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Neurodevelopmental Outcome in Neonates with Hypoglycaemia and Associated Risk Factors: A Follow up Study

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Abstract

Introduction: Neonatal hypoglycemia is a common problem requiring medical attention in newborn and a leading cause of preventable brain damage, physical and mental handicap and early deaths among infants.

Objective: To study the prevalence of neuro-developmental abnormalities and risk factors associated with poor outcome.

Materials and methods: This was a prospective study on 39 neonates with hypoglycemia who were admitted to neonatal intensive care unit (NICU) from November 2015 to December 2016 and were fulfilling the inclusion criteria. Gestational age at birth, sex, birth weight, age of presentation, duration and severity of hypoglycaemia were noted in all neonates. Neuro-developmental assessment was done on follow up at 3 and 6 months by Denver developmental screening test 2 (DDST 2) method.

Results: Out of 39 neonates, the prevalence of abnormal neurodevelopmental outcome according to DDST II method was 71.7% [n=28] at 3 months and 66.6% [n=26] at 6 months. Factors such as early onset, symptoms, longer duration of hypoglycemia, minimum blood glucose level, number of readings <25 mg/dl and maximum glucose infusion rate (GIR) were significantly associated with adverse outcome.

Conclusion: Neonatal hypoglycemia is associated with long-term neurodevelopmental handicaps. Mental and psychomotor developmental indices of the children who suffered from hypoglycemia during new-born period are significantly low. Hence, early diagnosis and treatment of neonatal hypoglycemia is mandatory to prevent neurological sequelae.

Keywords: Neonatal hypoglycaemia; Neonates with hypoglycaemia; Neurodevelopmental handicaps

Introduction

Neonatal hypoglycemia is a common disorder that can cause severe neurological sequelae in neonates, with incidence rates reported to range from 0.13 to 0.44% in term, and from 1% to 5.5% in preterm neonates [1,2]. There is no universal definition for hypoglycemia [3]. Various investigators have empirically recommended different blood glucose levels (BGLs) that should be maintained in neonatal period to prevent injury to the developing brain [4,5]. There is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia [6]. Hypoglycemia is defined as blood glucose level below 45 mg/dl in the neonatal period [1]. If hypoglycemia is prolonged or recurrent, it may result in acute systemic effects and neurological sequelae [2]. Neurological sequelae may present as cerebral palsy, mental retardation, refractory epilepsy, microcephaly, ataxia, loss of vision and learning disability [7,8]. The neurological symptoms of neonatal hypoglycemia are nonspecific and may present with irritability, tremor, jitteriness, seizures, hypotonia, exaggerated Moro reflex, acute encephalopathy and lethargy. Elevated glutamate impairs calcium homeostasis, leading to cytotoxicity and cell death.

The effect of pure hypoglycemia on the developing juvenile brain has been documented in animal models including primates [2]. These studies have found that cerebral injury occurs as a result of prolonged and severe hypoglycemia, rather than mild or short-term hypoglycemia. The parieto-occipital cortex, hippocampus, caudate and white matter were most sensitive to prolonged hypoglycemia.

While most hypoglycemic new-borns do not develop neurologic sequelae, a few will have some degree of neurological impairment. Neuroimaging, electroencephalographic, metabolic and histopathologic findings show that profound and recurrent episodes of hypoglycemia can cause brain damage in new-born infants [9].

We conducted this prospective study to evaluate the neurodevelopmental outcome in neonates with hypoglycaemia and to identify the risk factors associated with abnormal outcome.

Materials and Methods

This was a prospective observational study conducted at departments of Paediatrics and Gynaecology in Prince Bijay Singh

Memorial Hospital, Sardar Patel Medical College, Bikaner. This was a follow up study conducted over 14 months (1 November 2015 to 31 December 2016) in which subjects were followed up at 3 and 6 months. The study was approved by the ethical clearance committee of the institute. 45 neonates admitted in nenonatal intensive care unit (NICU) with hypoglycemia, requiring glucose infusion rate (GIR) of 6 or more as per standard treatment guidelines were included in the study. A written informed consent was taken from the parents. Neonates with birth asphyxia (Apgar score<6), birth weight<1200 g, gestational age<30 weeks, congenital anomalies, and shock (on inotropes) were excluded from the study. Gestational age, parity, sex, birth weight, and neonatal clinical course were recorded for all infants.

Blood glucose was measured by Accu-chek active glucometer, which is of ISO-15197 standard. Pre-warmed heel of a neonate was cleaned with sprit and after drying, skin puncture was done in posterolateral aspect by lancet. A good drop of blood touched the edge of glucometer strip and blood glucose was noted. Whenever blood glucose measured by glucometer was ≤ 50 mg%, venous blood 0.5 ml was sent to laboratory for "hexokinase" analysis and blood glucose level thus obtained was taken for study. Relevant investigations for e.g. septic screen, MRI were done. Patients were managed according to standard guidelines and were followed after discharge up to 6 months. Their neurodevelopmental assessment was done at 3 and 6 months age using Denver developmental screening test 2 (DDST 2), hearing assessment was done by behavior audiometry and tone was assessed by Amiel tison test.

DDST 2 is a test for screening cognitive and behavioural problems in preschool children. The data are presented as age norms, similar to a growth curve. The more items a child fails to perform (passed by 90% of his/her peers), the more likely the child manifests a significant developmental deviation that warrants further evaluation.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 for windows. Continuous data were analyzed by t-test when normally distributed or else by Mann–Whitney test. Categorical data were analyzed using Chi-square test or Fisher exact test.

Results

A total of 45 neonates were enrolled in the study, 3 died during follow up and 3 were drop outs. Hence, 39 neonates with hypoglycemia admitted to NICU and fulfilling the inclusion criteria were finally analysed in the study.

Twenty seven (69.2%) hypoglycaemic neonates were male and twelve (30.8%) were females. Among these, 48.7% were preterm (gestational age<37 weeks) and 51.3% were term (gestational age>37 weeks) neonates. No statistically significant difference in prevalence of neurodevelopmental outcome was observed [p>0.05] at any stage of follow up between male and female neonates (Table 1).

84% [16/19] of preterm neonates were observed to have abnormal developmental outcome at 3 months and 73.6% [14/19] at 6 months of corrected age. Out of 20 term babies, 60% [12/20] have abnormal outcome at 3 months and 65% [13/20] at 6 months (Table 2).

Sex	Outcome							
	3 Month				6 Month			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
Female	7	17.9	5	12.8	8	20.5	4	10.3
Male	21	53.8	6	15.4	19	48.7	8	20.5
χ^2	1.551				0.053			
p	0.213				0.817			

Table 1: Distribution of cases according to sex in relation to neurodevelopmental outcome at 3 and 6 months.

Term/ Preterm	Outcome							
	3 Month				6 Month			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
Preterm	16	41	3	7.7	14	35.9	5	12.8
Term	12	30.8	8	20.5	13	33.3	7	17.9
	2.82				0.345			
p	0.093				0.557			

Table 2: Distribution of cases according to gestation in relation to neurodevelopmental outcome at 3 and 6 months.

Ten per cent neonates had birth weight ranging from 1.2 to 1.5 kg, 53.9% had weight between 1.6 to 2.5 kg and 35.9% had birth weight>2.5 kg.

Abnormal neurological outcome was more common in neonates with very low birth weight (Table 3).

Birth Weight (kg)	Outcome							
	3 Month				6 Month			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
1.2-1.5	4	10.3	0	-	4	10.3	0	-
1.6-2.0	13	33.3	4	10.3	11	28.2	6	15.4
2.1-2.5	3	7.7	1	2.6	3	7.7	1	2.6
>2.5	8	20.5	6	15.4	9	23.1	5	12.8
Mean	2.1		2.44		2.15		2.3	
SD	0.52		0.57		0.53		0.59	
T	1.771				0.794			

P	0.085	0.432

Table 3: Distribution of cases according to birth weight (kg) in relation to neurodevelopmental outcome at 3 and 6 months.

The prevalence of abnormal neurodevelopmental outcome according to DDST 2 method was 71.79% [n=28] at 3 months and 66.6% [n=26] at 6 months. At 3 months follow-up, 85.7% infants had abnormality in fine motor function while 92.3% infants had abnormal gross motor function at 6 months follow-up (Table 4).

DDST II sectors	Gross motor	Fine motor	Language	Psychosocial
3 months [n=28]	22	24	18	16
6 months [n=26]	24	20	22	23

Table 4: Abnormal DDST sectors in hypoglycemic infants at 3 and 6 months corrected age.

Out of 27 infants who presented within 5 days of birth, 59.2% [16 cases] were observed to have abnormal neurodevelopmental outcome at 3 months and 62.9% [17 cases] at 6 months. Out of 7 infants, who presented between 6 to 10 days, all 7 cases [100%] and 6 cases [85.7%] were observed to have abnormal outcome at 3 and 6 months respectively. Out of two infants who presented between 11 to 15 days of life, both had abnormal outcome at 3 and 6 months. Out of 3 infants who presented after 15 days of life, 2 and 3 had abnormal outcome at 3 and 6 months respectively (Table 5).

Age Group (days)	Outcome							
	3 Month				6 Month			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
<5	16	41	11	28.2	17	43.6	10	25.6
6-10	7	17.9	0	-	6	15.4	1	2.6
11-15	2	5.1	0	-	2	5.1	0	-
>15	3	7.7	0	-	2	5.1	1	2.6
Mean	6.42		2.18		5.66		4.25	
SD	6.19		1.32		5.54		5.89	
t	2.236				0.723			
p	0.032				0.474			

Table 5: Distribution of cases according to age of presentation in relation to neurodevelopmental outcome at 3 and 6 months.

Symptoms	Outcome							
	3 months				6 months			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
Absent	1	2.6	4	10.3	1	2.6	4	10.3
Present	27	69.2	7	17.9	26	66.7	8	20.5
χ^2	7.598				6.525			
P	0.006				0.011			

Table 6: Distribution of cases according to symptoms in relation to neurodevelopmental outcome at 3 and 6 months.

Seventy nine per cent of infants [27/34] who had symptomatic hypoglycemia were found to have abnormal outcome at 3 months while only 20% [1/5] of asymptomatic neonates had abnormal neurodevelopmental outcome as shown in Table 6 ($p<0.006$).

All neonates with more than one reading (two to three) of RBS<25 mg/dl had abnormal outcome at 3 and 6 months while only 90% neonates with one reading of RBS<25 mg/dl were abnormal at follow-up (Table 7).

Number of readings of RBS<25 mg/dl	Outcome							
	3 Month				6 Month			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
0	10	25.6	10	25.6	8	20.5	12	30.8
1	10	25.6	1	2.6	11	28.2	0	-
2	6	15.4	0	-	6	15.4	0	-
3	2	5.1	0	-	2	5.1	0	-
Mean	1		0.09		1.07		0.91	
SD	0.94		0.3		0		0	
T	3.114				4.028			
P	0.004				<0.001			

Table 7: Distribution of cases according to number of readings of RBS<25 mg/dl in relation to neurodevelopmental outcome at 3 and 6 months.

All infants who had hypoglycaemia for >3 days, were observed to have neurodevelopmental abnormalities at 3 and 6 months whereas those who had hypoglycemia for <3 days, 42% had abnormal neurodevelopmental outcome at 3 and 6 months (p<0.001) (Table 8).

Duration of Hypoglycemia (days)	Outcome							
	3 Months				6 Months			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
1	2	5.1	9	23.1	1	2.6	10	25.6
2	6	15.4	2	5.1	7	17.9	1	2.6
3	9	23.1	0	-	8	20.5	1	2.6
4	8	20.5	0	-	8	20.5	0	-
5	3	7.7	0	-	3	7.7	0	-
Mean	3.14		1.18		3.18		1.25	
SD	1.11		0.4		1.07		0.62	
T	5.661				5.791			
P	<0.001				<0.001			

Table 8: Distribution of cases according to duration of hypoglycemia in relation to neurodevelopmental outcome at 3 and 6 months.

All neonates who required high glucose infusion rate (GIR>10) had abnormal neurodevelopmental outcome while 92% cases had abnormal outcome who required GIR=8 (Table 9).

Maximum GIR	Outcome

	3 Months				6 Months			
	Abnormal		Normal		Abnormal		Normal	
	No.	%	No.	%	No.	%	No.	%
6	2	5.1	10	25.6	1	2.6	11	28.2
8	12	30.8	1	2.6	12	30.8	1	2.6
10	9	23.1	0	-	9	23.1	0	-
12	5	12.8	0	-	5	12.8	0	-
Mean	9.21		6.18		9.33		6.16	
SD	1.75		0.6		1.66		0.57	
T	5.578				6.383			
P	<0.001				<0.001			

Table 9: Distribution of cases according to maximum glucose infusion rate in relation to neurodevelopmental outcome at 3 and 6 months.

Discussion

Neonatal hypoglycemia is a common problem requiring medical attention in new-born and a leading cause of preventable brain damage, physical and mental handicap and early deaths among infants. Hypoglycemia can be a normal transitional phenomenon but if it is symptomatic it can lead to subsequent death or lifelong neurological sequelae in surviving infants. Recent advances in molecular genetics have provided new insight into its biochemical and physiological basis and have led to more appropriate and specific treatment.

The cause and effect relationship between the neurodevelopment and the risk factors of hypoglycemia is more complex and we cannot simply presume that neonatal hypoglycemia and the presence of various risk factors will always lead to adverse neurodevelopmental outcome. Yet, because neonatal hypoglycemia is a known, treatable risk factor so early detection and regular follow up in these patients is important to initiate early interventional measures for better developmental outcome.

Some studies have shown no difference in neurodevelopmental outcome between babies who have normal blood glucose concentrations and those with hypoglycemia [10]. Others have shown that only babies with seizures have poor neurodevelopment outcomes [11] while others report poorer outcomes for all babies who have been hypoglycaemic [12,13].

In our study, the prevalence of abnormal neurodevelopmental outcome according to DDST 2 method was 71.79% [n=28] at 3 months and 66.6% [n=26] at 6 months. These results were comparable to the previous study done by Chandrashekaran et al. [14] on 60 infants. They observed abnormal neuromotor assessment and developmental delay in 19, 25 infants and 22, 17 infants at 3 and 6 months age, respectively. Both abnormal neuromotor assessment and developmental delay at 9 months CA were seen in 12 infants. Similarly, Alkalay et al. [15] in 2006 reviewed 22 early hypoglycemic cases and observed severe sequelae and persistent abnormal neuroscreening in 17 cases (74%).

The reported prevalence of abnormal neurodevelopmental outcome in neonatal hypoglycemia ranges from 40 to 70% [14,15]. The difference in the prevalence can be due to small sample size, the difference in the used tools for developmental assessment, different ages for follow up and different socio-demographic factors and variables associated with hypoglycemia.

We analyzed the relation of various demographic factors and risk factors of hypoglycemia on neurodevelopmental outcome.

In our study no statistically significant difference in prevalence of neurodevelopmental outcome was observed ($p>0.05$) at any stage of follow up between male and female neonates. Chandrashekaran et al. [14] did not found any significant association with gender, similar to our study.

In our study, we noticed high prevalence of abnormal neurodevelopment in neonates presented late in their life. In our study, there is significant relationship of age of presentation and neurodevelopmental outcome [$p<0.05$]. In contrast to this Alkalay et al. [15] who found that out of 23 cases half of the infants had visual impairment, and their median and range of plasma glucose values and postnatal age when hypoglycemia was first detected, were 7 mg/dL (range: 2-26 mg/dL) and 48 h (range, 1-72 h), respectively.

In the present study, we did not find significant difference in neurological outcome in relation to preterm and term neonates. The difference in prevalence to gestational age was also not found significant [$p>0.05$]. This observation is similar to Chandrashekaran et al. [14] who found no significant correlation between gestational age and neurodevelopmental outcome.

Although the prevalence of neurodevelopmental abnormalities was more in low birth weight babies than normal birth weight babies with hypoglycemia in our study but it was not statistically significant. In contrast to our study Chandrashekaran et al. [14] showed significant relationship between low birth weight and adverse neurodevelopmental outcome in babies with hypoglycemia.

Chandrashekaran et al. [14] said that it is the lowest blood glucose level which affects the neurodevelopmental outcome. Similarly, in our study we found a statistically significant correlation between lowest blood glucose level and neurodevelopmental outcome ($p<0.05$). Alkalay et al. [15] also found abnormal neuroscreening results with severe hypoglycaemia (blood glucose ≤ 25 mg/dL).

In our study, the number of readings of RBS<25 mg/dl was found to be positively associated with neurological abnormalities [p<0.05]. Haworth et al. [16] also found similar results in their study but in contrast to this, Chandrashekaran et al. [14] did not find any positive association between the two variables.

We noticed significantly higher prevalence of neurodevelopmental abnormalities in neonates with symptomatic hypoglycemia (p<0.05). Similar significant correlation was given by Chandrashekaran et al. [14] and Haworth et al. [16] in their study. Duvanel et al. [12] also reported a smaller head size at 5 years in infants who had neonatal hypoglycaemia. Koivisto et al. [11] have reported poorer outcomes in symptomatic hypoglycemic infants.

This indicates that severe and prolonged neonatal hypoglycemia causes cerebral lesions as found in our study with prolonged hypoglycaemia of >3 days. A review article from Vannucci et al. [8] emphasizes neurologic morbidity occurs particularly in those infants who have suffered severe, protracted or recurrent symptomatic hypoglycaemia.

Conclusion

This prospective observational study found a high prevalence of adverse neurodevelopmental outcome in neonates with hypoglycemia. Factors such as duration of hypoglycemia, presence of symptoms, lowest blood glucose level, number of readings <25 mg/dl, higher GIR requirement were significantly associated with adverse neurodevelopmental outcome as assessed by Denver Developmental Screening Test II (DDST II). In new-born infants, low blood glucose levels lead to neuronal and glial cell death, and hence associated with long-term neurodevelopmental handicaps. Early diagnosis and treatment of neonatal hypoglycemia is mandatory to prevent the long-term neurological sequelae.

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