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Clinical presentation of hypoglycemic brain injury suggested by neuroimaging in unanticipated term neonates: A retrospective study

Dr Sushree Smita Behura
Assistant Professor, Department of Paediatrics, KIMS Hospital Bhubaneswar, Odisha

Dr Avantika Dhanawat
Senior Resident, Department of Paediatrics, KIMS Hospital Bhubaneswar, Odisha

Dr Rama Krushna Gudu
Senior Resident, Department of Paediatrics, KIMS Hospital Bhubaneswar, Odisha

Dr Santosh Kumar Panda
Associate Professor, Department of Paediatrics, KIMS Bhubaneswar, Odisha,
Corresponding author email: doc.sant@yahoo.co.in

***Abstract*---**Objective- To evaluate the clinical characteristics of hypoglycemic brain injury (HBI) in unanticipated term neonates, confirmed by neuroimaging. Methodology- We reviewed Magnetic resonance imaging (MRI) of brain of term neonatal encephalopathy cases, from January 2018 to November 2020. Neonates with MRI topography suggestive HBI and documented hypoglycemia from case records were enrolled in study. Perinatal data, clinical characteristics and management of cases was recorded. Descriptive statistics was used to analyse the data. Result-Total 13 term neonates had brain MRI suggestive of HBI conducted at median postnatal age of 7 days. The mean birth weight of HBI neonates was 2582 ± 285 gram, mean gestational age 38.15± 0.48 weeks and five (38.4%) babies were low birth weight. Eight (61.5%) babies were delivered by caesarean section, eleven (84.6%) were first born, twelve (92.3%) were male and nine (69.2%) were on exclusive breastfeeding. Out of thirteen neonates twelve (92.3%) were outborn, mean age of symptom noticed was 2.83±0.53 days and mean age of admission was 3.84± 0.82 days. Mean blood glucose at admission was 28.84±3.23 mg/dl and four (30.7%) were diagnosed with hypoglycemia at referral hospital. In this study, seven (53.8%) neonates had sepsis, one required respiratory

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support and ten (76.9%) required multiple antiepileptic drugs. None of the cases died and mean duration of hospital stay was 12.5 days. Conclusion – Majority of term HBI neonates were outborn, early term, caesarean born, delivered to primiparous mother and exclusively breastfed. Poor feeding associated with neonatal sepsis could lead to symptomatic hypoglycemia. Adequacy of breast feeding assessment and timely blood glucose screening in term neonates may prevent HBI.

***Keywords*---**Neonatal hypoglycemia, Hypoglycemic brain injury (HBI), Magnetic Resonance Imaging(MRI), Antiepileptic drugs.

Introduction

Neonatal hypoglycemia manifests with short term clinical presentations, long term neurodevelopment delay and epileptic disorder. [1,2] Small for gestational age(SGA), preterm, large for gestational age(LGA) neonates and infants of diabetic mother are routinely monitored for blood glucose to prevent hypoglycemia. [3] The threshold of blood glucose level for diagnosis of hypoglycemia and intervention are still debatable. Blood glucose monitoring is one of the initial investigations in sick neonates presenting with altered sensorium and seizure. [4] Unnoticed hypoglycemia induced morbidities are a concern for raising medico legal issues. Hence we aimed to study the clinical events associated with a series of term neonates with magnetic resonance imaging (MRI) pattern suggestive of hypoglycemic encephalopathy/hypoglycemic brain injury (HBI) and documented hypoglycemia.

Methods

The case records and MRI brain neuroimaging of all term encephalopathy neonates of a tertiary care NICU, India were systematically analysed during the study period (from January 2018 to November 2020) after approval of institutional ethics committee. Topographic lesion in diffusion weighted images(DWI) of brain MRI, involving parietal-occipital cortex and white matter suggestive of hypoglycemic brain injury were noted. Corresponding case records were reviewed and those with documented random blood glucose <40 mg/dl were diagnosed as symptomatic hypoglycemia were enrolled. Hypoglycemia was diagnosed by glucometer screening (RBS<40 mg/dl) at referral hospital or during admission. Neonates who required aggressive resuscitation at birth, syndromic babies, neonates with multiple congenital malformation and neonates with persistent hypoglycemia were excluded. The clinical diagnosis of neonatal encephalopathy was based on altered sensorium with or without clinical seizure. Complete antenatal, intrapartum, postnatal events and family history of seizure disorder were documented in excel sheet. After initial stabilisation of airway, breathing and circulation, hypoglycemia was managed as per the unit protocol. After correction of hypoglycemia and hypocalcaemia, persistent or further episodes of neonatal seizures during euglycemia were managed with intravenous anticonvulsant. Phenobarbitne(PHB), Levetiracetam (LEV) were used as first line and second line antiepileptic medication respectively for management of neonatal seizure. Fosphenytoin (FP) was used as the next antiepileptic dug. Complete blood

count, C-reactive protein, arterial blood gas, serum electrolytes including serum sodium and calcium, blood culture, CSF analysis and neurosonogram were routinely documented. Presence of elevated C-reactive protein >6 mg/dL and any abnormal blood count (leucocyte count<5,000/mm^3, absolute neutrophil count <1,500 /mm^3, total platelet count <1,00,000/mm^3) in encephalopathy neonates were diagnosed as probable neonatal sepsis. Blood culture was considered as gold standard for the diagnosis of neonatal sepsis. Serum ammonia, lactate and metabolic screening were documented for few cases. The average timing of brain MRI for neonatal encephalopathy was conducted around 5^{th} to 7^{th} day of life. MRI was performed with sedation on a 1.5T GE SIGNA™. The axial and coronal T1-weighted, axial fast spin-echo T2-weighted images, and isotropic DWI were produced. Both DWI images and ADC maps were prioritised to localise the topography of lesion.
Statistical analysis was performed with Stata 14 software (Stata n Corporation, College Station, Texas). Descriptive statistics were used to characterize the cohort for hypoglycemic brain injury.

Result

In this study, total thirteen (N= 13) term neonates had hypoglycemia and MRI brain suggestive of hypoglycemic brain injury. The mean birth weight was 2582 ± 285 grams and mean gestational age was 38.15 ± 0.48 weeks. Out of thirteen cases included, five (38.4%) were low birth weight, eight (61.5%) babies were early term, eleven (84.6%) were male neonates, seven neonates (53.8%)were small for gestational age and one neonate (7.6%) was large for gestational age. In this series, twelve (92.3%) cases were out born, eight (61.5%) were delivered by caesarean section and eleven (84.6%)were delivered to primiparous mother. None of the mothers had gestational diabetes and two mothers had pregnancy induced hypertension. Nine (69.2%) neonates were on exclusive breast feeding, two babies were on mixed feeding and two neonates on formula feeding. Mean time of manifestation of seizure was 2.83±0.53 days and mean time of admission at study site was 3.84± 0.82 days. In four (30.7%) out of eleven outborn cases, hypoglycemia was diagnosed at referral hospital. Two neonates had associated hypocalcaemia. On laboratory investigation, seven (53.8%) neonates had probable neonatal sepsis, out of which three neonates had blood culture positive sepsis but CSF analysis were within normal range in all babies. Three (23%) babies required single antiepileptic drug (PHB), eight (61.5%) neonates required two antiepileptic drugs (PHB+ LEV) and two neonates required three anticonvulsants(PHB+LEV+FP). One baby required respiratory support and none of the babies required inotropes. Demographic profile and topography of DWI of all HBI neonates are depicted in Table 1 and 2.

In this study, nine neonates had parieto -occipital cortex, two neonates had tempero-parieto-occipital cortex and one neonate had bilateral occipital cortex abnormality in axial DWI (prototypes in Figure1-3). One neonate had isolated corpus callosum abnormality in DWI (Figure 4). Mean duration of hospital stay was 12.5 days with no mortality and all babies were discharged on breast feeding.

Discussion

Based on birth weight and gestational age, the neonates in this cohort were not routinely screened for blood glucose and hypoglycemia was diagnosed after symptomatic. In a UK based hypoglycemic series study all neonates were > 36 weeks with birth weight ≤ 2.5 kg where hypoglycemia could be prevented by appropriate care of feeding and timely intervention.[5] In Canadian surveillance study of symptomatic hypoglycemia in low risk term neonates, the mean gestational age was 39 ± 1.3 weeks and mean birth weight was 3143 ± 400 gm. Majority of HBI neonates were male as reported by Michel et al. .[6] One explanation for this could be less secretion of the counter regulatory hormones in males as compared to females during hypoglycemia.[7] Though term appropriate for gestational age neonate are not recommended for routine blood glucose monitoring, but enteral intake should be monitored and symptomatic neonates should be carefully evaluated.

In a case series of 23 neonates with HBI the median postnatal age of first detection of hypoglycemia was 48 hours (range, 1-72 hours) and plasma glucose level was 7 mg/dL (range, 2-26 mg/dL). [8] Hypoglycemia in early days of term neonate is found to be a result of imbalance between physiologic hyperinsulinemia induced impaired neoglucogenesis and enteral intake. [9] Majority of neonates were delivered by caesarean section(CS), breastfed and belonged to primiparous mother in this study. Elective CS, primi mother are found to be at greater risk of neonatal hypoglycemia as compared to vaginal delivery, multiparous mother.[8] The volume of milk transferred to infants born by CS was significantly less than that transferred to infants born by vaginal delivery on days 2 to 5 ($p < 0.05$) as demonstrated in a study by Evans, K C et al. [10] Delayed onset of lactation was observed in primiparae and in study participants with peripartum complications by Sievers, E et al .[11] Holtrop et al found the average times for finding low glucose levels in LGA and SGA infants were 2.9 h (range 0.8 h to 8.5 h) and 6.1 h (range 0.8 h to 34.2 h), respectively .[12] The timing of hypoglycemia developed in term neonates need further studies. Two neonates were born to mother with pregnancy induced hypertension and none of the mothers had gestational diabetes in this cohort. Hypertension in pregnancy is included in recent PES guidelines as a risk factor for neonatal hypoglycemia. [13] Seven out of 13 neonates were either less than or around 2.5 kg, considered as small for gestational age in our cohort. Around half of neonates in this cohort had neonatal sepsis supported by laboratory investigations and poor enteral intake in those could have resulted in hypoglycemia.

In a study by Gu Mei-Hong et al. neonates with prolonged duration of hypoglycemia or recurrent episodes were at higher risk for abnormal brain MRI findings. [14] In this study the mean duration of abnormal symptoms noticed by parents and hospital admission were 2.83±0.98 days and 3.75± 1.47 days respectively. Considering majority of neonates in our study being out born, there was significant time gap between initial symptoms noticed by parents and timing of hospitalisation and only four out of 12 out born babies were diagnosed hypoglycemia at referral hospital. Hence duration of persistent hypoglycemia and severity of brain injury need further study.

Though parieto–occipital pattern is well reported in HBI, hypoglycemia is associated with wide spectrum of brain injury and may involve cerebral cortex, white matter, basal ganglia and thalamus.[15-17] Among six cases of hypoglycemic encephalopathy there was diffusion weighted (DW) hyper intensity on occipital and/or parietal region in all cases .[17] In our study, the lesion of hypoglycemic brain injury are widely extended from bilateral occipital cortex to bilateral parietal-occipital cortex and bilateral tempero-parietal occipital cortex with or without corpus callosum involvement. One neonate had isolated diffusion weighted abnormality in corpus callosum. Hence further neurodevelopment follow-up is required for prediction of long-term morbidity based on severity of topography of brain lesions.

Random Blood glucose screening was done by glucometer and laboratory confirmation not done in most cases. Most of the babies were outborn and Apgar status were not documented in referral slip. The effect of duration of persistent hypoglycemia and recurrent episodes of hypoglycemia on neuroimaging could not be estimated from this study. Similarly, any association of severity of fall of blood glucose with brain injury could not be addressed.

Conclusion

Majority of term HBI neonates were outborn, early term, delivered by CS, belonged to primiparous mother and exclusively breast fed. Breast feeding assessment and timely blood glucose screening in term neonates may prevent HBI.

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Table 1- Maternal and neonatal characteristics of the 13 cases of neonatal hypoglycemia

S.No	Gestational age(Week)	SEX *M/F	BIRTH WEIGHT (Kg)	AT BIRTH 5min APGAR /CRY	MODE OF FEEDING (†BF/FF/MIX)	Day of symptom onset	Blood Glucose(mg/dl)	Presence of neonatal sepsis	Axial DWI MRI abnormality (‡TPOC/POC/OC/CC)
1	38	M	3.02	10	BF	3	25	+	POC, CC
2	37	M	2.9	CRY	BF	3	18	+	POC ,CC
3	37	M	2.56	CRY	MIX	1	25	+	OC
4	38	M	2.2	CRY	BF	2	28	+	TPOC
5	38	F	1.75	CRY	BF	5	38	-	CC
6	38	M	2.52	CRY	FF	2	36	+	POC,CC
7	39	M	3.3	10	BF	3	23	-	POC,CC
8	38	M	3.5	CRY	FF	3	34	+	POC,CC
9	39	M	2.4	CRY	MIX	4	31	-	TPOC,CC
10	40	M	2.9	CRY	BF	2	33	+	POC
11	39	M	2.6	9	BF	3	32	-	POC,CC
12	37	M	2.0	CRY	BF	3	22	-	POC
13	38	F	2.0	CRY	BF	3	30	-	POC

* M-MALE, F-FEMALE; †BF-Breast feeding, FF-Formula feeding, MIX-Mixed feeding; ‡POC- Parieto-occipital cortex, OC-Occipital cortex, CC-Corpus callosum, TPOC- Temporo-parieto-occipital cortex.

Table 2- Pattern of brain lesion observed in MRI Brain of the 13 cases of neonatal hypoglycemia

MRI BRAIN LESION PATTERN	
OCCIPTAL CORTEX (Fig.2)	1
PARIETO-OCCIPITAL CORTEX	3
CORPUS CALLOSUM (CC) (Fig.4)	1
PARIETO-OCCIPITAL CORTEX WITH CC	6
TEMPORO-PARIETO-OCCIPITAL CORTEX (Fig.1)	1
TEMPORO-PARIETO-OCCIPITAL CORTEX WITH CC(Fig.3)	1

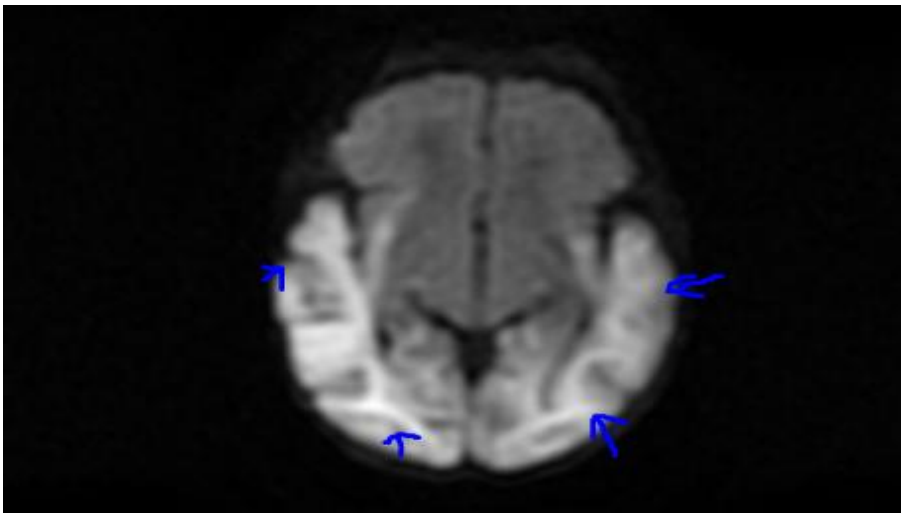

Figure 1- Axial Diffusion Weighted Image of Brain MRI: Bilateral temporo - parieto-occipital cortex diffusion abnormalities in Hypoglycaemic Brain Injury.

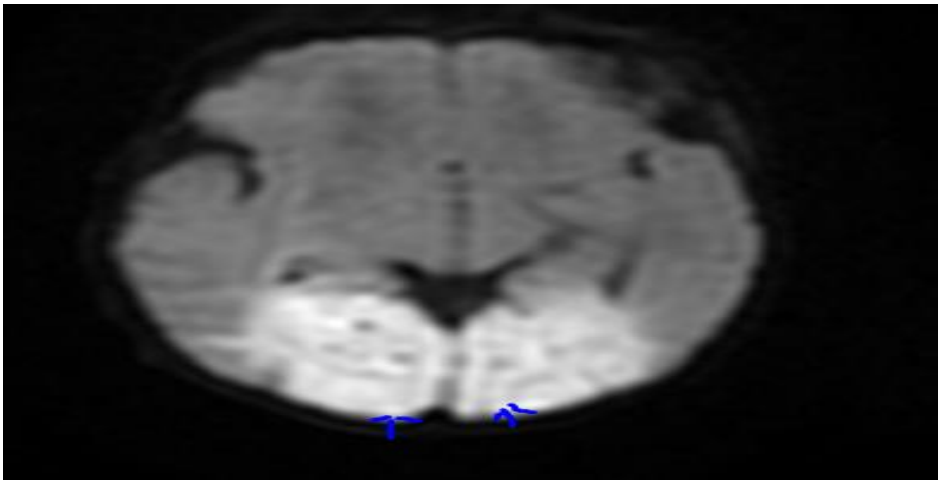

Figure 2- Axial Diffusion Weighted Image of Brain MRI: Bilateral occipital cortex involvement in a term neonate with Hypoglycaemic Brain Injury.

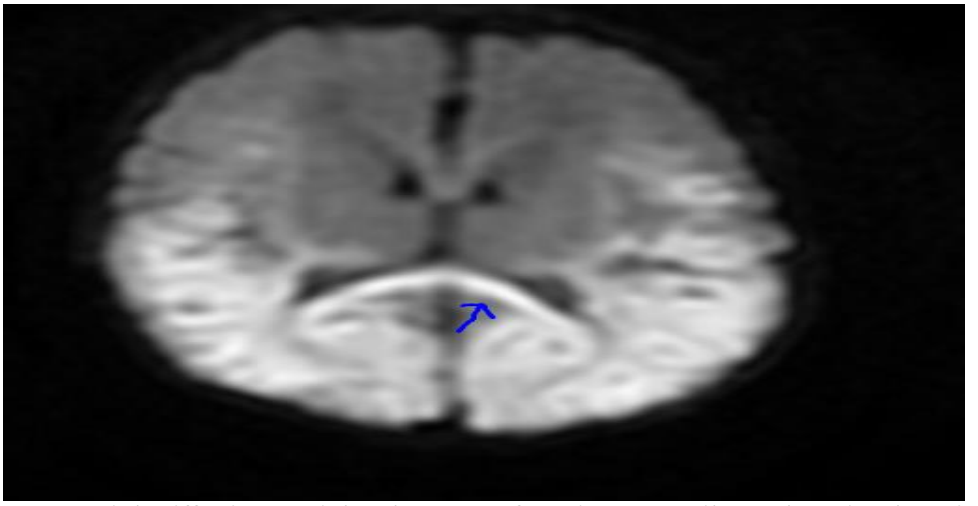

Figure 3- Axial Diffusion Weighted Image of Brain MRI: Bilateral parietal-occipital cortex with Corpus callosum abnormalities in term neonate with Hypoglycaemic Brain Injury. Arrow head suggest corpus callosum abnormality.

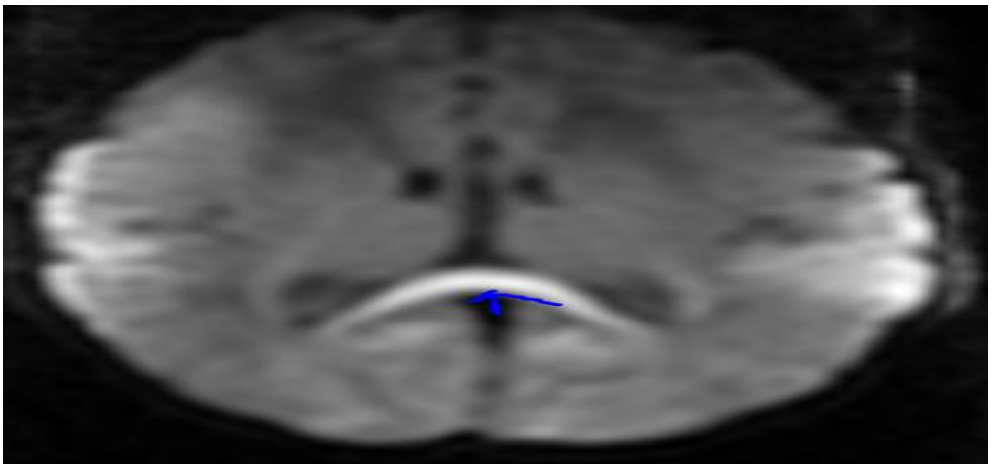

Figure 4- Axial Diffusion Weighted Image of Brain MRI: Predominant Corpus callosum involvement in term neonate with Hypoglycaemic Brain Injury.