

Neonatal Hypoglycemia: Role in Infantile Epilepsy

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Hypoglycemia remains a significant cause of brain injury in newborn infants(1), as highlighted by Udani, *et al.*(2) in this issue of *Indian Pediatrics*. The authors recruited 100 consecutively presenting infants with epilepsy, 83 of whom had brain imaging and/or a clear metabolic or genetic diagnosis. The majority of the 83 infants had evidence of brain injury of perinatal onset and in the largest subset of these, the injury pattern suggested hypoglycemia as a cause. Genetic, metabolic and documented postnatal causes constituted a much smaller group. Infants with acute symptomatic seizures, those without available imaging and those with uncertain age of epilepsy onset were not included; it would have been informative to know the number of children excluded to have a better understanding of how representative was the study cohort. It is somewhat surprising that only eight children had imaging evidence of acute perinatal hypoxia-ischemia; perhaps these are under-represented as their difficulties had been known from birth and the cause of seizures was already clear.

Burns, *et al.*(3) recently reported on the spectrum of neonatal MR imaging abnormalities in term-born infants having symptomatic neonatal hypoglycemia; these included arterial territory stroke, white matter change that was not confined solely to posterior parietal and occipital lobes, focal hemorrhage and also a diffuse increase in signal on T1-weighted imaging in the globus pallidum.

Of note is that the white matter findings associated with neonatal hypoglycemia can be subtle such that they might not be easily seen on imaging carried out after the neonatal period. In the present

study, 9 infants with hypoglycemia were not thought to have typical imaging patterns and hence were not included in that etiological category, potentially underestimating the contribution of hypoglycemia in their cases, as also pointed out by Udani, *et al.*(2). On the other hand, the injury pattern typically described in hypoglycemia is not pathognomonic and it is a concern that etiology was based, for many infants, solely on the imaging characteristics without confirmatory biochemistry – this may have resulted in an overestimate of the contribution of hypoglycemia to later epilepsy in some infants.

Typically, hypoglycemia does not affect the posterior putamen and ventrolateral thalamic nuclei or the main motor tracts as is seen with acute perinatal hypoxic-ischemic injury. The authors also found a striking lack of severe spasticity and dystonia in the infants with epilepsy following neonatal hypoglycemia. The more diffuse signal in the globus pallidum is different. It has been reported by Barkovich, *et al.*(4) and may be seen in a variety of conditions including mitochondrial problems, perhaps reflecting the effects of hypoglycemia on mitochondrial activity(5).

Interestingly, 9 children had stroke. Stroke has been reported in preterm(6) and term(3) infants with hypoglycaemia. However, the association was not explained in either of these studies. It is possible, at least in the term infant, that the stroke affected feeding resulting in secondary hypoglycemia.

Udani, *et al.*(2) compared the perinatal characteristics of infants with hypoglycemic injury to those with epilepsy due to developmental disorders arguing that these infants were least likely to have immediate perinatal problems. However

these infants are also more perinatally vulnerable and have a higher risk of being small and not feeding well, so this approach, though understandable, may have underestimated the differences between the hypoglycemic group and normal controls. Interestingly two-thirds of their infants were male; Burns, *et al.*(3) also found more males compared to controls supporting the observation in many domains of male vulnerability(7).

This study suggests that for infants presenting with epilepsy in early childhood evidence for neonatal hypoglycemia should be sought. Epilepsy of varying severity following hypoglycemia has been reported by others(8,9) as have learning deficits including severe mental retardation, microcephaly, visual impairments, behavioural problems, and autistic spectrum behavior(8-12). Udani, *et al.*(2) highlight an association with apraxia. Microcephaly and delay in visual maturation or other visual abnormality are features that can be looked for early after neonatal hypoglycemia and may serve as markers of later presenting difficulties – most children do not have severe cerebral palsy and longer term neuro-developmental follow up is needed to ensure the early detection of the learning, behavioral and other difficulties that are not easy to evaluate in the first months after birth.

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