

Paediatric Cerebral Venous Thrombosis

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Abstract

Cerebral venous thrombosis (CVT) in children is a multifactorial serious disease. It is being increasingly diagnosed, mainly because of more sensitive diagnostic procedures and increasing clinical awareness. The clinical manifestations can be life-threatening and cause long-term neurological deficits. Thromboembolism in children is a multifactorial disorder in which both genetic and acquired risk factors play a role. CVT occurs in various clinical settings, including infection, dehydration, renal failure, trauma, cancer and haematological disorder with multiple risk factors. Clinical manifestations of CSVT are non-specific and may be subtle. 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. CVT can have an extremely variable clinical presentation, mode of onset, imaging appearance and outcome. Its prognosis remains largely unpredictable. Diffusion and perfusion MRI may play a role in detecting venous congestion and CT or MR venography are now the methods of choice for investigation of cerebral venous thrombosis. 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. Specific treatment with anticoagulation is controversial in children, but has been established as appropriate therapy in adults. Anticoagulant treatment with heparin is probably safe and beneficial for children with sinus thrombosis, even those with intracranial haemorrhages.

Introduction

Cerebral venous thrombosis (CVT) in children is a multifactorial disease that, in the majority of cases, results from a combination of prothrombotic risk factors and/or the underlying clinical condition.¹ It is a serious disease that is being increasingly diagnosed, mainly because of more sensitive diagnostic procedures and increasing clinical awareness of the disease. The clinical presentation shows a wide spectrum of symptoms, eg, seizures, papilloedema, headache, lack of consciousness or lethargy, and focal neurological deficits.²

The incidence of cerebral venous sinus (sinovenous) thrombosis (CSVT) is at least 0.67 per 100 000 children per

year, 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.³ 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. 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.^{1,4-6}

Thromboembolism in children is a multifactorial disorder in which both genetic and acquired risk factors play a role. In the first year of life, thrombosis usually occurs either in association with in-dwelling catheters or as renal vein thrombosis. In older children, catheterization remains one of the most frequent risk factors for development of thrombosis.² Additionally, surgery, malignancy, infections, autoimmune disorders, homocysteinuria and trauma have been described as the other contributory risk factors. Although trauma has been shown to be one of the major risk factors for thrombosis in the adult population, only a few publications exist in children. The factor V Leiden (FVL) mutation is the most widely recognized cause of hereditary thrombophilia.^{3,7-9}

Etiology

The importance of genetic and acquired prothrombotic disorders has been emphasized in recent series of paediatric CSVT. However, although single cases of homocysteinuria and severe anaemia have been reported as associations, there are few data on the relative importance of milder anaemia or genetic determinants of hyperhomocysteinaemia both of which might be modified with low risk by nutritional supplementation. High factor VIII levels appear to be associated with CSVT in adults, but factor VIII is not commonly performed in children.⁷

CSVT occurs in various clinical settings, including infection, dehydration, renal failure, trauma, cancer and haematological disorders. Many children have multiple risk

factors. 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. Infection appears to be a particularly common trigger in previously well children, as is microcytosis suggestive of iron deficiency.² 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.

Anaemia as an association with CSVT has received little attention in the adult literature, but iron deficiency anaemia has been described in other children with CSVT, sometimes in association with thrombocytosis, and was found in half of this series.⁴ 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.⁸

Thromboembolic events are known to complicate nephrotic syndrome. Membranous glomerulonephritis is the commonest lesion causing nephrotic syndrome in adults and is most commonly associated with thrombosis. Compared with adults minimal change nephrotic syndrome is the commonest lesion in childhood and has the least risk of thrombosis.¹ Thromboembolic complications occur in 2-5% of children with nephrotic syndrome.² The most commonly affected vessels are deep leg veins, followed by inferior vena cava, renal veins and pulmonary vessels. Involvement of cerebral vessels has been rarely reported in this condition.⁹ Sinovenous thrombosis is probably less recognized or remains an under reported disorder in children with nephrotic syndrome.² Fatal neurological symptoms with sagittal sinus thrombosis, and non-fatal thalamic stroke with sagittal sinus thrombosis and sinovenous thrombosis with associated iron deficiency have been reported in children with nephrotic syndrome. Multiple risk factors are common and the incidence of cerebral venous sinus thrombosis in children with nephrotic syndrome is not known.¹⁰

Factors involved in the development of venous and arterial thromboemboli include events leading to dehydration, renal loss of anticoagulant factors, reactive haematological changes and autoimmune factors. Reactive haematological changes such as thrombocytosis, increased levels of fibrinogen and coagulation factors, and alpha2-anti-plasmin (a major fibrinolytic inhibitor) and loss or deficiency of anticoagulant factors such as plasma antithrombin III, plasminogen and protein S can contribute to thrombosis.⁶ The coagulation inhibitors can be broadly divided into two main

groups, protein C and its activator protein S on the one hand and antithrombin III on the other. Massive proteinuria contributes to urinary loss of anticoagulant proteins.² This results in compensatory increased hepatic synthesis of coagulation inhibitors, and the plasma levels of these proteins are the sum of loss and gain. Both elevation and reduction of protein C and protein S concentrations has been reported in nephrotic syndrome.¹¹

The risk of thrombosis is higher at the onset of the disease or during a relapse where there may be acute intravascular volume depletion. Early recognition of signs of hypovolaemia may help to prevent complications.¹²

Pathophysiology

The origin and pathophysiology of CVT in the paediatric population is still poorly understood, mainly because of its low incidence, which is estimated at 0.67 per 100 000 children. The disease is serious, and predisposing and influencing factors should be unraveled to identify patients at risk and to establish treatment regimens in children.¹¹ Local or systemic infections, vascular trauma, cancer, acute lymphoblastic leukaemia, drug toxicity, lupus erythematosus, nephrotic syndrome, dehydration, asphyxia, maternal problems during pregnancy, Behçet's disease, and metabolic disorders have been described as predisposing factors.⁸⁻¹³

Stroke has certain differences between paediatric patients and adults.

1-it is common in adults, which results in rapid recognition and the potential for early treatment.⁸

2-Vascular occlusive strokes in adults are mostly secondary to arteriosclerosis which is not the case in paediatric patients.

3-There are special properties of haemostatic system during infancy and childhood.

4-There are several developmental differences in the cerebrovascular and neurologic systems.¹⁴

It is important to note that the incidence of thrombotic stroke in children appears to increase. This is probably due to the enhanced sensitive diagnostic tests and surviving of the children with previously lethal diseases such as congenital heart disease, prematurity and acute lymphoblastic leukemia. These factors led the pediatricians to become aware of the problem.¹⁵

Although several causes or potential risk factors exist for the occurrence of stroke in children, in about one third of these patients, no obvious cause or underlying disorder can be diagnosed.¹⁶

The majority of children (65%) have at least two risk

factors with 40% having more than three risk factors.¹⁴ Numerous clinical and environmental conditions leading to a prothrombotic state such as the use of central catheters, trauma, surgery, vessel abnormalities, malignancies, sickle cell disease, autoimmune diseases, cardiac malformations, renal diseases, endocrine disorders, infections etc. were reported.¹⁵ Various prothrombotic disorders particularly affecting the physiological anticoagulant systems have attributable risk for stroke. Prothrombotic disorders can be classified as either congenital or acquired (anticardiolipin antibodies, or Lupus anticoagulants.⁵ Congenital disorders include activated Protein C resistance (APCR) and gene defects. Most common gene defects include G-A transition at nucleotide 1691 in exon 10 of the Factor V gene causing APC resistance and a G-A transition in the 3' untranslated region of the prothrombin gene at nucleotide position 20210 (G-A) which is associated with increased levels of prothrombin activity.¹⁷

Clinical manifestations of CSVT are non-specific and may be subtle. 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, anaemia, diabetes and head injury, may be complicated by CSVT, but as there is difficulty in making the diagnosis, data for incidence remain a minimum estimate.¹² Although presentation with pseudotumour cerebri has been well documented, there are few data on the prevalence of CSVT in otherwise unexplained hydrocephalus or in convulsive and non-convulsive seizures and status epilepticus. CSVT may also be an important determinant of outcome in non-traumatic coma.¹⁸

Cerebral venous thrombosis can have an extremely variable clinical presentation, mode of onset, imaging appearance and outcome. Its prognosis remains largely unpredictable.¹⁹ Intracranial hypertension may be the only manifestation if the thrombus is limited to superior longitudinal sinus or a predominant lateral sinus. Thrombosis of cortical veins, alone or in association with a sinus thrombus causes venous infarction. Partial or complete recovery is possible even with a severe initial presentation emphasizing the need for early diagnosis and treatment.^{15,20} CT scan is usually the first investigation performed on an emergency basis. Although it sometimes detects the hyperdense thrombosed sinus, it usually shows non-specific changes such as hypodensities, hyperdensities and contrast enhancement and in a third of cases it is normal in the first 3 days after clinical onset.²¹ MRI has a sensitivity of 90% and MRI and magnetic res-

onance venography (MRV) together provide diagnosis in all cases.⁴² For a proper interpretation the radiologist needs to be informed about suspected cerebral thrombosis when a scan is being requested.

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.^{11,23}

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.²⁴

Diagnosis

Cerebral venous thrombosis in children is a serious but uncommon diagnosis that can be associated with several underlying systemic conditions. Deficiencies of physiological anticoagulants such as antithrombin, protein C or protein S have been considered as being associated with childhood venous thrombosis. The frequency of protein C and protein S deficiency is 3.8% and 3%, respectively in selected patients with venous thrombosis.⁵

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.¹⁶

Superior sagittal and lateral sinus thrombosis is diagnosed more frequently in most series. However, this may reflect the current difficulties in diagnosing thrombosis in the deep system or cortical veins, 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.¹⁷ As the thrombus becomes less dense, contrast may demonstrate the 'empty delta' sign, a filling defect, in the posterior part of the sagittal sinus. However CT scan with contrast misses the diagnosis of CSVT in up to 40% of patients. 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 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.²⁵

Laboratory

Prothrombotic disorders were found in between one-third and half the cases in recent series of paediatric CSVT. 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.⁶

Genetic polymorphisms appear to be important as risk factors in adults but although there is evidence for an excess of prothrombotic risk factors in paediatric CSVT²⁵, the relative importance of the factor V Leiden or prothrombin 20210 mutations is less clear.¹⁹ Hyperhomocysteinaemia and its genetic determinants may be worth excluding or treating with folic acid, B6 and B12 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 and international collaboration will be required to address that issue.²⁶

Treatment

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.²⁷ 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.¹⁴ Anticoagulant treatment was well tolerated, with no extensions of the CSVT. Johnson et al. have also reported encouraging data on the safety of anticoagulation in children with CSVT and 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 but more data are needed for children.²⁸

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 structures²⁸, 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.²⁴

Specific treatment with anticoagulation is controversial in children, but has been established as appropriate therapy in adults. Anticoagulant treatment with heparin is probably safe and beneficial for children with sinus thrombosis, even those with intracranial haemorrhages. Some studies show that the outcome after sinovenous thrombosis may be less favourable than reported previously and may not be significantly influenced by treatment. A thrombophilia screen to detect a hypercoagulable state including antithrombin III, protein S, protein C, anti-phospholipid antibodies (anti-cardiolipin antibodies, lupus anticoagulant), plasminogen, thrombin time or reptilase time and fibrinogen may be helpful.²⁹ Laboratory should be requested to perform urgent analysis for correctable factor deficiencies such as protein S, protein C and antithrombin III, and preferably a paediatric haematologist should be consulted before initiating therapy with factor replacement using fresh frozen plasma or specific factor concentrate. It is being observed that ATIII level in nephrotic syndrome are decreased due to both increased catabolism and urinary loss. Replacement therapy may be helpful in correcting the thrombophilic state, however as this condition is rare, collaborative international studies are required to optimize the therapy in this condition for any specific interventions.³⁰

References

1. Armstead WM, Cines DB, Higazi AAR. Plasminogen Activators Contribute to Impairment of Hypercapnic and Hypotensive Cerebrovasodilation After Cerebral Hypoxia/Ischemia in the Newborn Pig. *Stroke* 2005;36: 2265-69.
2. Zahuranc DB, Brown DL, Lisabeth LD, Morgenstern LB. Is It Time for a Large, Collaborative Study of Pediatric Stroke?. *Stroke* 2005;36: 1825-29.
3. Canhao P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F, for the ISCVT Investigators. Causes and Predictors of Death in Cerebral Venous Thrombosis. *Stroke* 2005; 36: 1720-25.
4. Stam J. Thrombosis of the Cerebral Veins and Sinuses. *NEJM* 2005; 352: 1791-98.
5. Sebire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain* 2001;128: 477-89.
6. Ochoa R, Goldstein J, Rubin R. Clinicopathological Conference: Lemierre's Syndrome. *Acad Emerg Med* 2005;12:152-57.
7. Ferriero DM. Neonatal Brain Injury. *NEJM* 2004;351:1985-95.
8. Fumagalli, M, Ramenghi, L A, Mosca, F. Palpebral ecchymosis and cerebral venous thrombosis in a near term infant. *Arch. Dis. Child. Fetal Neonatal Ed.* 2005;89:F530-F530.
9. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic Therapy in Children*: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2005;126: 645S-87S.
10. Kuhle S, Mitchell L, Andrew M, Chan AK, Massicotte P, Adams, M, deVeber G. Urgent Clinical Challenges in Children With Ischemic Stroke: Analysis of 1065 Patients From the 1-800-NOCLOTS Pediatric Stroke Telephone Consultation Service. *Stroke* 2005; 37:116-22.
11. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F, for the ISCVT Investigators. Prognosis of Cerebral Vein and Dural Sinus Thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004;35: 664-70.
12. Hankins GDV, Speer M. Defining the Pathogenesis and Pathophysiology of Neonatal Encephalopathy and Cerebral Palsy. *Obstet Gynecol* 2003;102: 628-36.
13. Jaremko JL, Kirton A, Brenner JL. A 12-year-old girl with pharyngitis, meningitis and sinovenous thrombosis. *Can Med Assoc J* 2003;169: 811-12.

14. Heller C, Heinecke A, Junker R, Knofler R, Kosch A, Kurnik K, et al. Cerebral Venous Thrombosis in Children: A Multifactorial Origin. *Circulation* 2003;108: 1362-67.
15. Tormene D, Simioni P, Prandoni P, Franz F, Zerbinati P, Tognin G, et al. The incidence of venous thromboembolism in thrombophilic children: a prospective cohort study. *Blood* 2005; 100: 2403-05.
16. Wu YW, Miller SP, Chin K, Collins AE, LomeliBarkovich AJ, Ferriero DM. Multiple risk factors in neonatal sinovenous thrombosis. *Neurology* 2004; 59: 438-40.
17. Fullerton HJ, Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. *Neurology* 2002;59: 34-39.
18. S. C, Chuang NA. Pediatric Cerebral Sinovenous Thrombosis: Risk Factors and Complications. *Journal Watch Neurology* 2001;10:78-80.
19. Meyer MA, deVeber G, David M, Mitchell L. Cerebral Sinovenous Thrombosis. *NEJM* 2001;345:1777-78.
20. Balcer LJ, Liu GT, Forman S, Pun K, Volpe NJ, Galetta SL, et al. Idiopathic intracranial hypertension: relation of age and obesity in children. *Neurology* 1999; 52: 870-2.
21. Barnes C, Newall F, Furmedge J, Mackay M, Monagle P. Cerebral sinus venous thrombosis in children. *J Paediatr Child Health* 2004; 40: 53-5.
22. Barron TF, Gusnard DA, Zimmerman RA, Clancy RR. Cerebral venous thrombosis in neonates and children. *Pediatr Neurol* 1992; 8: 112-6.
23. Baumgartner RW, Studer A, Arnold M, Georgiadis D. Recanalisation of cerebral venous thrombosis. *J Neurol Neurosurg Psychiatry* 2003; 74: 459-61.
24. Belman AL, Roque CT, Ancona R, Anand AK, Davis RP. Cerebral venous thrombosis in a child with iron deficiency anemia and thrombocytosis. *Stroke* 1990; 21: 488-93.
25. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. *Neurology* 1999; 53: 1537-42.
26. Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. *Am J Ophthalmol* 2003; 135: 437-46.
27. Boncoraglio G, Carriero MR, Chiapparini L, Ciceri E, Ciusani E, Erbetta A, et al. Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis. *Eur J Neurol* 2004; 11: 405-9.
28. Bonduel M, Sciuccati G, Hepner M, Torres AF, Pieroni G, Frontroth JP. Prethrombotic disorders in children with arterial ischemic stroke and sinovenous thrombosis. *Arch Neurol* 1999; 56: 967-71.
29. Bonduel M, Sciuccati G, Hepner M, Pieroni G, Torres AF, Mardaraz C, et al. Factor V Leiden and prothrombin gene G20210A mutation in children with cerebral thromboembolism. *Am J Hematol* 2003; 73: 81-6.
30. Bousser MG, Ross Russell R. Cerebral venous thrombosis. W.B. Saunders; Philadelphia 1997;pp 267-71.