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Maternal risk factors for neonatal ischaemic stroke

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This commentary is on the original article by Mann et al. on pages 58–64 of this issue

Mann et al.[1] give important insight into the risk factors and possible pathophysiology not only on ischaemic neonatal stroke (becoming symptomatic during the neonatal period), but also congenital ischaemic stroke (evolving during the first year of life). By analyzing these two entities in parallel they give some answers as to whether we have two different entities here or a similar entity becoming symptomatic at different times. Although neonatal and congenital ischaemic stroke are associated with considerable lifetime burden, their aetiology is still a matter of debate.[2] Various articles have reported risk factors associated with neonatal stroke (some of them also for congenital ischaemic stroke), but most studies were rather small and lacked a comparison group. Reported risk factors for ischaemic neonatal and ischaemic stroke included prothrombotic states, acute systemic illness, infection, cardiopathy, maternal and obstetrical factors, and placental pathology.[2]

The study of Mann et al. is important, as the authors have linked maternal and infant information of a huge retrospective dataset of 226 117 patients, analyzing differences between mothers and children with and without neonatal/congenital ischaemic stroke. The main aim was to assess maternal conditions associated with neonatal/congenital ischaemic stroke. Their hypothesis, that maternal hypertension, intrapartrum fever, and diabetes were significantly associated with the odds for neonatal/congenital ischaemic stroke, could only be confirmed in the first two. This points to the importance of monitoring and potentially treating these risk factors suspiciously. Considering the many missed diagnoses of ischaemic strokes during the neonatal period, the study also underlines the importance of closely monitoring these infants after birth. Besides maternal conditions, this study also provides important information on infant characteristics which should increase the vigilance on diagnosing possible ischaemia early on; birth trauma, birth asphyxia, sickle cell disease/trait, thrombophilia, and neonatal and congenital infections. Confirmation of these results are given in two recently published articles: Kirton et al.[3] published a large series of 347 infants diagnosed with neonatal stroke. Besides birth complications, neonatal comorbidities, and prothrombotic diseases, this study also reported gestational hypertension and/or preeclampsia in 10% of the cases. A recent case control study report from the Netherlands confirmed the importance of maternal fever in association with neonatal stroke; further risk factors were low Apgar score, hypoglycaemia, and early onset sepsis/meningitis.[4] All studies support the theory that neonatal and congenital ischaemic stroke have to be considered a multiple risk problem and that some important maternal and infant risk factors might be positively influenced.

Although the study of Mann et al. provides very important insights on the association between maternal and infant risk factors and neonatal/congenital ischaemic stroke, their pathophysiology and the interactions between single risk factors remain unclear. The study strengthens the concept that maternal medical conditions play a role in the pathogenesis of neonatal/congenital ischaemic stroke, but does not provide a causative explanation. Maternal hypertension might lead to a structural alteration of placental vessels which could result in the formation of clots. On the other hand, inflammatory processes in the mother could induce chorioamnionitis, which might lead to thrombus formation in the placenta and – by embolism to the fetal circulation and passing the foramen ovale – might lead to ischaemic infarctions in the newborn infant's brain. The co-occurrence of maternal and neonatal risk factors associated with neonatal/congenital ischaemic stroke raises the question of whether birth complications and neonatal comorbidities in infants with neonatal/congenital ischaemic

stroke are mainly the result of impaired neurological function due to an ischaemia to the newborn infant's brain occurring before or during the delivery. In contrast, other processes taking place later during the neonatal period – such as inflammatory processes, changes in cerebral blood flow, metabolic changes, etc. – might mainly be responsible for the ischaemic lesions. Consecutively, it also remains unclear whether birth complications and asphyxia are mainly the result of a prenatal/perinatal event or may independently increase the risk for neonatal/congenital ischaemic stroke. Thus the question regarding the 'chicken or the egg' in the pathogenesis of neonatal stroke is still open and leaves opportunity for future research.

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Childhood basilar artery thrombosis: reassuring outcomes in younger patients

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Basilar artery occlusion (BAO) and associated brainstem arterial stroke (BAS) are a dreaded subtype of arterial ischemic stroke (AIS) because they are associated with a very high frequency of death and disability in adults. Outcomes in children with this subtype of stroke are not known.

In their study, Goeggel Simonetti et al.[1] report outcome data in 90 children with BAO/BAS. The authors combined outcomes from seven children with BAO in the Swiss Pediatric Stroke Registry with outcomes from 83 cases pooled from the published literature. Among these 90 children with BAO/BAS overall mortality was 8% while another 35% survived with a modified Rankin Scale score of 4 or above, and an overall 'poor outcome' frequency of 43%. Comparative outcome data from 619 adults with BAO participating in the Basilar Artery International Cooperation Study (BASICS) study[2] are 39% mortality, 31% surviving with a modified Rankin Scale score of 4 or above, and an overall 'poor outcome' frequency of 70%. Based on these data adults with BAO are twice as likely to have a poor outcome as children (χ^2 $p<0.001$; RR=1.89, CI 1.57–2.2; authors' calculations).

Clearly, children with BAO have much better outcomes than adults with BAO. This difference is important given that children in the Goeggel Simonetti et al. study were treated mainly with conservative approaches: fewer than 20% received intra-arterial thrombolytic medication (tPA: 16 of 96 children) or endovascular mechanical treatment (two cases). In contrast, in the BASICS study over half of the adults (328/619) received intra-arterial tPA or endovascular mechanical treatments.

The Goeggel Simonetti et al. study underlines the importance of considering the differences in the risks and benefits of stroke therapies in children compared with adults. The goal of acute endovascular therapy in AIS is to restore perfusion to the ischemic brain by prompt recanalization of the occluded artery. Risks of hemorrhagic conversion and reperfusion injury increase with increasing time from stroke onset. Intravenous tPA up to 4.5 hours post-onset has proven beneficial and evidence strongly supports intra-arterial tPA up to 6 hours post onset. Currently, mechanical thrombolysis treatments are frequently provided in adults with acute AIS. However, the efficacy of the latter approach remains unproven in adults. Increasingly, adult stroke treatments are applied to the pediatric stroke population. This is not necessarily appropriate. It is important to consider any novel treatment including endovascular device approaches in the light of age-specific risks and benefits. Given that traditional treatments are associated with much better outcomes in children compared to adults, novel treatments that are justifiable in adults are less likely to be of sufficient added benefit in children to offset the risks.

Several individual case reports and small case series of endovascular treatment have been reported in children with acute AIS in various vascular territories, including BAO.[3] Among 35 reported pediatric AIS cases with endovascular treatment, the mean age was 11 years (range 2–18y);