Neurology Asia 2011; 16 (Supplement 1) : 17 – 19

Epilepsies due to perinatal brain injuries: Focus on prevention

Vrajesh Udani

PD Hinduja National Hospital & Medical Research Centre, Mumbai, India

Abstract

Epilepsy due to perinatal brain injury remains an important problem in developing countries. Brain injury can be prominent in perinatal asphyxia, neonatal hypoglycemia, sepsis- meningitis, late hemorrhagic disease of the newborn and perinatal ischemic arterial stroke. The types of epilepsy and a focus on possible prevention in each condition is discussed.

Epilepsy is a major neurological burden affecting 0.5-1% of the population. Risk factors identified in case control studies from the developing nations in Asia, the Middle East and Africa[1,2,3] suggest perinatal risk factors being an important contributor to the epilepsy burden vis-à-vis studies from the developed world where familial factors, malformations and febrile seizures are more important.[4-7] This contribution is even more significant in the childhood epilepsies.[3,6] Conceptually perinatal risk factors often underlie a neonatal encephalopathy with or without seizures which then either resolves without epilepsy as a sequel or goes on to develop remote symptomatic epilepsy after a variable latent period. During this time the process of epileptogenesis marches ahead and is often associated with an epileptiform EEG. Often cognitive, motor and other deficits compound the problem and in an unfortunate few an epileptic encephalopathy develops adding to the final disease burden.

Risk factors with a high propensity of later development of epilepsy include severe perinatal asphyxia, hypoglycemic brain injury and perinatal arterial ischemic stroke with an ~ 50% risk of developing remote symptomatic epilepsy. Periventricular leukomalacia – a pathology often seen in preterms and late hemorrhagic disease of the newborn (due to vitamin K deficiency) carry a moderate risk of about 25% while neonatal meningitis, bilirubin encephalopathy, mild-moderate perinatal asphyxia and intraventricular hemorrhage (especially in preterms) carries a mild risk of remote symptomatic epilepsy.

The nature of the epilepsies following perinatal brain injuries was studied in 62 children at our tertiary center in Mumbai (Udani, unpublished data). About 75% had a history of neonatal encephalopathy and the median age of epilepsy onset was only one year. Epileptic spasms were seen in about a 1/3 while Lennox-Gastaut syndrome developed in about 5% highlighting the high prevalence of epileptic encephalopathy in this group. Another common seizure type encountered in hemiplegic / quadriplegic children were reflex audiogenic / somatosensory epilepsies. The epilepsy was refractory in about 40% while three or more antiepileptic drugs were used in about a third. Almost a third had motor deficits while about half had mental and or visual disability.

The severity of the hypoxic-ischaemic encephalopathies decided the risk of epilepsy with no increased risk for mild, about 15% risk for moderate and about 50% risk for severe hypoxic-ischaemic encephalopathies where motor co-morbidity was almost universal. Electronic fetal monitoring is routine in all developing countries and may reduce the risk of severe hypoxic-ischaemic encephalopathies. However, experience in developing nations like India is limited as the vast majority of deliveries in rural areas is at home. Response time is less than adequate even if electronic fetal monitoring is done as was shown in a South African survey.[8] Recent studies[9] have shown that moderate hypothermia within 6 hrs of birth reduces neurologic morbidity significantly, though effects on the risk of epilepsy have not been studied adequately. Another less technologically demanding intervention might be parenteral magnesium sulfate which has improved short term outcome in hypoxic-ischaemic encephalopathies patients.[10]

A hidden epidemic of neonatal hypoglycemia associated brain injury is raging on in India and

Address correspondence to: Dr. Vrajesh Udani MD, Consultant- Child Neurology & Epilepsy, P.D. Hinduja National Hospital & Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai 400 016. India. Tel.No.:+91 22 24447206/24447216(Sec), Fax.No.:+91 22 24440425

is responsible for many infants and children with remote symptomatic epilepsy.[11] Mild injuries have little disability besides the occipital epilepsy but the more common moderate to severe injuries often have refractory epilepsy / epileptic encephalopathy with visual impairment, autism/ mental retardation and a characteristic apraxia of hand use. Tone abnormalities are rare. In a study of infantile remote symptomatic epilepsy 23% of patients had seizures due to neonatal hypoglycemic associated brain injury.[11] On analysis of risk factors caesarian delivery, poor feeding and low birth weight were strongly associated. In a study from South India similar risk factors were confirmed along with a delay in establishment of feeding.[12] Caesarian deliveries are often associated with this sue to maternal pain / sedation etc. Our own survey of feeding histories of our patients revealed that >80% of babies did not establish feeding on day one. Often physicians insist on exclusive breast feeding even in situations where it is not established and result in the baby being starved and finally ending in a hypoglycemic encephalopathy. Proposals to prevent this unfortunate chain of events is to establish feeding in normal weight babies by 6 hours and in low birth weight babies by 2 hours, monitor feeding closely in hospital and avoid early discharge in low birth weight newborns and finally when there are delays is establishment of breast feeding, allow temporary use formula milk.

Neonatal sepsis, with and without meningitis wrecks havoc to the brain in developing countries. Though post-meningitis epilepsy has a generally lower risk (<5%) of epilepsy and cognitive problems in developed countries[13], in India the experience is much more dismal. Often neonatal meningitis remains undiagnosed for several weeks in the neonatal period being transiently suppressed by the routine antibiotic overuse that characterizes medical practice in our nurseries. Also there is a general anathema to allowing a CSF amongst Indian patients. Many of these infections localize and persist in the ventricles leading to aqueductal obstruction and hydrocephalus in a few weeks to months.[14] Often shunts are placed without CSF sampling complicating matters further. At the end of it all a horribly damaged brain with all its morbidities including epilepsy persists in about 2/3 of the survivors. Sepsis even without meningitis can induce cytokine-mediated white matter injury in preterm newborns leading to periventricular leukomalacia with all its attendant morbidities. Preventing sepsis – mediated brain injury is a tall order as it would involve optimal neonatal care in a country where deliveries in rural areas are at home and decent neonatal care is often several hundred miles away without optimum transport availability for newborns. Also good clinical practices like early CSF examination in sepsis and rational use of antibiotics require changing of mindsets of large number of physicians. A start has been made in Gadchiroli, central India where Bang and co-workers trained local village health workers to recognize and treat sepsis with IM antibiotics and reduced mortality from about 17% in control villages to about 3% in intervention villages.[15] Another promising intervention to reduce cystic periventricular leukomalacia might be antenatal steroids given to the mother in preterm labor.[16]

Another very preventable brain-damaging event in the neonatal period and early infancy is late hemorrhagic disease of the newborn caused by vitamin K deficiency. The risk factors for this catastrophic encephalopathy include exclusively breast fed infants, maternal use of drugs like anti-epileptics, acute gastrointestinal illness and use of broad-spectrum antibiotics.[17] The already precarious levels of breast-fed infants can dramatically reduce leading to intracranial hemorrhage. About a third die and another third develop epilepsy. This disorder is almost eliminated with routine IM vitamin K at birth. Special circumstances like use of antibiotics may need additional doses.

The last important contributor of perinatal morbidity is perinatal arterial ischemic stroke. This usually occurs in the middle cerebral artery territory before birth but after 28 weeks. Clinically this may present with neonatal seizures or as a delayed recognition of hemiplegia. About two-thirds develop epilepsy and about a quarter have severe refractory epilepsy. Though focal motor seizures are predominant, spasms are seen in about 8%.[18] About 60% have a hemiplegia. The risk factors like maternal chorioamnionitis, fetal / maternal thrombophilia and congenital cardiac defects are difficult to modify.

In summary, perinatal brain injuries are significant contributors to the burden of epilepsy in the developing world. Early onset refractory epileptic spasms and focal seizures predominate. Quality of life is further compromised by associated co-morbidities like mental retardation, autism and cerebral palsy. Easily modifiable risk factors like hypoglycemia, late hemorrhagic disease of the newborn need urgent attention while more complex risk factors like hypoxic-ischaemic encephalopathies and periventricular leukomalacia will need more innovative solutions.

REFERENCES

1. Kannoth S, Unnikrishnan JP, Santhosh Kumar T, *et al*. Risk factors for epilepsy: a population-based case-control study in Kerala, southern India. *Epilepsy Behav* 2009; 16(1):58-63.
2. Daoud AS, Batieha A, Bashtawi M, *et al*. Risk factors for childhood epilepsy: a case-control study from Irbid, Jordan. *Seizure* 2003; 12(3):171-4.
3. Edwards T, Scott AG, Munyoki G, *et al*. Active convulsive epilepsy in a rural district of Kenya: a study of prevalence and possible risk factors. *Lancet Neurol* 2008; 7(1):50-6.
4. Casetta I, Monetti VC, Malagù S, *et al*. Risk factors for cryptogenic and idiopathic partial epilepsy: a community-based case-control study in Copparo, Italy. *Neuroepidemiology* 2002; 21(5):251-4.
5. Rocca WA, Sharbrough FW, Hauser WA, *et al*. Risk factors for generalized tonic-clonic seizures: a population-based case-control study in Rochester, Minnesota. *Neurology* 1987; 37(8):1315-22.
6. Nelson KB, Ellenberg JH. Antecedents of seizure disorders in early childhood. *Am J Dis Child* 1986; 140(10):1053-6.
7. Sidenvall R, Heijbel J, Blomquist HK, *et al*. An incident case-control study of first unprovoked afebrile seizures in children: a population-based study of pre- and perinatal risk factors. *Epilepsia* 2001; 42(10):1261-5.
8. Buchmann EJ, Pattinson RC. Babies who die from labour-related intrapartum hypoxia: a confidential enquiry in South African public hospitals. *Trop Doct* 2006; 36(1):8-10.
9. Edwards AD, Brocklehurst P, Gunn AJ, *et al*. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 2010; 9;340:c363.
10. Bhat MA, Charoo BA, Bhat J, *et al*. Magnesium sulfate in severe perinatal asphyxia: A randomized, placebo-controlled trial. *Pediatrics* 2009; 123;e764-e769.
11. Udani V, Munot P, Ursekar M, *et al*. Neonatal hypoglycemic brain Injury - A common cause of infantile-onset remote symptomatic epilepsy. *Indian Pediatr* 2009: 46: 127-32.
12. Sasidharan CK, Gokul E, Sabitha S. Incidence and risk factors for neonatal hypoglycaemia in Kerala, India. *Ceylon Med J* 2004; 49(4):110-3.
13. Stevens P, Eames M, Kent A, et al. Long term outcome of neonatal meningitis *Arch Dis Child Fetal Neonatal Ed* 2003;88:F179–F184.
14. Udani V, Udani S, Merani R, *et al*. Unrecognised ventriculitis/meningitis presenting as hydrocephalus in infancy. *Indian Pediatr* 2003; 40(9):870-3.
15. Bang AT, Bang RA, Baitule SB, *et al*. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet* 1999; 354(9194):1955-61.
16. Baud O, Foix-L'Helias L, Kaminski M, *et al*. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Engl J Med* 1999; 341(16):1190-6.
17. Pansatiankul B, Jitapunkul S. Risk factors of acquired prothrombin complex deficiency syndrome: a case-control study. *J Med Assoc Thai* 2008; 91(Suppl 3):S1-8.
18. Golomb MR, Garg BP, Carvalho KS, Johnson CS, Williams LS. Perinatal stroke and the risk of developing childhood epilepsy. *J Pediatr* 2007; 151(4):409-13.