

Outcome in childhood cerebral venous thrombosis—new insights

Original article Kenet G *et al.* (2007) Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. *Lancet Neurol* 6: 595–603

SYNOPSIS

KEYWORDS anticoagulation, cerebral venous thrombosis, children, outcome, recurrence

BACKGROUND

Cerebral venous thrombosis (CVT) in children is associated with considerable mortality and morbidity, but the long-term risk of a second cerebral or systemic venous thrombosis (VT) event has not received much attention in the literature. The effect of predisposing factors on the risk of recurrence is, therefore, unknown, and the guidelines for secondary prophylactic anticoagulation in children with CVT have been adapted from adult protocols.

OBJECTIVE

To determine the recurrence rate of symptomatic VT, and to identify predictors of VT recurrence.

DESIGN AND INTERVENTION

This European cohort study enrolled 396 consecutive patients from Belgium, Germany, Israel and the UK who had a first symptomatic CVT; patients were recruited regardless of the presence of prothrombotic risk factors. The enrollment period was July 1996 to August 2005. CVT was diagnosed using standard imaging methods, i.e. duplex sonography (in neonates only), MRI, and CT or magnetic resonance venography and angiography. Preterm infants and patients older than 19 years were excluded. Acute anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH) was administered to 250 (65%) children. Secondary anticoagulation prophylaxis with LMWH or warfarin was provided in 165 (43%) cases. Surviving patients were followed up for a median of 36 months (range 0.1–85 months). The Cox proportional hazards model was used to evaluate the independent

contributions of age at onset, underlying medical conditions, nonadministration of secondary prophylactic anticoagulation, neuroimaging data, and presence of prothrombotic risk factors to the risk of recurrent VT.

OUTCOME MEASURES

The primary outcome measure was the recurrence rate of symptomatic VT per 1,000 person-years. Secondary outcome measures included the time to relapse and the relevance of clinical, laboratory and radiological risk factors to symptomatic recurrence.

RESULTS

Of the 396 children enrolled, 12 died immediately, so the final analysis included 384 patients (60% boys) with a median age of 5.2 years. A second VT event occurred in 22 of the surviving children, at a median of 6 months (range 0.1–85 months) after the index event. VT recurred only in patients who were older than 2 years (range 2.5–16.2 years) at the index event. The recurrence rate per 1,000 person-years was 21.2 (95% CI 13.9–32.1) for the entire cohort and 29.1 (95% CI 18.9–44.7) for children older than 2 years. The risk of relapse was significantly increased in patients who did not receive anticoagulation before the relapse event (hazard ratio [HR] 11.2, 95% CI 3.4–37.0; $P < 0.0007$), those with persistent occlusion on repeat venous imaging (HR 4.1, 95% CI 1.1–14.8; $P = 0.032$), and those with heterozygosity for the G20210A mutation in factor II (HR 4.3, 95% CI 1.1–16.2; $P = 0.034$). Underlying medical conditions had no effect on VT recurrence.

CONCLUSION

The risk of VT recurrence in children with CVT is increased in those who are older than 2 years, those who do not receive secondary anticoagulation prophylaxis, those who fail to recanalize, and those who have the G20210A mutation in factor II.

COMMENTARY

Rebecca Ichord

Cerebral sinovenous thrombosis (CSVT) is a rare but serious condition affecting 0.7 per 100,000 children annually, with a mortality rate of 3–10% and long-term neurological sequelae in 60% of affected children.¹ The need for evidence-based treatment guidelines specifically for children is related to marked age-dependent changes in hemostasis and cerebrovascular physiology. Current treatment guidelines are consensus-based (Grade 2C), adapted from adult treatment guidelines,² and indicate that it is reasonable to consider acute treatment with unfractionated heparin or LMWH, followed by 3–6 months of LMWH or warfarin.

Two cohort studies of outcome after childhood CSVT describe symptomatic recurrence in 12–13% of 180 long-term survivors followed for a median of 12–18 months after initial presentation.^{3,4} Although these studies were not designed specifically to address predictors of recurrence, they indicated that treatment with anticoagulation influences long-term outcome. The recently published study by Kenet *et al.* provides important new knowledge concerning long-term outcomes of CSVT in childhood that sheds new light on treatment.

Kenet and colleagues have reported the results of a well-designed prospective cohort study of 396 children who were followed up for a median of 36 months. This is the first study of childhood CSVT designed specifically to evaluate risk factors and timing of recurrence. Individuals were well characterized at onset of illness with comprehensive laboratory and radiological diagnostic studies, and there was careful end point evaluation, with radiologic confirmation of recanalization at follow-up. The most important contribution of this study is the finding of increased risk of symptomatic recurrence with age >2 years, a mutation of the prothrombin gene, or persistent venous occlusion on follow-up imaging. These factors could be useful to practitioners when selecting children for long-term treatment. The finding of increased

recurrence risk in children not receiving anti-coagulation at the time of recurrence is more difficult to interpret due to the observational nature of the study and the wide variation in treatment, with long-term (>6 months) anti-coagulation used in as few as 3% and as many as 78% of cases across centers. Marked variation in treatment practices is an important feature of this study, and appropriately reflects the current worldwide state of uncertainty about optimal therapy.

A number of important treatment questions remain unanswered. It is unclear from this study whether, and to what extent, the duration of initial therapy influences the rate of recanalization. As failure to recanalize is an important recurrence risk factor, it would be very helpful to know if early treatment decisions affect the rate of recanalization, and thereby indirectly affect long-term recurrence. As recurrence is low overall (3% in 3 years), one would need to treat a large number of children in order to prevent a single recurrence. Although anticoagulation is generally well tolerated, it is burdensome and costly, and can be associated with hemorrhagic complications. On the other hand, the consequences of recurrence are severe, with a high rate of mortality and morbidity. This study provides important direction for practitioners making these difficult decisions, and also helps to define the rationale and factors to be taken into account when designing a clinical trial for treatment of CSVT in children.

References

- deVeber G *et al.* (2000) Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neural* **15**: 316–324
- Monagle P *et al.* (2004) Antithrombotic therapy in children: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* **126** (Suppl): S645–S687
- deVeber G *et al.* (2001) Cerebral sinovenous thrombosis in children. *N Engl J Med* **345**: 417–423
- Sébire G *et al.* (2005) Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain* **128**: 477–479

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Acknowledgments

The synopsis was written by Martina Habeck, Associate Editor, Nature Clinical Practice.

Competing interests

The author declared no competing interests.

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Received 28 August 2007

Accepted 9 October 2007

Published online

27 November 2007

www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0685

PRACTICE POINT

Children >2 years old with CSVT and the prothrombin gene mutation, or persistent venous occlusion on follow-up imaging, should be considered for long-term anticoagulation and monitored for recurrence through adolescence