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Determinants of epilepsy in infancy in Bangladesh: A case-control study

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Abstract

Background: Very little research has been done on childhood epilepsy in Bangladesh. Greater knowledge on risk factors of epilepsy in the early years of life could help to improve understanding of epilepsy, can tell us about its prognosis and allow early intervention. *Objective:* This study was designed to explore the determinants of epilepsy in infancy, in Bangladesh. *Method:* A case- control study involving 63 patients with epilepsy was performed in two specialized hospitals in Bangladesh. Children with epilepsy were the study population. *Result:* Birth asphyxia, neonatal seizure and history of consanguinity were significantly associated with epilepsy in infancy (OR 7.4, 95% CI 2.37 – 6.57, OR 4.13, 95% CI 1.67-4.65 and OR 10.85, CI 2.11-41.08 respectively). Complication during antenatal period of pregnancy was found to be higher in children who develop epilepsy in infancy but it was not significant (OR 2.76; 95% CI 1.08 – 4.89). Coexisting impairments were highly significant in children having seizure onset in infancy (OR 5.9; p=.000); these were -developmental delay, speech and language delay, mental retardation and cerebral palsy.
Conclusion: Birth asphyxia, neonatal seizure and parental consanguinity, were significantly associated with epilepsy in infancy in Bangladesh. Antenatal complications were higher in infancy though not significant. Epilepsy starting at this age was significantly associated with neurodevelopmental impairments.

INTRODUCTION

Epilepsy is a heterogeneous collection of neurological conditions and syndromes characterized by recurrent, unprovoked, paroxysmal seizure activity.[1] It is estimated that 10.5 million children under 15 years have active epilepsy, representing about 25% of the global epilepsy population.[2] Of the 3.5 million people who develop epilepsy annually, 40% are younger than 15 years, and more than 80% live in developing countries.[2] Epilepsy is an important cause of neurological morbidity in children.[3]

The incidence of epilepsy is higher during the first year of life than at any stage of life.[4,5] The immature brain is more prone to seizure due to an imbalance between cerebral excitability and inhibition.[6,7] The consequences of seizures in the developing brain is different compared with the mature brain and can result in irreversible alterations in neuronal connectivity.[7] Clinical experience and experimental models have found that seizures during early postnatal brain development may result in chronic epilepsy and/or other neurocognitive deficits.[8] Studies have also found that onset of seizures in the first year of life may be a risk factor or is associated with mental retardation, psychobehavioral disturbances and cerebral palsy.[9-11] All these coexisting impairments lead to a devastating clinical consequence and can have significant implications for development of the child.

Family history of epilepsy, neonatal complications, perinatal brain damage, congenital cerebral malformations, intracranial infection, neonatal seizures, febrile seizure were found as predictors of childhood seizure disorder in many of the studies.[3,9,12-14] In early onset epilepsy perinatal asphyxia, neonatal meningitis and neonatal seizure was found to be the important predictors.[5,9,15,16] There is not much research on etiological factors with a special emphasis on early onset epilepsy in Bangladesh. This study is an attempt to make predictions about determinants of developing epilepsy in infancy. This might help in predicting the prognosis and planning management on a broader spectrum along with helping in reduction of common causal factors for developing epilepsy in children.

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METHODS

This case-control study was conducted in the Neurology Foundation Hospital and Centre for Neurodevelopment and Autism in Children (CNAC). The later is a centre with special support for neurological and neurodevelopmental problems of the Bangabandhu Sheikh Mujib Medical University (BSMMU), a tertiary care University Hospital in Dhaka, Bangladesh. The study population consisted of children with a history of seizure who visited the two centres during June 2010 and November 2010. Participants enrolled in the study were aged in between 2 months to 16 years. Ethical clearance was obtained from the Ethical Committee of the Neurology Foundation Hospital, Dhaka. Verbal consent was obtained from each patient's parent before proceeding with the interviews.

The study cases were defined as children who came to these hospitals with onset of seizure during first year of life and had been diagnosed with epilepsy. The control was children with seizure onset and diagnosis of epilepsy after the age of 1 year. Approximately two controls were taken against each case. The sample size was calculated using the following considerations. Ratio of control and case: 2; Incidence of exposure among control: 16%; Power: 80%; Confidence level: 95%; Odds ratio: 3. A total number of 63 cases and 117 controls were selected for the study.

Selection criteria for case: Child aged up to one year who had onset of two or more unprovoked seizures; had routine EEG done for diagnosis and were willing to participate in the study.

Selection criteria for control group: Patients who had two or more unprovoked seizures starting after the age of one year; had routine EEG done for diagnosis and were willing to participate in the study.

Exclusion: Patients who were out of age range; or if there were other confounding factors/ disease that had provoked the seizure/epilepsy.

Definitions

Epilepsy: A condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause.[17,18]

Epilepsy in infancy: Recurrent unprovoked seizures in the first year of life.

Birth Asphyxia: History of baby's cry delayed for more than 10 minutes after birth or duration of labour more than 18 hours with baby born blue or flaccid or hospital record indicating birth asphyxia.[19] Seizure within 48 hours of birth in association with delayed cry was also considered as having 'birth asphyxia' in this study.

Neonatal Seizure: History of seizures occurring in the newborn within 48 hours to 28 days of birth, that was not associated with delayed cry, not cyanosed or no hospital record indicating birth asphyxia or neonatal encephalopathy was the working definition in this study.

Consanguinity: A marriage solemnized among persons descending from the same stock or common ancestor with biological relations.[20]

Family history of epilepsy: A family history was positive if there were one or more first-degree relatives with epilepsy.

Antenatal complication: Complications during pregnancy that included premature rupture of membrane, preeclampsia, eclampsia, prolonged obstructed labour, ante partum hemorrhage, history of abortion or miscarriage, history of taking any drugs or abortificants, history of trauma or fall, hypertension, chronic asthma or any chronic illness.

Investigation procedures and diagnoses

All patients had interictal electroencephalography (EEG) examination. Fifty one children underwent computed tomography and 27 were examined with magnetic resonance imaging brain scans. A review of baseline clinical information, psychological assessment, EEG reports, other investigations, and follow-up records were performed.

Data collection procedure

Two Paediatric Neurologists were responsible for the input of all relevant data using a structure questionnaire. Data has been taken from medical records, investigations reports and interviews of the patients' relatives regarding past history.

Data analysis

Determinants for developing epilepsy and coexisting impairments were identified and matched with case and control. The Chi square test was conducted to show the statistical significance. Odds ratio (OR) was calculated at a

Table 1: Determinants for developing epilepsy in infancy and after infancy

Determinants	Onset in infancy	Onset after infancy	OR	95% CI	P
Birth Asphyxia					
Present	34 (54%)	16 (13.7 %)	7.4	2.37 – 6.57	<0.001
Absent	29 (46%)	101 (86.3%)			
History of neonatal seizure					
Present	27 (42.9%)	18 (15.4%)	4.13	1.67 –4.65	<0.001
Absent	36 (57.1%)	99 (84.6%)			
Consanguinity					
Present	10 (15.9%)	2 (1.7%)	10.85	2.11 – 41.08	0.001
Absent	53 (84.1%)	115 (98.3%)			
Antenatal complications					
Present	14 (22.2%)	11(9.4%)	2.76	1.14-4.89	0.17
Absent	49 (77.8%)	106 (90.6%)			

95% confidence interval using statistical software EP16.Descriptive analysis was performed using the Statistical Package for the Social Sciences (Windows version 17.0; SPSS Inc., Chicago).

RESULTS

We recruited 63 cases (42 were boys, 21 girls) with a mean age of 19 months (SD±2.5) and 117 cases (78 boys and 39 girls) with a mean age of 77.8 months (SD±4). Minimum age of child was 3.2 months, whereas maximum age was 16 years.

The age of onset of epilepsy and the determinants for epilepsy are summarized in Table 1. As shown, consanguinity (OR 10.85), birth asphyxia (OR 7.4), and neonatal seizure (OR 4.13) were significant determinants for developing epilepsy in infancy. Complications during antenatal period of pregnancy were also found to be a determinant, although it was not statistically significant. We also found family history of epilepsy in both the groups but it had a negative relation with onset in infancy (OR 0.59; 95% CI 0.21-1.8). Close to three fifths (57.8%) of children with epilepsy had coexisting impairments. It was found in almost 83% cases in the infancy, and in 44% of children in the control (OR 5.9; p<0.001). Table 2 shows the coexisting impairment of the study cases. As shown, there was significant association of epilepsy in infancy with developmental delay (OR 9.87), speech and language delay (OR 8.38), mental retardation/ cognitive delay (OR 6.24) and cerebral Palsy (OR 2.84) in children developing epilepsy in infancy.

DISCUSSION

Birth asphyxia was found as an etiological factor in 55% of cases in a study conducted by Khreisat on children developing epilepsy under 2 years of age.[21] Studies done on infants also found perinatal asphyxia to be a common cause of epilepsy.[4,22] Epidemiological studies done in China found it to be the most frequent cause of epilepsy in children.[23] Birth asphyxia is a serious clinical problem worldwide and it causes epilepsy along with other neurological sequelae each year.[24] Its incidence is very high in developing countries like Bangladesh. We found birth asphyxia as one of the major contributors to the development of epilepsy, which was 54% in infancy. It was more than 7 fold higher than the comparative group. Asphyxial insult to the fetus or newborn might have resulted in epilepsy appearing in early year of life.

In this study, history of neonatal seizure was found to be strongly associated with development of epilepsy in infancy. It was present in 42.9% of cases and was significantly higher than those children who developed epilepsy after first year of life. Association of neonatal seizure with high incidence of postnatal epilepsy is mentioned in the study of Da Silva *et al*.[25] They found an epilepsy rate of 22% within 12 months of follow up and 33.8% within 48 months. Song *et al*. found

Table 2: Coexisting impairments of infancy and after infancy in children with d epilepsy

Impairments	Onset in infancy	Onset after infancy	OR	95% CI	P
Developmental delay					
Present	13 (20.6%)	3 (2.6%)	9.87	2.38 – 27.2	<0.001
Absent	50 (79.4%)	114 (97.4%)			
Speech and language delay					
Present	39 (61.9%)	19 (16.2%)	8.38	2.42 – 6	<0.001
Absent	24 (38%)	98 (83.8%)			
Mental retardation/cognitive delay					
Present	43 (68.3%)	30 (25.6%)	6.24	1.87 – 3.78	<0.001
Absent	20 (31.7%)	87 (7.4%)			
Cerebral Palsy					
Present	29 (46%)	27 (23%)	2.84	1.3 – 3	0.001
Absent	34 (54%)	90 (76.9%)			

neonatal seizure to be an independent risk factor of epilepsy in children.[26] Neonatal seizure has also been found to be associated with adverse effect on neurodevelopment and may also predispose cognitive and behavioral complication later in life.[27,28]

Parental consanguinity was also found to be associated with development of epilepsy. It was found in 15.9% of cases who had onset of epilepsy in infancy, versus 1.7% in children who developed epilepsy after first year of life. Recent studies have shown a significantly higher rate of epilepsy among family members with consanguineous marriage.[29-31] Case-control study in infants has also shown consanguinity to be a major risk factor for epilepsy.[23] The detrimental effects associated with consanguinity are caused by the expression of recessive genes inherited from a common ancestor(s). This probably applies to rare gene conditions as well as to multigene disorders with multifactorial inheritance.[32] The finding of 10 folds higher rate of epilepsy in infancy in our study might be explained by the expression of inborn metabolic, multifactorial, multigene disorders in very early years of live.

Antenatal complications were present in 22.2% of our patients who developed epilepsy. It was more common that those who developed epilepsy later in life (9.4%). But the difference was not statistically significant. Antenatal factors like eclampsia, preeclampsia and placental abruption, infections during pregnancy were found to be an important risk factor for epilepsy.[26,33] The fetal brain is vulnerable to several factors that can disrupt its development and predispose a child to seizures. Population-based cohort study conducted by Sun *et al.* reported association of prenatal exposure of maternal infections with epilepsy in children.[34] In developing countries like Bangladesh, with limited financial resources, antenatal checkups and antenatal investigations are often limited. This might have caused difficulties in identifying antenatal contributions in developing epilepsy, with less than optimum obstetric care. Some of the antenatal factors like antepartum haemorrhage, maternal toxaemia, prolonged rupture of membrane and poor nutritional status of the mother, are also associated with higher incidence of asphyxia.[35]

We also studied the association of family history of epilepsy, which was not statistically significant. Montenegro *et al*. reported a family history of epilepsy being associated with an earlier age at seizure onset in patients with focal cortical dysplasia.[36]

Previous studies have found association of mental retardation, cerebral palsy or both with epilepsy.[8,11,37-41] Gururaj *et al*. found a significant developmental delay with onset of epilepsy in infantcy.[16] Most studies indicate that early age of onset of epilepsy is an important correlate of poor cognitive function in epilepsy.[42-45] It is likely that the same brain injury might have caused all these disabilities. Coexisting impairments of mental retardation, speech and language delay, cerebral palsy and developmental delay were also found to be significantly associated with development of epilepsy in infancy in our study.

In conclusion, we found a history of birth asphyxia, neonatal seizures, parental consanguinity, and coexisting neurological impairments to be significantly associated with the development of epilepsy in infancy in our studies in Bangladesh. We hope that the identification of these risk factors will help the clinician to focus even more on the preventable risk factors and improvement of antenatal care, to plan and arrange for multidisciplinary management and to provide appropriate counseling to families whose child may be at risk of developing multiple disabilities. Since our sample size in this study is small, a larger sample size with longitudinal study is recommended for future study.

DISCLOSURE

Conflict of interest: None

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