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Original Articles

Neurodevelopmental Evaluation in Full-term Newborns with Neonatal Hypoxic Ischemic Encephalopathy (HIE): A Case Control Study

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Abstract

Background: *Newborns with Hypoxic Ischemic Encephalopathy (HIE) are at risk of neuro-developmental disabilities. Early identification of their neuro-developmental impairments (NDI), immediate intervention and reassessment might be a useful method to measure and prevent major disability. This study was performed to identify impairment in different developmental domains among the babies admitted with moderate to severe degree HIE, and evaluate their outcomes after intervention with developmental therapy and stimulation.*

Methodology: *The exploratory case control study was conducted during April 2008 till February 2012. We enrolled 81 full-term babies admitted to the special care neonate unite with HIE as 'case'. The 'control' group included age and sex matched 81 babies who did not have HIE. Neurodevelopmental assessment was performed using age specific rapid neurodevelopmental assessment tool (RNDA) by trained developmental therapists (DT). Intervention with developmental therapy and stimulation was provided for every child. Those who had assessment at least twice, (at entry and after 1 year age) were included for this study.*

Results: *Male were predominating (66.7%). Mean age was 18 and 19 days on the 1st ; 17 and18 months on last assessment day in case and control group respectively. NDI was identified in 89% and 35% in case and control group respectively. On last assessment, 42% developed disability (permanent functional deficit), 35.8% achieved age appropriate developmental skills, 20% were lost to follow up, and 2 children died among the case group. These were 16% (13/81), 72% and 12% respectively among the control group. Significant correlation was found between the 1st and last assessment result among the case and control group.*

Conclusion: *Early identification of NDI using a valid assessment tool and immediate intervention could probably reduce the disability in babies with HIE. A long time evaluation of this cohort would provide valuable information.*

Key words: *HIE, Neurodevelopmental outcome, rapid neurodevelopmental assessment (RNDA), early intervention, NDI.*

Introduction

With over 80% home delivery,[1] difficult and prolonged labor followed by hypoxic Ischemic encephalopathy (HIE) is common in Bangladesh. Referral of the newborns with birth related and neonatal problems after home or hospital delivery is increasing with reducing neonatal mortality rate,[2,3] and increasing awareness among the parents and professionals (personal experience). However, study on the HIE survivors' quality of life, appearance of neurological impairment and disabilities among these population is lacking here.

HIE is the most important consequence of perinatal hypoxia.[4] This has immediate and long term effect on the nervous system leading to motor, visual, hearing, speech and cognitive deficit, which may manifest as cerebral palsy, learning disability and epilepsy.[5]

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Perinatal brain damage has been reported to account for 57.5% of all neonatal deaths, 30% of admission to special care nursery and 12.5% of mental retardation, epilepsy and cerebral palsy at the age of 14 years.[6] Early identification, intervention with developmental therapy and stimulation might be a solution to this problem.[7]

We conducted a prospective study on the neonates admitted with HIE, defined as term infants having difficulty with initiating and maintaining spontaneous respiration, depression of tone and reflexes, subnormal level of consciousness and seizures, with history of prolonged–difficult labor,[8] and a control group without HIE. We are intended to perform a follow up study on this cohort later during their school age period.

Objective of this study was to identify impairment in different developmental domains among babies who presented with moderate to severe degree of HIE to a Special Care Neonatal Unit (SCANU) and evaluate their neurodevelopmental outcome after intervention.

Methodology:

An exploratory case control study was conducted at the Institute of Child Health and Shishu Sasthya Foundation Hospital, Mirpur. The institute started a special care neonatal unit in 2003 with 29 beds to provide emergency management within short time after delivery. Daily 1-5 out-born neonates are admitted. They present with perinatal asphyxia and neonatal seizures, septicemia, umbilical cord infection, pneumonia, small-for-date, low birth weight, prematurity and some are referred for monitoring, e.g., babies of diabetic mother. The multidisciplinary neurology service for infants and children was started in 2008 at the same institute. Neurodevelopmental assessment was introduced by the neurology team for the neonates admitted to the SCANU.

Babies were enrolled and followed up from April 2008 to February 2012. The cases were the full-term babies admitted to the SCANU with history and clinical evidence of moderate to severe degree HIE, i.e., history of perinatal asphyxia and neonatal seizures, supported by the findings of hypotonia, postural abnormality, abnormal moro and tendon reflexes, mydriasis or miosis of pupils on examination.[8] Controls were the full-term babies without above mentioned features of HIE. They were admitted to the SCANU or IPD with poor cry after birth, small for date, low birth weight, jaundice, septicemia, pneumonia, neonatal seizures not associated with prolonged, difficult labor or perinatal asphyxia. Infants who came for vaccination at the expanded program of immunization (EPI) center of the hospital were also included in the control group. Babies with complex and severe medical or surgical problems, congenital anomaly, with dysmorphic feature or microcephaly, suspected or diagnosed metabolic disorder, and gestational age less than 37 wks were excluded from the study. The gestational age was mostly based on the maternal information about the duration of pregnancy, and on the discharge certificate when available.

Diagnosis of HIE was based upon the clinical history and examination findings,[8,9] which included a history of perinatal asphyxia or prolonged-difficult labor followed by delayed cry (more than 1 min after complete delivery), repeated seizures, and the signs of HIE stage 2 and 3 (hypotonia, postural abnormality, abnormal moro and tendon reflexes, mydriasis or miosis of pupils on examination). Although HIE grading was not considered due to a lack of more specific information, it was assumed that all cases would fall into the 'moderate' to 'severe' categories.[8] Neonatal intensive care and mechanical ventilation facility were not available in this hospital therefore most severe cases with HIE were referred to the centers with ICU facility.

Neuro-developmental assessment was performed by the developmental therapists (DT) using the 'Rapid Neurodevelopmental Assessment' (RNDA) tool for 0-5 year age.[10,11] The test instrument is simple, less time consuming and can be used by trained professionals at the health centers. The RNDA manual for 0-2 years and >2-5 years includes several age specific testing methods and questionnaire organized in twelve forms for specific age groups. The testing items are arranged under the specific developmental domains (gross and fine motor, vision, hearing, speech, behavior, cognition and seizure). The strength of this tool (RNDA) is that it is able to evaluate mild to severe degrees of impairments in the following developmental domains, primitive reflex (for 0-<1mo), gross and fine motor, vision, hearing, speech, cognition, behavior and seizures. Impairment grading at each developmental domain was made following the guideline provided by International classification of functioning[12] as mild, moderate and severe if functions were >50%, 25% to 50%, or <25% of the child's normal developmental skills for the chronological age, respectively.

In addition to the babies' functional assessment, a detail history of pre-, peri- and postnatal period was taken during the rapid neurodevelopmental assessment (RNDA).

The 'first RNDA' was performed after complete recovery from the acute illness, on discharge or later depending on the parents' comfort and willingness. Subsequent assessments were performed at one to three months interval and the 'last RNDA' after 12 month to 36 months of the child's age. The persisting neurodevelopmental deficit or regression on any domain at the last assessment would confirm a 'developmental disability', defined as permanent functional limitation. For the sake of simplicity of the study and considering early age at the last assessment, severity grading of the disability were not reported in this article.

The care givers (mother and other family members) were informed about milestone of normal developmental skills. They were also trained on baby care and handling, developmental therapy and stimulation. The DT started providing developmental therapy and stimulation, that included motor, sensory, speech and cognitive stimulation on the first contact day at the SCANU or at the OPD. These were reinforced during later visit for RNDA at the follow up clinic. Parents' contact (mobile phone) numbers were kept, to minimize the 'lost to follow' cases. A yellow card with patient identification number, summary of the assessment findings and some common advice on child care was provided for each family. The children identified with disability and epileptic seizures were enrolled as regular patients of the neurosciences department for appropriate medical and other intervention by the multidisciplinary team.

Statistic analysis: Data analysis was performed on the SPSS. Descriptive analysis was performed to report the family, birth related problem and neonatal state after delivery in two groups. A comparison of developmental impairment identified among the case and control group were analyzed with the chi square test and confidence interval to explore the relative risk of occurrence of neurodevelopmental deficit among the case and the control group.

Ethical considerations: A verbal consent for enrollment and follow up visits was taken from every mother. The study was given ethical clearance from the ethical review committee (ERC) of the hospital.

Results:

Total 162 infants (81 in case and 81 in control group) were enrolled for this study, mean age at first assessment was 18 days (range: 3 day to 48 days standard deviation .099), among the case and 19 days (range: 2 day to 48 days, standard deviation -121) among the control. On the last assessment day mean age was 17 month in case and 18 month in the control with standard deviation .619 in both the groups. Male predominated in both the group, with higher proportion in the case (2.7:1 *vs* 1.5:1, *p*- .06). The majority of control group resided near the hospital, in Mirpur area (75%), which was 53% in the case group (*p*-.003).

Mode of delivery was reported as "normal vaginal delivery without prolonged and difficult labor" in 96.3% among the control group. In the contrary among the case group prolonged and difficult labor was reported in 94% and questionable uneventful labor at home was reported by 5 families. Delivery by emergency caesarian section was reported in 2 children in the control, none in case group (p-.001). The majority of the case group was born at home or at the nearest maternities, Obstetrics Gynecology Society of Bangladesh (OGSB) or BRAC center in Mirpur. Newborns were referred by the professionals or brought by the families to the hospital. Immediate resuscitation and medical care was provided at the SCANU.

Poor or delayed cry without need for hospital resuscitation was reported in 9(10%), and neonatal seizures not associated to any difficulty in establishing spontaneous respiration after birth was reported in 11 (13.6%) among the control group. Main concern on admission were categorized as neonatal seizures (NS) in 81(100%) and 11(13.6%), neonatal Jaundice (NJ) in 18(21%) and 12(14.8%), infection (septicemia or pneumonia) in 12(14.8%) and 15(18.5%) in the case and control group respectively (table I). In addition, the control group included 13(16%) babies with low birth weight, small for date, high risk mother admitted for monitoring , and 35(43%) babies who came for vaccination at the EPI center.

On the first assessment, NDI was identified in 88.8% (72/81) among the case and 34.6% (28/81) among

Table-I

Patient demography, birth related information and clinical problems among the case (N-81) and control (N-81) group.

Item	Case N(%)	Control, N(%)	Total, N (%)	P- value
Age at 1st assessment				
2wk or less	34 (42.0)	32(39.5)	66 (40.7)	0.730
>2- 4 wk	37(45.7)	38(46.9)	75 (46.3)	
>4 wk	10 (12.3	11(13.6)	21 (13)	
Total	81(100)	81(100)	162 (100)	
Sex				
Male	59(72.8)	49(60.5)	108 (66.7)	0.06
Female	22(27.2)	32(39.5)	54 (33.3)	
Total	81	81(100)	162 (100)	
Residence				
Mirpur	43 (53.1)	61(75.3)	104 (64,2)	.003
Other part of Dhaka	12(14.8)	11(13.6)	23 (14.2)	
Other district	26(32.1)	09(11.1)	35 21.6)	
Total	81	81	162 (100)	
Mode of delivery	0.001			
Normal vaginal delivery without prolonged or difficult labor	5(6.2)	78(96.3)	83 (51.2)	
Vaginal delivery with history of prolonged and difficult labor	76(93.8)	1(1.2)	77 (47.6)	
Emergency cesarean section	0	2(1.5)	2 (1.2)	
Total	81	81	162 (100)	
Cry after birth				
Immediate normal	00	73(90.1)	73 (45.1)	.001
Delayed	81(100)	8(9.9)	89 (54.9)	
Total	81	81	162 (100)	
Concern on admission				
Seizures	81(100)	11(13.6)	79 (48.8)	16.0
Jaundice	18(21.0)	12(14.8)	29 (17.9)	
Infection	12(14.8)	15(18.5)	27 (16.7)	
Small for date, poor sucking, poor cry or excessive cry	0	13(16.0)	22 (14.2)	

control group. Proportion of infants identified with NDI with their severity grading among each group is shown in table II. Majority among the case group had impairment in more than 3 domains. Among the control population 28.6% (8/28) had impairment in more than 3 domains.

Frequently affected domains were motor function 68% (49/72) and 64.3% (18/28) followed by speech 52.7% (38/72) and 39.2% (11/28), and seizure 38% (28/72), and 42.8% (12/28) among the case and the control group respectively.

Table-II

Neurodevelopmental impairment (NDI) by specific domains in cases (n=81, 100%) and controls (n=81, 100%) by severity rating

Domain	Mild NDI		Moderate NDI		Severe NDI		Total NDIs in	Total NDIs in
	Case	Control	Case	Control	Case	Control	Cases (%)	Controls (%)
Primitive reflexes	26(32.1)	7(8.5)	12(14.8)	6(7.8)	11(13.6)	2(2.5)	**49 (60.5)**	15 (18.5)
G.Motor	14(17.3)	13(16.0)	23(28.4)	3(3.7)	12(14.8)	2(2.5)	**49 (60.5)**	18 (22.2)
F.Motor	6(7.4)	4(4.9)	9(11.1)	1(1.2)	8(9.9)	5(6.2)	23((28.4)	10 (12.3)
Vision	13(16.0)	5(6.2)	4(4.9)	1(1.2)	3(3.7)	2(2.5)	20 (24.7)	8 (9.9)
Hearing	2(2.5)	3(3.7)	3(3.7)	3(3.7)	3(3.7)	1(1.2)	8 (9.9)	7 (8.6)
Speech	15(18.5)	6(7.4)	17(21.0)	1(1.2)	6(7.4)	4(4.9)	**38 (46.9)**	11 (13.6)
Cognition	16(19.7)	4(4.9)	7(8.6)	0	2(2.5)	3(3.7)	25 (30.9)	7 (8.6)
Behavior	5(6.2)	2(2.5)	7(8.6)	3(3.7)	1(1.2)	1(1.2)	13 (16.0)	11 (13.6)
Seizures	17(21.0)	9(11.1)	10(12.3)	1(2.5)	11(13.6)	2(2.5)	**28 (34.6)**	12 (14.8)
NDI total							72(88.8)	28(34.6)

Among total 162 infants 134 (63 case, 71 control) could be followed up for the last RNDA at the targeted age. Sixteen (20%) in case and 10(12%) in control group were lost to follow up, 2 babies died at home in the case group, cause could not be identified. The mean age at the last assessment was 17 months and 18months respectively in case and control group.

On last RNDA, normal developmental skill was achieved in 58/71(81%) and 29/63 (46%) among the control and case group respectively. Developmental disability was identified in 34/63 (54%) in case group. Among them 32/63(56%) had motor disability (half of them had mild degree deficit), 16/63(25%) had cognitive disability, 11/63(17.5%) had speech disorder, 5 children had visual and 1 child had hearing disability. In the control group 13/71 (16%) had identified with disability, among them 12/71(29.5%) had motor disability (three fourth of them with mild degree deficit), 4/71 had cognitive deficit, 2/71 had speech disorder, 1/71 had hearing and none had visual disability. Epilepsy with active seizures was diagnosed in 18/63(28.6%) and 5/71(7%) in case and control group respectively. There was a significant risk of neurodevelopmental “impairment” and “disability” , giving 95% confidence interval for the relative risk of 1.24 - 1.95 and 1.25 to 2.05 respectively among the case group (table III).

Table-III

Rapid neurodevelopmental assessment (RNDA) findings and their correlation among the case and control group on the first and last time assessment.

	Case	Control	Total	CI	p- value
1st assessment :					
Neurodevelopmental Impairment					
Present	72 (88.8%)	28 (34.6%)	99(61.1%)	1.24-1.95	0.001
Absent	9(11.1%)	53 (65.4%)	63(38.9%)		
Total	81(100)	81(100)	162 (100)		
Last assessment:Disability					
Present	34 (42.0%)	13 (16.0%)	47(29.0%)	1.25-2.05	0.01
Absent	29 (35.8)	58 (71.6 %)	87(53.8%)		
Not known (Lost to follow up)	16(19.8)	10(12.4%)	26(16.9%)		
Died	2(2.4)	0	0		
Total	81(100)	81 (100)	162(100)		

Discussion:

This study revealed that moderate to severe degree perinatal hypoxic ischemic encephalopathy had significant effect on the neurodevelopmental outcome among the survivors. The incidence of neurodevelopmental impairment and disability was 2.5 and 3.4 times higher among the babies with HIE on1st (88.8% vs 34.6%) and the last (54% vs16.0%) assessment compared to the control population (CI 1.25 -2.05, p-<0.01). The disabilities identified among the control group was milder in the majority. This was supported partially by other long term studies, which particularly focused on the school performance and cognitive function. In Marlow's study with 65 children neuropsychological and educational problems at school was present in 42% and 6% of the severe and moderate encephalopathy group at 7 year of their age.[13] The Indian study found disability in 43% and 29% of children who had HIE grade 2,3 and HIE 1 respectively at 12 years age.[14] Both are long-term study result. The Indian study has uneven population (41childrne with grade 1-HIE and 5 with HIE 2,3). Robertson et al, found incidence of disability in 16% among 145 children with mild to moderate degree neonatal encephalopathy, at 8 year of age.[15] A significant proportion among the control group had identified with NDI in this study, this is probably because of the mixed population in the control group, i.e. some had neonatal jaundice, septicemia, pneumonia, other had no history of such incidence. In addition, with high incidence of infection including central nervous system infection among our child population the immediate and later effect on the development should be considered. One of the 'not at risk' babies at 1st assessment later developed neuro-developmental disability on 2nd assessment in the control group, that baby had an episode of encephalitis, which was the cause of her later developing disability.

Our study had labeled the disability at different domains and identified the commonest domains affected which were motor, speech, seizure and cognitive function in the case and control group. The impairment found in the control group was less in severity. Probably that was why a significant proportion of infants later outgrew their impairment in the control group (p- <0.01) compared to those in case group (p- 0.13).

A comparable proportion of the study population (28% in case and 7% in control) had epilepsy diagnosed at the mean age of 16 months. The improvement in this domain was significant in the control group compared to that in case group (over one third of the case group were still having seizures). From extrapolated information of the epilepsy studies it is found that HIE is related to a high percentage of epilepsies, however, these data vary from study to study ranging from 26% to 46%.[16,17,18,19,20,21,22,23,24] Active epilepsy starting at early age i.e., within 12 month of age if not well controlled and monitored, may affect the rate of developmental skills. Good seizure control probably had facilitated to grow out of the functional limitation among the control population. The diagnosed cases with such disorder need regular seizure and antiepileptic drug monitoring at the epilepsy clinic.

Mortality among the HIE survivors was 2.5% during 3-6 month of age among the case group in our study, cause of death could not be identified. This could not be compared with other studies as most of them are the long-term outcome studies with the survivors.

This comparatively short term outcome study provided rather valuable information for a country like ours where pre-, peri-, and post-natal care is not optimum in the majority of the population.[25] Particulalry in acknowledgement of the temporal relationship between impairment (i,e,, temporary functional limitation) and disabilities (permanent functional limitation) as defined by the international classification of functioning (ICF) of world Health Organization,[12] there is a need to identify specific NDI in at risk babies in order to prevent or ameliorate progression to disabilities. Early identification of impairment, immediate intervention and regular monitoring will probably reduce the family burden by preventing severe disability. With more surviving newborns at present time (mortality rate reduced from 63/1000 live birth in 1995 to 34/1000 in 2006, World Bank report 2010) it is presumed that number of at risk infants for neuro-developmental disability is increasing (unpublished data at the Child Development Center, Dhaka Shishu Hospital; NZ Khan). Their quality of life in terms of functional, social and neurological development should be evaluated and assisted in appropriate time to reduce the family and national burden. This study was performed to explore the effect of HIE on achieving the neuro-developmental skill within very short time, i.e., after recovery from the acute condition, and later after one year and 3 year of life.

Reporting of this cohort study later at their school age would provide invaluable information that would help develop an integrated system of referral and monitoring of newborns at risk from primary to tertiary health care in this country.

There are some drawbacks in this study, such as the cases were identified from the clinical history of birth related problems examination findings and neonatal seizures. Specific feature of HIE i.e., APGAR score or biochemical investigation and electro-encephalography (EEGs) were not included. Place of delivery, immediate resuscitation method, oxygen inhalation, recording of muscle tone and reflexes on admission were not recorded either, which are very important clinical factors that may influence later neurodevelopmental outcomes. The initial aim was to identify the early impairments and their evaluation at later age while the infant would go through regular stimulation. Later we decided to compare the outcome with a control group. There was a mixed population contributing to the one third having identified with NDI in the control group, i.e., a proportion had been referred for monitoring, about 10% had history of delayed or poor cry, 13% had seizures but did not have perinatal asphyxia, indicating they might had CNS infection and a proportion were enrolled from the EPI center having no problem. This also suggests the possibility of having impairment among the neonates admitted for problem other than HIE, that need to be addressed.

This is the first hospital based study of this type, that had been mainly planned with the developmental therapists this is reporting a shift of medical paradigm. The investigation findings, medicine used could be included, however, that would muddle the role of developmental therapists which had a tremendous effect (no statistic data) on the parental and professional caregivers' awareness regarding early child development. Clinical categorization of neonatal encephalopathy associated with perinatal asphyxia was our main criteria of patient enrolment to include more infants and to make it simple. This was also found to be a helpful indicator of long-term outcome in many studies.[15,22,23,24] The neuro-developmental intervention was started for all infants enrolled with or without identified NDIas a potential neuroprotective strategies. Disability grading at specific domain was not reported in this study, which would be more informative, however, that should be a target on subsequent reporting of this cohort. Continuation of this study should include more infants and followed up for a longer period.

Conclusion:

Newborns with HIE, birth related problems and disorder(s) needing hospital admission during neonatal period should go through a rapid neurodevelopmental assessment on discharge or within a short period. Early identification of neurodevelopmental impairment and immediate intervention may reduce the severity of functional disability among the babies at risk. With appropriate intervention, the non HIE babies may grow out the impairment rather rapidly compared to those having HIE. However, a long time evaluation of this cohort would provide valuable information.

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