 2.89)	0.3	3.64 (0.98, 13.5)	0.05
Persistent occlusion (n = 20)			0.15 (0.01, 2.18)	0.2
Anaemia acutely	3.79 (0.39, 37.2)	0.2	1.73 (0.51, 5.91)	0.4
Microcytosis acutely	2.59 (0.26, 26.3)	0.4	1.16 (0.27, 4.93)	0.8

thromboplastin time (APTT) of 2.5, although he had pseudotumour cerebri at follow-up. Another child with confusion and personality change in the context of SLE and sagittal sinus thrombosis improved within 12 h of starting unfractionated heparin and remained well 1 year later on steroids and low molecular weight heparin. Of the 12 patients with chronic pseudotumour cerebri, six had been anticoagulated acutely (Fisher's exact test for comparison with those without pseudotumour cerebri, $P = 0.4$).

Treatment of chronic intracranial hypertension

Pseudotumour cerebri was treated with steroids and/or acetazolamide. Shunts for hydrocephalus were performed in infancy in two children with confirmed CSVT (one before and one after the diagnosis) and the child with haemoglobin SC disease, who may have had unrecognized CSVT in infancy. One child required a lumboperitoneal shunt.

Follow-up MRI

Of the 21 patients for whom follow-up MRI was available, complete reversal of the parenchymal change and CSVT were seen in three patients with haemorrhage. One patient had only a small residual lesion associated with complete clinical recovery (Fig. 2), although the acute imaging showed bilateral ischaemic changes in the thalami, subthalamic nuclei, left internal capsule and left temporal lobe. Mature infarcts developed in the remaining nine children who had parenchymal defects (two haemorrhagic) at the time of diagnosis, while the other eight MRIs remained normal.

Follow-up MRV showed complete ($n = 8$) or partial ($n = 8$) restoration of flow except in three patients who had persistent occlusion, two with a subacute presentation (Fig. 3). One of these cases had both sagittal and straight sinus thrombosis, one had sagittal and one had lateral sinus thrombosis. Multiple collateral veins were seen in all three patients, in one at the time of the diagnostic angiogram (Fig. 3) and in two on follow-up imaging. The prodrome was significantly longer in those with persistent occlusion than in those with complete or partial restoration of flow (Kruskal–Wallis test, $P = 0.04$). Haemoglobin was significantly higher at original presentation in those with recanalization at follow-up than in those with improvement or persistent occlusion (Kruskal–Wallis test, $P = 0.02$). There was no evidence that multiple vessel involvement (χ^2, $P = 0.2$), involvement of the deep sinuses (χ^2, $P = 0.6$) or anticoagulation (χ^2, $P = 0.4$) had an effect on recanalization. However, the numbers were small and some of the percentage differences quite large. For example, anticoagulation was given in 78% of those with complete restoration compared with only 33% of those with persistent thrombosis. There was no association between persistent thrombosis and death, cognitive sequelae or pseudotumour cerebri, but two of the three patients with epilepsy as an outcome had persistent occlusion.

Recurrence and systemic thrombosis

One child with congenital Finnish-type nephrotic syndrome had radiologically confirmed recurrent sagittal sinus thrombosis and died of raised intracranial pressure secondary to haemorrhage and oedema. Another child with thrombosis of the sagittal sinus and right internal jugular vein in the context of acute lymphoblastic leukaemia (not anticoagulated) had further transient episodes, one of dysarthria and ataxia and one of hemiplegia, hemisensory loss and hemianopia soon after her leukaemia relapsed. MRI and MRV were reported as normal and she has remained symptom-free 8 years after a

bone marrow transplant. Three children developed systemic venous thrombosis.

Predictors of outcome

The only statistically significant association with death was an admission Glasgow coma score <12 (Table 5). Mortality, cognitive outcome and pseudotumour cerebri were not related to anaemia or microcytosis (Fisher's exact test, Table 5). Good cognitive outcome was commoner in older children, those without parenchymal abnormality and those with lateral and/or sigmoid sinus involvement (Table 5), although chronic pseudotumour cerebri was commoner in the latter group (χ^2, $P = 0.01$). In multiple logistic regression, older age (OR 1.54, 95% CI 1.12, 2.13, $P = 0.008$), involvement of the lateral and/or sigmoid sinus (OR 16.2, 95% CI 1.62, 161, $P = 0.02$), lack of parenchymal abnormality (OR 0.17, 95% CI 0.02, 1.56, $P = 0.1$) and anticoagulation (OR 24.2, 95% CI 1.96, 299) were all independent predictors of good cognitive outcome.

Discussion

It is apparent from our study and review of the literature that the clinical manifestations of CSVT are non-specific and may be subtle (Bousser and Ross-Russell, 1997). Most of the clinical scenarios occur at all ages and the clinician should consider this diagnosis in a wide range of acute neurological presentations in childhood, including seizures, coma, stroke, headache and raised intracranial pressure. Common illnesses, including ear infections, meningitis (Kastenbauer and Pfister, 2003), anaemia (Belman *et al*., 1990), diabetes (Keane *et al*., 2002) and head injury (Stiefel *et al*., 2000), may be complicated by CSVT, but as there is difficulty in making the diagnosis, data for incidence remain a minimum estimate (de Veber *et al*., 2001). Although presentation with pseudotumour cerebri has been well documented (Biousse *et al*., 1999), there are few data on the prevalence of CSVT in otherwise unexplained hydrocephalus (Norrell *et al*., 1969) or in convulsive and non-convulsive seizures and status epilepticus (Wang *et al*., 1997). CSVT may also be an important determinant of outcome in non-traumatic coma (Krishnan *et al*., 2004).

Anatomically, the spectrum of venous infarcts includes unilateral and bilateral infarcts and haemorrhages of the deep grey structures (secondary to thrombosis of the deep cerebral veins and straight sinus) or of the cortex and subjacent white matter (secondary to thrombosis of the sagittal, transverse or sigmoid sinuses). Diffusion-weighted imaging has demonstrated that venous infarcts have restricted diffusion (cytotoxic oedema) in the early stages (Forbes *et al*., 2001), supporting the theory that retrograde venous pressure decreases cerebral blood flow causing tissue damage, akin to arterial infarction (Rother *et al*., 1996). However, follow-up imaging of both the venous sinuses and any parenchymal damage is usually reported as normal. If emergency imaging of the venous sinuses is not undertaken, the diagnosis is very likely to be missed in children presenting with acute symptomatology and in otherwise unexplained hydrocephalus, as well as those with pseudotumour cerebri and cavernous sinus syndrome (Bousser and Ross-Russell, 1997).

In childhood, CSVT is relatively equally distributed according to the different age groups, except for a high incidence in neonates (de Veber *et al*., 2001). We excluded those presenting to neonatal paediatricians, as the clinical dilemmas are different (Shevell *et al.*, 1989; Rivkin *et al*., 1992), but suspect that our patient with haemoglobin SC disease had CSVT as the cause of his neonatal seizures, intraventricular haemorrhage and communicating hydrocephalus, especially as he presented at the age of 2 weeks rather than at birth (Ramenghi *et al*., 2002; Wu *et al*., 2003).

There are few data on the clinical presentation in older children and it is likely that the diagnosis is often delayed or missed altogether in this group as well. It has been suggested that toddlers frequently present with seizures and focal signs, mainly hemiparesis, whereas older children present with headache and changes in mental status and seizures may be less common (Carvalho *et al*., 2000). In our series, there was no pattern relating symptomatology to age, perhaps reflecting the recent trend to emergency imaging of the venous sinuses in children with acute coma, seizures or stroke as well as those presenting with pseudotumour cerebri. The manifestations of deep cerebral venous thrombosis are typically characterized by altered consciousness, decerebrate posturing, changes in extrapyramidal tone and psychiatric symptoms such as confusion as a result of infarction in the thalami and basal ganglia and white matter structures (Kothare *et al*., 1998; de Veber *et al*., 2001). Thus, as we observed in our series, the clinical presentation of CSVT is highly variable, extending from discrete symptoms, such as isolated headache, to severe and often multifocal neurological deficits.

The evaluation of children with suspected CSVT has been made considerably easier by modern neuroimaging techniques. In the largest studies, around half of infants and children had multiple sinuses and/or veins involved and 40% had associated parenchymal infarcts (Barron *et al*., 1992; Carvalho *et al*., 2000; de Veber *et al*., 2001). In our series, 41% had more than one sinus involved whereas 57% had parenchymal changes, probably reflecting our interest in childhood stroke and the associated support for vascular imaging. Superior sagittal and lateral sinus thrombosis is diagnosed more frequently in most series (Heller *et al*., 2003; Johnson *et al*., 2003). However, this may reflect the current difficulties in diagnosing thrombosis in the deep system (Di Roio *et al*., 1999) or cortical veins (Garcia, 1990; Jacobs *et al*., 1996), which may require conventional angiography, which is difficult to justify after late presentation in coma and/or status epilepticus. Unenhanced CT scans may detect deep venous thrombosis as linear densities in the expected locations of the deep and cortical veins. As the thrombus becomes less dense, contrast may demonstrate the 'empty delta' sign, a filling defect, in the posterior part

of the sagittal sinus (de Veber *et al*., 2001). However CT scan with contrast misses the diagnosis of CSVT in up to 40% of patients (Barron *et al*., 1992; de Veber *et al*., 2001). Diffusion and perfusion MRI may play a role in detecting venous congestion in cerebral venous thrombosis and in the differentiation of cytotoxic and vasogenic oedema (Forbes *et al*., 2001) but does not differentiate venous from arterial infarction. CT venography or MRI with venous MR (MRV) are now the methods of choice for investigation of CSVT (Medlock *et al*., 1992). The diagnosis is established by demonstrating a lack of flow in the cerebral veins with or without typical images of brain infarcts. Parenchymal MR and MRV are important in the demonstration of both the infarct and the clot within the vessels. On MRI, the thrombus is readily recognizable in the subacute phase, when it is of high signal on a T1-weighted scan and MRV is often not required. In the acute phase, the thrombus is isosignal on T1-weighted imaging and of low signal on T2-weighted imaging. This can be mistaken for flowing blood but MRV will demonstrate an absence of flow in the thrombosed sinus. However, MRI and MRV are techniques prone to flow artefacts and in equivocal cases an endoluminal technique such as high-resolution CT venography or digital subtraction angiography may be required as a final arbiter.

CSVT occurs in various clinical settings, including infection, dehydration, renal failure, trauma, cancer and haematological disorder (Barron *et al*., 1992; Carvalho *et al*., 2000; de Veber *et al*., 2001; Heller *et al*., 2003). Many children have multiple risk factors (Heller *et al*., 2003). In our series, clinical risk factors (pre-existing diagnoses and/or infection and/or dehydration) were found in all patients. Although the frequency of septic thrombosis is decreasing, due to antibiotic development, recent studies have shown that it was still responsible for a substantial proportion of thrombosis in older children (Barron *et al*., 1992; Carvalho *et al*., 2000) and in our series there was an infectious trigger in nearly three quarters, in contrast to the much lower proportion in adults (de Bruijn *et al*., 2001). Infection appears to be a particularly common trigger in previously well children, as is microcytosis suggestive of iron deficiency. Before the widespread use of early corrective surgery, CSVT used to be a common complication of congenital cyanotic heart disease, in which it occurred predominantly in patients over 2–3 years of age, usually with iron deficiency (Cottrill and Kaplan, 1973; Phornphutkul *et al*., 1973). Anaemia as an association with CSVT has received little attention in the adult literature (Nagpal, 1983), but iron deficiency anaemia has been described in other children with CSVT (Belman *et al*., 1990; Hartfield *et al*., 1997; Meena *et al*., 2000; Keane *et al*., 2002), sometimes in association with thrombocytosis, and was found in half of this series. In addition, four of our patients had microcytosis without frank anaemia. Anaemia is commonly obscured by relative haemoconcentration in the acute phase and ferritin may be an acute-phase protein, so the diagnosis of iron deficiency should be comprehensively excluded or treated.

In five patients, CSVT occurred in the context of chronic haemolytic anaemia, as has been occasionally described previously (Shiozawa *et al*., 1985). In a recent series of patients with focal neurological deficits in the context of β-thalassaemia major, it was suggested that chronic anaemia might predispose to CSVT (Incorpora *et al*., 1999). Although the diagnosis was not made definitively in that series, the distribution of lesions in those who were imaged would certainly be compatible with CSVT and our series contains one patient with β-thalassaemia and lateral sinus thrombosis. Proven venous sinus thrombosis appears to be relatively uncommon in sickle cell anaemia (Garcia 1990; Oğuz *et al*., 1994; Di Roio *et al*., 1999; van Mierlo *et al*., 2003), although this may be because neuroimaging is delayed because of the priority for emergency exchange transfusion. The radiological diagnosis was not obvious in either of our cases and it is possible that CSVT is missed in sickle cell disease and other chronic anaemias. High erythropoietin levels and the accompanying increase in adhesive reticulocytes might predispose to CSVT in recovering iron deficiency, haemolytic and aplastic anaemias and paroxysmal nocturnal haemoglobinuria, and it is of interest that CSVT has been reported in a patient treated with epoetin alfa (Finelli and Carley, 2000).

Prothrombotic disorders were found in between one-third and half the cases in recent series of paediatric CSVT (Bonduel *et al*., 1999; de Veber *et al*., 2001) and in 62% of our screened patients. Some of these are acquired prothrombotic states, such as acute protein C and S and antithrombin deficiency secondary to infection or protein loss, e.g. in nephrotic syndrome, or antiphospholipid antibodies, and are often normal on repeated investigation. In our series, high factor VIII levels, which may be determined by genetic and acquired factors (Cakmak *et al*., 2003), were common but there were only three cases of acquired antithrombin and one of free protein S deficiency and three patients with anticardiolipin antibodies. Genetic polymorphisms appear to be important as risk factors in adults (Lüdemann *et al*., 1998; Hiller *et al*., 1998; Reuner *et al*., 1998; Cakmak *et al*., 2003) but although there is evidence for an excess of prothrombotic risk factors in paediatric CSVT (Heller *et al*., 2003), the relative importance of the factor V Leiden or prothrombin 20210 mutations is less clear (Bonduel *et al*., 2003; Johnson *et al*., 2003) and none were diagnosed in out series. However, there was a trend for an excess of homozygotes for the thermolabile variant of the methylene tetrahydrofolate reductase gene compared to our control population, as in an adult series of CSVT (Hiller *et al*., 1998). Hyperhomocysteinaemia and its genetic determinants may worth excluding or treating with folic acid, B_6 and B_{12} vitamin supplementation, as this has few risks, but further studies will be important. There are no data on whether longer-term treatment for any of the other prothrombotic disorders reduces the significant recurrence risk (de Veber *et al*., 2001) and international collaboration will be required to address that issue (Heller *et al*., 2003).

Treatment of CSVT has historically involved general supportive or symptomatic measures, such as hydration,

antibiotics for septic cases, control of seizure activity with anticonvulsants, and measures aimed at decreasing intracranial pressure. Antithrombotic therapy of CSVT in childhood has been influenced by clinical trials in adults (Einhaupl *et al*., 1991; de Bruijn and Stam, 1999). De Veber and colleagues initiated a prospective cohort study of anticoagulant therapy in 30 children with CSVT from 1992 to 1996 and reported a mortality rate of 3/8 in untreated compared with 0/22 in treated children (de Veber *et al*., 1998*b*). Anticoagulant treatment was well tolerated, with no extensions of the CSVT. Johnson *et al*. (2003) and Barnes *et al*. (2004) have also reported encouraging data on the safety of anticoagulation in children with CSVT. Our data confirm these observations, with very similar results on safety and likely better cognitive outcome. The development of pseudotumour cerebri may not be influenced by anticoagulation (Higgins *et al*., 2003) but more data are needed for children. Although we observed one fatal haemorrhage in a child with intractable nephrotic syndrome and recurrent CSVT, the other children who died were not anticoagulated and there was no evidence of a detrimental effect. The options for treatment of infants and children include standard or low molecular weight heparin for 7–10 days followed by oral anticoagulants for 3–6 months. Thrombolytic therapy and mechanical thrombectomy are sometimes used for extensive thrombosis of superficial and deep venous structures (Griesemer *et al*., 1994; Soleau *et al*., 2003), but our experience and data from other studies suggest that in the current state of knowledge early anticoagulation would be a better strategy except perhaps in unconscious patients, in whom the mortality is higher, possibly justifying trials of chemical and mechanical thrombolysis (Soleau *et al*., 2003).

CSVT has a variable and sometimes a poor prognosis in adults (Preter *et al*., 1996; de Bruijn *et al*., 2000, 2001; Buccino *et al*., 2003) and children (de Veber *et al*., 2000, 2001). In our series, the positive associations with death in our series were similar to those seen in adults who died or were dependent (de Bruijn *et al*., 2001), although numbers were very small and only coma was statistically related. It is possible that pseudotumour cerebri was underdiagnosed as it is difficult to diagnose in young children, particularly those with learning difficulties; fundoscopy and visual acuity should be checked routinely at follow-up whether or not the child is irritable or complains of headache. Older age, involvement of the lateral and/or sigmoid sinuses and lack of parenchymal abnormality were associated with good cognitive outcome. Further studies documenting long-term neuropsychological evolution (de Schryver *et al*., 2004) are justified.

The proportion of patients with complete and partial recanalization in our series is similar to that reported by the German collaborative group (Heller *et al*., 2003). Our data suggest that some children with chronic conditions, e.g. anaemia or congenital nephrotic syndrome, are at risk of CSVT recurrence over very long periods of time. There have been few studies of the natural history of the thrombosed veins in relation to treatment or clinical outcome, but our data suggest that the venous system may be altered in a way which may predispose to further neurological events in some children, perhaps specifically those with chronic anaemia. It is of interest that iron deficiency may be associated with pseudotumour cerebri in adults (Biousse *et al*., 2003); although there is no evidence for an association in our series, microcytosis was very common and further studies, including the effect of treatment, are required. In adults, there is no evidence that recanalization improves overall outcome (Baumgartner *et al*., 2003; Stolz *et al*., 2004); in this small paediatric series there was no evidence that those with persistent occlusion had worse outcome. However, the effect of permanent occlusion of portions of the venous drainage of the brain, with or without collateral formation, may be different in the developing brain and studies with detailed long-term follow-up are required. In addition, the aetiology of the discontinuity on venography of the lateral and sigmoid sinuses seen in association with intracranial hypertension (Farb *et al*., 2003; Higgins *et al*., 2004) remains to be established and could have its origin in childhood, perhaps in association with relative nutritional deficiency and local infection. As many patients receive antibiotics and perhaps a better diet in the context of the acute illness accompanying CSVT whether or not the vascular diagnosis is made, it may be difficult to prove a link but treatable problems such as iron deficiency, hyperhomocysteinaemia and chronic infection should be looked for in patients with chronic symptoms. The evolution may depend on the extent and location of parenchymal damage, haemoglobin, age and perhaps the rapidity of diagnosis and treatment in the acute phase. Multicentre collaborative studies will be needed to understand the risk factors for death, cognitive sequelae, pseudotumour cerebri and recurrent CSVT and the effects of treatment before acute and long-term management is evidence-based.

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