

# A common cold is no stroke of luck

## Risk for cerebral ischemia in children

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Chronic and acute (minor) infections or inflammatory conditions are associated with an increased risk for cerebral ischemic stroke in adults.<sup>1–3</sup> Stroke etiology is different in children, is probably multifactorial, and may be elusive. Minor infections are common in children and lead to similar systemic and especially prothrombotic changes as in adults. Because conventional vascular risk factors are less prevalent in children, inflammatory conditions may be more relevant contributors to stroke risk in children. However, data on the association of inflammation and pediatric stroke are scarce. In this issue of *Neurology*®, Hills et al.<sup>4</sup> present their work on the association of minor infections with the risk of stroke in children.

In this nested case-control study, Hills et al.<sup>5</sup> used data from the large Kaiser Pediatric Stroke Study (1993–2007), which represented about 2.5 million children within 1 health care organization in California. They performed a rigorous medical record and imaging review, identifying 102 non-neonatal children with ischemic stroke without associated major infection and matching them with 306 control children without stroke. They screened for evidence of minor infections up to 2 years prior to the index event. They identified a strong association between infection (doctors' visits for signs of infection) and subsequent stroke within 3 days with a remarkable odds ratio of 12.1. By contrast, the cumulative number of infections over a 2-year period was not associated with stroke risk. The authors concluded that minor infections seem to have a short-lived but notable effect on pediatric stroke risk and speculate about possible pathophysiologic mechanisms, which ultimately are uncertain.

This well-conducted, yet retrospective, study provides interesting and novel information on an issue that so far has not been addressed in detail. With the advantage of accessing a very large dataset in a well-defined population with a well-established methodology, the authors could add consolidated findings about a fortunately rare condition. However, the retrospective nature of the study poses some limitations. First, many children will not have sought medical

attention for minor infections, underestimating the true exposure. Second, no laboratory tests were available in order to assess the individual infectious burden. Third, no information on possible nonprescription medication use with possible antithrombotic effects could have been collected.

The same study group produced some interesting data previously on the link between infection and childhood stroke, which was the motive for conducting the current study.<sup>5</sup> That work showed that minor infections were an independent risk factor for pediatric ischemic stroke in the same large cohort. In the current study, the authors provide important information that was missing in that earlier study, especially regarding timing and number of infections.

It is not surprising that inflammatory processes contribute to a higher risk for ischemic stroke in children because this has already been shown in several studies in adults. Classical risk factors such as hypertension, diabetes, and atrial fibrillation, responsible for the majority of strokes in adults, are much less frequent in children. Hence, it can be speculated that inflammatory conditions contribute more to the stroke risk in children. Nevertheless, in many children completely different factors like congenital heart disease, hematologic problems, or metabolic disorders are important.

There is an ongoing and lively discussion about why inflammatory processes play an important role in the development of thromboembolic events. Research in this area is heterogeneous and ranges from measuring platelet activity<sup>6</sup> to examining arteriosclerotic plaques and exploring possible endothelial damage.<sup>7</sup> Due to its design, the current study by Hills et al. cannot clarify the underlying pathophysiology, but it provides some interesting possibilities that are worth pursuing. Inflammatory long-term effects requiring many years to develop can hardly be expected to have an effect in children. In fact, no evidence of an association between a cumulative effect of infections over the years and ischemic stroke was demonstrated in the current study. This and the relatively short time period in which the risk seems to be

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increased after infection suggests the particular mechanistic importance of acute prothrombotic effects, a finding that might also be important in adults. Much more work is needed to fully understand the connection between inflammation and stroke, both in children and adults.

It is difficult to discern a direct effect on practice based on these results. Minor infections are common in children; strokes are rare. In this respect, despite these findings there is no reason to be alarmed if a child catches a simple cold, a point worth emphasizing to parents. Furthermore, without additional scientific evidence, these data should not lead physicians to treat all minor infections immediately with antibiotic or anti-inflammatory medications. This could cause more harm than good.

In general medicine as in stroke, this vital knowledge applies: children are not small adults. Nevertheless, it is important to recognize the similarities as well as the differences, as this study points out.

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#### REFERENCES

1. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nat Rev Neurol* 2010;6:681–694.
2. Bornstein NM, Bova IY, Korczyn AD. Infections as triggering factors for ischemic stroke. *Neurology* 1997;49(suppl 4):S45–S46.
3. Grau AJ, Bugge F, Becher H, et al. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. *Neurology* 1998;50:196–203.
4. Hills NK, Sidney S, Fullerton HJ. Timing and number of minor infections as risk factors for childhood arterial ischemic stroke. *Neurology* 2014;83:890–897.
5. Hills NK, Johnston SC, Sidney S, Zielinski BA, Fullerton HJ. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. *Ann Neurol* 2012;72:850–858.
6. Marquardt L, Ruf A, Mansmann U, et al. Course of platelet activation markers after ischemic stroke. *Stroke* 2002;33:2570–2574.
7. Jickling GC, Chaturvedi S. Carotid plaque inflammation in stroke assessed by PET: a burning issue? *Neurology* 2014;82:1672–1673.