Neonatal encephalopathy: etiology and outcome

The original study by Badawi et al.1,2 investigated risk factors for neonatal encephalopathy (NE) and/or neonatal seizures in term infants. They used a broad definition appropriate for examining etiology and capable of asking such questions as: what proportion of NE arises after birth asphyxia? The answer was: some, but not much. That study was, and still is, the only large population-based investigation of multiple potential risk factors for NE, and it identified novel risk factors such as maternal thyroid disease, family history of seizures, and placental abnormalities. Several of these factors have been found to be risk factors for NE, neonatal seizures, or cerebral palsy (CP) in other studies.

Among the novel risk factors for NE previously identified by Badawi et al. was a history of maternal treatment for infertility. A recent paper noted that maternal history of infertility was a strong risk factor for perinatal ischemic stroke.3 Thus, a potentially important pathway to adverse outcome, perhaps modifiable to reduce risk, was identified in the original report.

The new paper from Badawi et al.4 is about outcome at 5 years of age in children who survived NE. Of children with moderate or severe NE, as defined by the authors, 87% did not develop CP (which might suggest that the diagnosis included too many mildly affected children); and three-quarters of children with CP were not obviously neurologically ill in the neonatal period (which does not suggest that the diagnosis of NE was too inclusive). These findings are in general agreement with an earlier and more limited population-based study.5 We have a long way yet to go in identifying specific etiologies for both NE and CP.

The authors stress that CP in children who had had moderate or severe NE was more often severely and multiple disabling than CP in children who had not had NE. Aside from brain malformations, we know fairly little about causes of CP in infants who were apparently neurologically well in the early days of life. However, there is new evidence: perinatal stroke is a common cause of CP, and the majority of children with CP due to perinatal stroke are not encephalopathic at birth.6 Some children with CP without prior NE had perinatal stroke, a diagnosis that requires neuroradiologic confirmation. Studies are needed that will connect the dots, putting together maternal characteristics, neonatal state, brain imaging findings, and outcome, to provide information on pathways to disability.

Among things which the current study by Badawi et al. did not do was to examine whether outcome differed according to the presence or absence of the previously-identified risk factors. Nor did this study include neuroimaging information, nor whether other neurologic diagnoses have emerged in these children or their close relatives in the years since the original study was performed.

One reason for being interested in etiology is that knowledge of causal pathways is critical to the development of effective strategies for prevention. Another reason is that cause may influence outcome as, for example, neonatal seizures due to hypocalcemia have a different outlook from those due to meningitis or brain malformation. Now that there is an intervention (hypothermia) that may reduce brain injury in term infants with moderate NE,7 it may be more important than ever to know whether and how etiology of NE influences prognosis. If it does so there will be a need to take major causal factors into account in the design and interpretation of clinical trials, and in counseling families.

The original study by Badawi et al. was the first large controlled study of risk factors for NE. As the toll in lifelong disability following NE is high, there is need for additional controlled studies that will cast an even wider net in investigating the antecedents and outcome of this disorder.

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References