Original Article

The pattern of visual impairment in the spectrum of hypoxic ischemic encephalopathy

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Purpose: This study aimed to evaluate the relationship between visual impairment, social maturity, and clinical severity of hypoxic-ischemic encephalopathy (HIE) in the Indian population. **Methods:** An observational study was conducted in children with HIE sequelae aged between 6 months and 5 years. Sixty diagnosed cases of perinatal HIE were recruited, with twenty children in each of clinical grades 1, 2, and 3 according to the Sarnat clinical staging. All children underwent cycloplegic refraction using atropine 1% eye ointment, visual Acuity (VA) testing by teller acuity cards (TAC), anterior and posterior segment examination, FLASH visual evoked response (VER), strabismus workup, and social maturity assessment using the vineland social maturity scale (VSMS). **Results:** Sixty children, including 14 preterm and 46 term infants, with a mean age of 26.11 ± 16.06 months were studied. Normal birth weight was observed in 54% of the cases, whereas 42% had low birth weight and 4% had very low birth weight. There was no statistically significant difference between birth weight and the clinical severity of HIE (P = 0.970). A significant relationship between VA and clinical severity (TAC- $p < 0.0001$) and between VA and social maturity was observed. Optic disc pallor was present in 85% of grade 3 HIE cases. Among the 37 children with strabismus, the convergent type was predominant (86.4%). Refractive error was comparable across all grades of HIE. **Conclusion:** Visual impairment was significantly related to the clinical severity of HIE and had a negative impact on the social maturity of these children.

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Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is an acute, nonstatic encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia.[1] HIE is a significant cause of permanent damage to neural tissues, which can result in neonatal death or later manifest as cerebral palsy or developmental delay. Approximately 20%–30% of infants with HIE die in the neonatal period, and about 33%–50% of those who survive are left with permanent neurodevelopmental abnormalities such as cerebral palsy and mental disabilities.[2] Sarnat grading classifies hypoxic encephalopathy into three grades of increasing severity, with grade 1 being the least severe and grade 3 being the most severe [Table 1].[3] A variety of ocular morbidities, including optic atrophy, nystagmus, strabismus, ocular motor deficits, visual field defects, and functional deficits (e.g. acuity, assimilation, attention, apraxia) are commonly associated with asphyxial insults during the perinatal period.[4]

However, a limited number of studies have evaluated the relationship between visual morbidities and the severity of hypoxic-ischemic encephalopathy.[5] Hence, we conducted this study to document the spectrum of ocular morbidities in HIE and explore the relationship between visual impairment, clinical stages of HIE, and social maturity.

Methods

This observational study was conducted at a tertiary eye center over a period of one year and was performed in accordance with the Tenets of the Declaration of Helinski. Institutional ethics committee clearance was obtained before the commencement of the study. The study included diagnosed cases of perinatal HIE (gestational age 28 weeks to seven days postpartum) and children aged between six months and five years, with 20 children in each group. Exclusion criteria included hemodynamically unstable and acquired cases of encephalopathy. A complete pediatric neurological and systemic assessment was performed, and children were classified by a pediatrician into three clinical grades of severity according to the Sarnat grading system[3][Table 1].

All children included in the study underwent a thorough ocular examination, including anterior segment and fundus evaluation. Cycloplegic refraction was performed using

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1% atropine eye ointment. Best-corrected visual acuity was assessed with Teller's acuity cards during a follow-up visit after glasses were prescribed. Flash visual evoked potentials (VEP) were recorded using the MonPack one visual stimulator (METROVISION, France).

Each child's cognitive development was assessed by a pediatrician using the Vineland Social Maturity Scale (VSMS), which measures an individual's social capabilities.[6,7] The VSMS evaluates adaptive behavior, defined as the ability to perform daily activities essential for personal and social independence, across eight social domains: Social Quotient = Social Age × 100/Chronological Age. The social quotient scores obtained were categorized as mild, moderate, or severe.

Magnetic resonance imaging (MRI) was performed in 21 cases. MRI grading was conducted by a pediatric neurologist following the method described by Cioni *et al*.[8] The scoring and grading of MRI findings in this study have been reported separately.[9]

Statistical analysis

Data were recorded in Microsoft Excel spreadsheet. The children were classified into three clinical severity grade according to the Sarnat grading system, and a comparative analysis was conducted between groups. Visual acuity obtained from Teller's acuity cards was converted into logMAR for analysis, with the eye showing better vision used for this purpose. Statistical analysis was performed using STATA software (version 12.3; Stata Corporation, College Station, Texas, USA). The Chi-square test or Fisher's exact test was used for categorical variables, while the *t*-test and ANOVA were used for parametric continuous data, and the Mann–Whitney test for nonparametric data. A P value < 0.05 was considered statistically significant.

Results

Sixty diagnosed cases of HIE meeting the inclusion criteria were recruited in the study, with 20 patients in each of the three clinical stages of severity. The mean age of the 60 children was 26.11 ± 16.06 months (range 6–60 months), including 46 males

Table 1: Sarnat grading of clinical severity of HIE

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stupor
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebrate
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
• Suck	Weak	Weak or absent	Absent
• Moro	Strong	Weak	Absent
• Oculovestibular	Normal	Overactive	Weak or absent
• Tonic neck	Slight	Strong	Absent
Autonomic functions	Generalized sympathetic depressed	Generalized parasympathetic depressed	Both systems depressed
Pupil	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased	Variable
Seizures	None	Common	Uncommon
Electroencephalogram	Normal	Early – low voltage continuous delta and theta Late – periodic pattern	Early – periodic pattern with isopotential phases Late – totally isopotential
Duration	Less than 24 hours	2-14 days	Hours to weeks

Table 2: Ocular features of patients within different grades of HIE

Parameter	HIE grade1	HIE grade 2	HIE grade 3
Visual acuity (Teller's acuity card)	0.82±0.23	1.28±0.40	1.43±0.19
Refractive error (Spherical equivalent range)	+1-+6.5	−4.5-+5.5	−7-+5
Optic disc pallor/cupping			
Temporal	6	16	17
Nystagmus	1	7	7
VEP amplitude (micro volt)	11.20±4.64	14.24±2.96	13.65±3.95
VEP latency (Mili seconds)	114.05±6.99	124.05±10.44	126.6±9.71

and 14 females. Forty-seven children had a history of term birth, while 13 were preterm. Due to the unequal sample size between the two groups, we did not compare term and preterm groups.

Twenty-six children had normal birth weight (2.5–4 kg), 20 had low birth weight, (22–.5 kg), and 2 had very low birth weight (<2 kg). For statistical analysis, low and very low birth weights were combined into a single group. No statistically significant difference in the clinical severity of HIE was found between normal and low birth weight patients (*P* Value = 0.97).

The ocular features of patients with Grade I, Grade II, and Grade III HIE are summarized in Table 2. A significant difference in visual acuity was found among all three groups. Significant difference were observed between Grade I and Grade II, as well as between Grade I and Grade III ($P < 0.001$); however, no significant difference was found between Grades II and III.

No statistically significant relationship was found between VEP amplitude and clinical severity (*P* Value - 0.214); however, a significant relationship was observed between VEP latency and clinical severity (*P* Value - 0.0233). No significant difference was observed between Grades II and III.

Similarly, the distribution of other ocular features showed significant differences between Grade I and both Grade I and III; however, no difference was found between Grades II and III. No significant difference in refractive error was found among the three grades [Table 2]. Assessment of strabismus pattern revealed that 23 children were orthophoric, 32 had convergent stratbismus, and 5 had divergent strabismus. Additionally, inferior oblique overaction and superior oblique overaction were each observed in 15% of cases, lateral rectus palsy in 7%, and normal extraocular movements in 63% of patients.

Social maturity was assessed using the VSMS. Nineteen children had mild impairment, 20 had moderate impairment, and 21 had severe impairment of social maturity. A trend was observed where better visual acuity was associated with less impairment in social maturity impairment, and vice versa. [Table 3]

Discussion

Cerebral visual impairment (CVI) has become a common cause of acquired bilateral visual impairment in developed countries.[4] HIE is a significant cause of brain injury leading to CVI. With improvements in the survival rate of children with HIE and increased awareness of the condition, CVI has also become a concern in developing countries.[1,4] The aim of this study was to examine the relationship between visual impairment and the clinical stages of HIE, as well as to document the spectrum of ocular morbidities associated with HIE. HIE produces a characteristic and heterogenous pattern of brain injuries with a wide spectrum of clinical manifestations.[10,11] In term children, hypoxic injury commonly causes watershed infarctions, resulting in cortical lesions. In preterm children, however, brain insult typically affects the subcortical white matter, leading to the characteristic finding of periventricular leukomalacia (PVL). We could not compare preterm and term infants in this study, as 80% of our sample consisted of term infants. In low-income countries such as India, prematurity remains a leading cause of neonatal and infant mortality. Higher mortality rates in preterm infants could explain the lower prevalence of preterm cases in our study.

Table 3: Relationship between the social maturity and visual acuity

Social maturity (*n*)	TAC in logMAR
Mild impairment (19)	0.84±0.27
Moderate impairment (20)	1.19±0.33
Severe impairment (21)	1.51±0.23

We found a significant difference in visual acuity across the three grades of patients with HIE. Children with Grade II and Grade III had significantly poorer visual acuity compared to those with Grade I. Mercuri *et al*.[5] in their study on 31 children found that visual function was normal in Grade I HIE, variable in Grade II, and severely impaired in Grade III HIE. They also observed that normal imaging features were generally associated with normal visual function in majority of the cases, irrespective of severity of HIE, and concluded that MRI findings were better predictors of visual impairment than the clinical grade of HIE. As previously reported, neuroimaging severity scores in our study were higher in Grade III compared to Grades I and II, suggesting a relationship between the severity of MRI lesions and the clinical severity of HIE. We also found a statistically significant correlation between MRI scores and visual acuity.[9]

The prevalence of refractive errors in these children is reported to range from 10% to 60%.[12] In this study, 70% of patients had significant refractive error (SE> +2). The range of refractive error was wider in Grade III severity compared to Grades I and II, with a hyperopic median refractive error in all three grades. The median of refractive error in clinical Grade I was + 1.42, in Grade II + 1.95, and in Grade III + 2.46. James *et al*.[13] reported mean refractive errors of + 1.99 D, +1.46, and − 0.63 in Grades I, II, and III, respectively.

Whether electrophysiology is more accurate than behavioral testing in assessing visual function in children with brain damage is debatable.[14] In our study, we did not find any significant difference in amplitude between the three groups; however, there was a significant relationship between VEP latency and clinical severity (*P* Value = 0.0233). VEP interpretation may be challenging in children with CVI, with most studies reporting VEP results as normal, abnormal, or absent in these patients.[4] While VEP may have limited diagnostic value for CVI, it has been reported to have some prognostic value in children with this condition.[15,16] In the present study, increased latency in Grade III may serve as an indirect marker for more severe visual pathway damage in higher-grade HIE cases. Sweep VEP is considered a more accurate quantitative measurement of visual function in these children; the lack of such an evaluation is a major limitation of this study.[17]

Optic disc pallor in these children was analyzed across the three clinical grades of HIE. We found a statistically significant difference between Grades I and, as well as between Grades II and III; however, no significant difference was seen between Grades III and II. Optic atrophy may result from partial or total damage to the anterior visual pathways due to the disease process. Brodsky *et al*.[18] in their study found that children with hypoxic damage showed normal optic discs in 56%, optic atrophy in 24%, optic nerve hypoplasia without atrophy in 8%, and combined hypoplasia with atrophy in 12%.

In this study, we found that among 60 children evaluated, 23 were orthophoric, 32 had convergent strabismus, and 5 had divergent strabismus. Of the HIE children with strabismus, 86.4% presented with a convergent type. Esotropia is commonly seen in children with PVL, whereas exotropia is typically observed in cases with other forms of cortical involvement.[19] Dyskinetic strabismus, a condition where the exotropia alternates to esotropia with variable deviations, has been reported in premature infants with PVL.[19]

Good vision is imperative for normal physical growth and neuropsychosocial development of a child. Multiple studies have shown that vision impairment affects motor development, as visual stimuli in infants drive motor skill development, such as grasping and hand-eye/foot coordination.[20] Similarly, vision is also crucial for cognitive and social development.[21] Cioni *et al*.[8] in their study suggested that visual impairment is a more important predictor of neurodevelopmental outcomes than imaging or motor disabilities. In this study, we found that better visual acuity was associated with lower social maturity impairment, indirectly suggesting that children in Grade I, who generally had better visual acuity, showed improved social interactions. However, the potential confounding effect of associated neurological deficits in severe cases of HIE on the overall development of the child's social behavior cannot be overlooked. Functional vision, a measure of a child's interaction with their environment through various visual tasks, was not evaluated in this study, limiting the detection of the full extent of visual impairment. Nonetheless, the study suggests that visual acuity and ocular manifestations are related to the clinical grade of HIE.

Conclusion

Visual impairment and clinical severity of HIE were significantly related with each other. This further led to a negative impact on the social maturity of these children.

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