RESEARCH PAPER

Neonatal Hypoglycemic Brain Injury - A Common Cause of Infantile-onset Remote Symptomatic Epilepsy

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Objectives: To study the etiology of remote symptomatic epilepsy with onset in the first 3 years of life. Patients with neonatal hypoglycemic brain injury (NHBI), were further studied for risk factors and clinical features.

Methods: The study was conducted at a tertiary pediatric neurology service between May-August 2004. Consecutive patients were recruited prospectively. The probable etiological diagnoses were based primarily on cranial imaging. Two radiologists, blinded to the etiological diagnosis, reviewed the cranial imaging and suggested the likely etiology based on published imaging criteria. There were three categories i.e, (*i*) perinatal encephaloclastic conditions (PEC) e.g., hypoxic ischemic encephalopathy (HIE) etc, (*ii*) developmental (DV) e.g., tuberous sclerosis, etc and (*iii*) postnatal (PN) e.g., trauma, etc. Three risk factors (birth weight, type of delivery, feeding difficulty) were compared between NHBI and developmental etiology (DV) groups. Neurological findings were compared between the NHBI *vs* the other perinatal groups. Seizure details were studied only in the NHBI group.

Results: 63 boys and 37 girls were recruited. Mean age of seizure onset was 13.9 months. PEC were seen in 50 patients, DV in 28 patients and PN in 5. NHBI was seen in 23 patients and was the most frequent cause of epilepsy. Low birth weight (LBW), neonatal feeding difficulties and cesarean delivery were significant risk factors for NHBI *vis-à-vis* the DV group. Microcephaly, autism, visual impairment and apraxia of hand use were common while spasticity or dystronia were rare in NHBI. Spasms were the commonest seizure type.

Conclusion: Neonatal hypoglycemia is the most common etiology of remote symptomatic infantile onset epilepsy. LBW, poor neonatal feeding and cesarean delivery are significant clinical correlates.

Keywords: *Epilepsy, Etiology, Hypoglycemia, Infant, Seizure.*

Epilepsy has its highest incidence in infancy(1). At this time a unique interface exists between normal brain maturation and the epilepsy, which may have profound effects on the infant's cognitive development. The etiology of infantile remote symptomatic epilepsy is different from those at other ages. In developed countries these appear to be mainly developmental disturbances of cortical architecture *i.e.,* cortical dysplasias (CDs), agyria-pachygyria complex, tuberous sclerosis (TS) *etc*.(2,3). Experience from developing nations(4-9) and past studies from many developed nations(10) implicate perinatal encephaloclastic (PE) (brain-damaging) conditions as major contributors for remote symptomatic epilepsy, especially for West syndrome. Neonatal hypoglycemic brain injury (NHBI) seemed to be an important risk factor in the 1960s in Finland; however it ceased to be a risk factor in a subsequent study by the same authors(10).

Initially we determined the probable etiology of remote symptomatic epilepsy with onset within the first three years of life. We then studied the patients with probable NHBI in greater detail as an extension of the first study as this was found to be the single most frequent cause.

METHODS

The study was conducted in the child neurology section at a tertiary care outpatient service in a large metropolitan Indian city between May-August 2004. Consecutive patients were prospectively recruited if they had onset of remote symptomatic epilepsy (RSE) in the first three years of life. Only those with imaging documented lesions or confirmed genetic/ metabolic disorders underlying their epilepsy were included. Children with acute symptomatic seizures, patients without available imaging and where the age of seizure onset was not clear were excluded. Seizure details, developmental milestones, and response to therapy were obtained from the primary caregiver and supplemented with available records. Gestational age, birthweight, presence of encephalopathy (defined as a combination of seizures, altered sensorium) and the day it occurred, feeding difficulties, mode of delivery and details of laboratory investigations were specifically noted in the perinatal history.

Two radiologists, blinded to the clinical history, reviewed the cranial MRIs or CTs and suggested a probable etiological diagnosis, using standard imaging criteria. Whenever required new imaging (usually MRI) was performed. The criteria used were previously published criteria for diagnosis of PEC *i.e*. NHBI(11,12), periventricular leucomalacia (PVL)(13) HIE(14), focal infarcts(FI) and others *e,g.*, disproportionate involvement of parietal and occipital cortices and sub-cortical white matter lesions are the hallmark of neonatal hypoglycemia(11,12) (***Fig.*1**) while white matter hyperintensity with or without loss of white matter and ventriculomegaly is typical of PVL (***Fig.* 2**)(13). The kappa coefficient was determined to quantify the degree of inter-observer variation.

The study patients were ascribed a 'probable etiological diagnosis' based primarily on the imaging findings. The three etiological categories were (1) Perinatal enceplialoclastic conditions (PEC) *e.g.,* HIE, NHBI, PVL, FI; (2) developmental (DV) *e.g.,* tuberous sclerosis (TS), cortical dysplasia (CD), metabolic, and (3) postnatal (PN) *e.g.,* trauma, meningitis. The diagnosis was regarded as confirmed only if both radiologists concurred. In

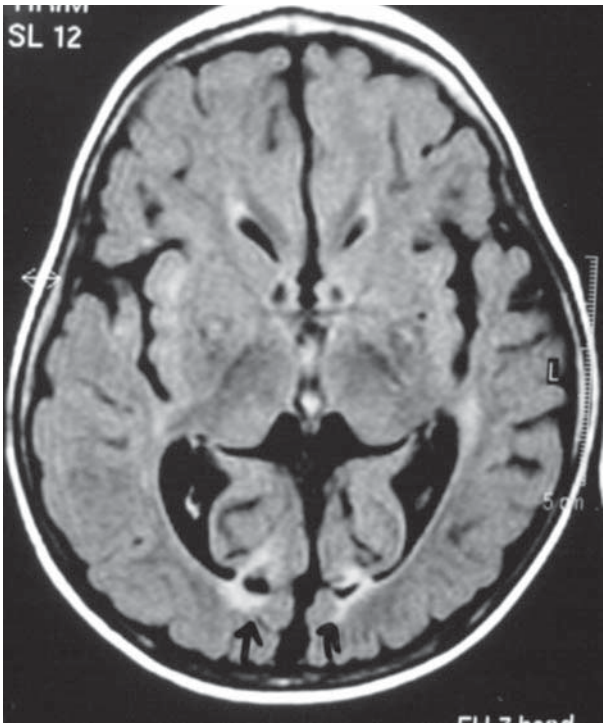

FIG. 1 *Bilateral occipital lesions typical of neonatal hypoglycemic brain injury (MR FLAIR image).*

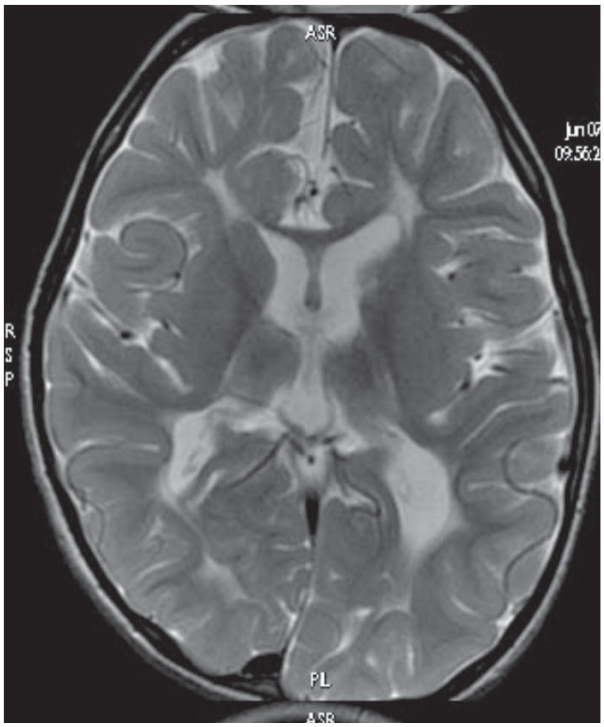

FIG.2 *Periventricular leukomalacia hyperintensities in white matter, loss of white matter and ventriculomegaly (T2 MR image).*

case of disagreement between the two observers, laboratory tests and / or a suggestive history were used to finally include or exclude the patient from a particular diagnostic category. A few patients had unequivocal diagnoses not based on imaging but on past clinical or non-imaging methods. In those where the radiologists disagreed and there was no supportive evidence to back any diagnosis, the case was classified as undefined.

Neonatal hypoglycemic brain injury (NHBI) was found to be the single most frequent risk factor in the study and hence was studied further. In the NHBI group the diagnosis (primarily based on MRI) was correlated with the neonatal clinical history and blood glucose levels (if available). We ascertained the frequency of three risk factors (birthweight, mode of delivery and perinatal feeding difficulties) in the NHBI group. These three were chosen as the caregivers reliably remembered these three factors even when birth records were unavailable (which is often the case in our country). We used the DV group as controls and compared the same three factors in the two groups using a univariate analysis. We chose the DV group as controls as this group would be more likely to have an uneventful perinatal period and resemble healthy controls.

Neurological and developmental findings were described and compared in the different perinatal groups by the chi-square test. Types of seizures and response to treatment were studied however only in the NHBI group.

RESULTS

One hundred patients (63 M 37 F) were recruited over a period of three months. Mean age of seizure onset was 13.9 months (1-36 months). In 88/100 patients, the diagnoses of the radiologists completely concurred. The kappa coefficient for diagnosis of NHBI was 0.83, for HIE 0.79, for PVL 0.63 and for developmental anomalies, 1. The etiological diagnosis was reached in only 83 study patients as in 5 patients the imaging abnormalities were considered not specific by both radiologists. PE etiologies were seen in 50 patients (NHBI 23, HIE 8, PVL 7, focal infarcts 9, multiple etiology 3), DV in 28 (tuberous sclerosis and migration defect 9 each; Aicardi syndrome 4; metabolic 3 and others 3) and post-natal in 5 (post encephalitic 2, head injury, neurocysticercosis and medial temporal sclerosis in 1 each). In 17 the diagnosis remained undefined.

In the NHBI group, 14/23 children had documented low blood glucose in the neonatal period; the remaining 9 did not have any birth records available though all had a compatible perinatal history with encephalopathy between day two and four. Conversely, 9 patients with documented low blood glucose in the neonatal period did not have the characteristic imaging findings of NHBI and were thus not included in this group as our diagnoses were based primarily on imaging criteria.

Low birthweight (<2.5 kg) (LBW), history of poor feeding in the newborn period and lower segment cesarean section (LSCS) delivery were all found to be significant risk factors for NHBI on univariate analysis (***Table* I**). Surprisingly, 6/19 patients where birth weights were available were >2.5 Kg, with 3 having a weight of >3 kg.

***Table* II** lists and compares the neurological findings in patients with NHBI with patients from other PEC *e.g.* HIE, PVL *etc.* The clinical discriminatory features that seemed to separate the NHBI group from other perinatal etiologies were the relative lack of spasticity/ dystonia in these patients. Other features frequently observed in children with NHBI in our study were microcephaly (100%), autism (57%), apraxia of hand use (65%) and cortical visual impairment (48%). Infantile spasms were the most common seizure type in children with NHBI (*n*=12, 52%) followed by partial (22%), generalized (17%) and mixed (9%) seizures. More than half of the patients had refractory seizures.

DISCUSSION

We used neuroimaging as the primary method for establishing the etiology of the epilepsy as clinical histories / hospital birth records are often unavailable or incomplete in our country. Ideal methods to establish an etiology would be to rely on clinical, laboratory and imaging findings in cohorts who are either prospectively followed up from the newborn period or looking at carefully documented antecedent of patients with early onset epilepsy. In India,

these two approaches are rarely possible in the general population. Often clinical details of the perinatal period are sketchy and laboratory investigations are either not performed or poorly documented. The parents are often unaware of the details or have forgotten them. Moreover, prospectively followed up cohorts from tertiary care centers (where neonatal care is of a high standard and homogeneous) may not reflect the reality in general populations where perinatal care is much more heterogeneous. The reliability of neuroimaging in diagnosing etiologies in epilepsy syndromes is well established(11-14). The excellent inter-observer agreement for imaging findings noted in our study further reinforces the accuracy of the study results.

Our findings on causes of remote symptomatic epilepsy have been reported earlier in retrospective series from developing nations(4-9) and from older studies in Finland(10). However our results are in contrast with the etiology of infantile remote symptomatic epilepsy from developed nations where progressive encephalopathies and developmental disturbances of cortical architecture (cortical dysplasias, neuronal migration disorders, tuberous sclerosis) are the main causes(2,3). Perinatal care in developing countries is often rudimentary in many primary centers and is the probable explanation for this difference. NHBI has been almost eliminated from Western world nurseries as blood glucose is routinely monitored in high risk groups including LBW infants. It remains an important cause of epilepsy in developing countries like Argentina(15), where 13/15 patients had typical parietooccipital lesions as in our study and many had mental retardation and visual impairment on followup. It is possible that the contribution of NHBI was underestimated in our study, as 9 children with documented neonatal hypoglycemia were not included because their MRIs were not characteristic.

TABLE I RISK FACTORS FOR NEONATAL HYPOGLYCEMIC BRAIN INJURY (NHBI)

Risk Factors	NHBI (Cases) *N*= 23	Controls *N*=28	*P* value
Birthweight			
<2.5 kg	13	3	<0.001
2.5-3 kg	3	9	
>3 kg	3	12	
Unknown	4	4	
Poor feeding	19	5	<0.001
Cesarean delivery	11	6	0.046

An interesting observation in our study is the occurrence of NHBI even in appropriate for gestational age (AGA) newborns. Maternal diabetes may have been a risk factor though details are unavailable in our cohort. Late establishment of feeding even in AGA babies may also predispose to hypoglycemia and NHBI.

LSCS rates were significantly higher in the NHBI group *vis-à-vis* the DV group. We took the latter as controls as this group presumably had

TABLE II NEUROLOGICAL FINDINGS IN CHILDREN WITH PRE/PERINATAL ENCEPHALOCLASTIC ETIOLOGY FOR EPILEPSY

Neurological finding	NHBI	Other perinatal etiology				*P* value
	N=23	PVL	HIE	FI	Total	
Dystonia	2	1	5	2	8	0.09
Spasticity	4	2	5	9	16	<0.001
Autism	13	4	7	1	12	NS
Severe MR	11	3	7	1	11	NS
Visual impairment	11	3	7	3	13	0.07

NHBI: neonatal hypoglycemic brain injury, PVL: periventricular leucomalacia, HIE: hypoxic-ischemic encephalopathy, FI: focal infarcts, NS: not significant.

WHAT IS ALREADY KNOWN?

- In developed nations, the etiology of epilepsy with onset in the first 2-3 years of life is usually due to prenatal etiologies.

WHAT THIS STUDY ADDS?

- Perinatal brain-damaging etiologies, especially neonatal hypoglycemia are responsible for half the symptomatic epilepsies in the first 3 years of life.

similar risk factors as healthy newborns. Higher LSCS rates could be partly explained on the general higher rates in LBW infants(16) as well as the general increase in LSCS rates in India(17). An LSCS delivery is often responsible for delayed establishment of breastfeeding(18) (due to maternal sedation / pain) and the risk of hypoglycemia is increased in LBW babies. Our study reinforces the need to maintain vigilance for hypoglycemia in all babies delivered by LSCS, especially those below 3 kg.

Children with NHBI had lower rates of dystonia and spasticity. Epilepsy, mental retardation, microcephaly and visual disturbances were seen often and have been reported following NHBI(19). However, the high frequency of autism and apraxia of hand use, which was seen in more than half our patients, has not been highlighted in the literature. Autism may be related to uncontrolled infantile spasms(20) and apraxia of hand use may be because of the frequent damage to the parietal association areas in NHBI. The lack of damage to motor pathways including the basal ganglia probably explains the low frequency of tone abnormalities in NHBI. The absence of significant motor changes discriminates these infants from survivors of HIE, PVL and stroke.

The seizure types commonly encountered were infantile spasms and partial seizures, which are similar to other series(21). What was alarming was the high incidence of refractory epilepsy, though there were others who had only infrequent epilepsy with near normal development suggesting that there is a wide spectrum of disabilities. This is also highlighted in the Argentinian study where many patients had a fairly good outcome(15). Microcephaly was seen even in those mildly affected, as in our group.

These results from a child neurology center would be subject to a selection bias and therefore certain etiologic groups may have been over-represented. However, it emphatically establishes the contribution of perinatal insults, particularly neonatal hypoglycemia as an important cause of the childhood epileptic burden and invokes a need to improve perinatal care in our country.

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