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Hypoglycemia and neurological outcome in neonates: A retrospective study in a tertiary care hospital in Henan, China.

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Abstract

This is a retrospective study done on 170 children, aged 3 to 5 years, who were delivered in the third affiliated hospital of Zhengzhou university, Henan, China between Jan 2019 to Dec 2020. With the help of hospital records, a systematic detection of hypoglycemia (<2.2 mmol/L or 40 mg/dL) was carried out in the study population from birth to 28 days after birth. Main outcomes were a compiled neurological or neurodevelopmental outcome; any developmental delay; motor developmental delay; and cognitive developmental delay. For analysis, the study population was divided into two groups: one group consisted of children who suffered from 5 or more episodes of hypoglycemia in neonatal period (n=42) and the second group consisted those who suffered with less than 5 episodes (n=128). We noted that the group having 5 or more hypoglycemic episodes had a higher proportion of premature or small for date children than the other group (76.2% Vs 60.9%), and the difference is statistically significant. In adjusted regression analyses, the odds ratio (OR) of any neurological or neurodevelopmental outcome was 1.48 (95% confidence interval: 1.17–1.88) in group with 5 or more hypoglycemic episodes as compared to the other group. The adjusted risk of any developmental delay was more than doubled (OR 2.53 [1.71–3.73]), the adjusted risk of motor developmental delay was almost doubled (OR: 1.91 [1.06–3.44]) and the adjusted risk of cognitive developmental delay was almost tripled (OR 2.85 [1.70–4.76]) in the group that had more than 5 hypoglycemic episodes in neonatal period.

Keywords: Children, Blood glucose, Hypoglycemia, Neurological outcome, Developmental delay.

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Introduction

Hypoglycemia may be caused by various defective pathways in the production and metabolism of glucose, as well as defective pathways to maintain euglycemia [1]. Plasma glucose levels are maintained at ~55–60 mg/dL after birth, and then increase to 70 mg/dL at approximately 2 days of life [2]. The newborn period is reflected by a plasma glucose requirement of approximately 6 mg/kg/min, which changes relative to prematurity and increasing age [3]. Premature or growth restricted infants may have reduced ability to maintain euglycemia, due to reduced glycogen stores, increased metabolic needs, or poor counter-regulatory response to hypoglycaemia [4]. In children, conditions that cause hypoglycemia are often complex, diverse, and unique; therefore, evaluation and management of the hypoglycemic child requires a substantial knowledge of all physiologic mechanisms that maintain euglycemia [5].

Longstanding discussion and research continue in order to define clinical hypoglycemia. This can be defined as a plasma glucose level below 68 mg/dL, the cutoff glucose value for when counter-regulatory processes can occur [6]. However, other studies and guidelines have proposed various plasma glucose cutoff values which could be associated with increased risk for long-term adverse outcomes [7]. Official guidelines and others have noted that among infants who are symptomatic, plasma glucose level less than 50 mg/dL (<48 hours of life), and less than 60 mg/dL (>48 hours of life) should be evaluated [1].

Despite extensive literature on the subject, hypoglycemia in infants and children remains a puzzling yet urgent diagnostic and therapeutic challenge. Neonatal hypoglycemia is a common condition, and though many children do not develop sequelae, a few can develop severe neurological damage [8]. The neurological symptoms of neonatal hypoglycemia are non-specific. These symptoms may appear gradually, with irritability, tremor, jitteriness, eye rolling, seizures, hypotonia, exaggerated Moro reflex, and progression to seizures, and acute encephalopathy, lethargy and coma [8]. The most common clinical finding reported by many researchers is an altered level of alertness,

characterized as a combination of jitteriness or stupor [9]. At follow up, neonatal hypoglycemia may lead to reduced head circumference, lower than expected psychomotor scores, motor deficit and mental retardation [8].

The aim of the study was to investigate the neurological effects of neonatal hypoglycemia in the third affiliated hospital of Zhengzhou university, Henan, China.

Materials and Methods

The current study is a retrospective study done on 170 children, aged 3 to 5 years, who were delivered in the third affiliated hospital of Zhengzhou university, Henan, China between Jan 2019 to Dec 2020. The inclusion criteria was a reported hypoglycemic episode or repeated episodes of hypoglycemia in these children in the neonatal period. With the help of hospital records, a systematic detection of hypoglycemia (<2.2 mmol/L or 40 mg/dL) was carried out in the study population from birth to 28 days after birth. The children who had incomplete hospital records were excluded from the study. Apart from that, children with congenital malformations, admitted in neonatal intensive care unit, born with inborn errors of metabolism and those with diabetic mothers were excluded. Exposure was neonatal moderate hypoglycemia. Main outcomes were the following (Table 1).

Table 1: *Statistical Analyses.*

Outcome	ICD-10 codes
Any neurological outcome:	
Intellectual disabilities	F70, F71, F72, F73, F78, F79
Specific developmental disorders	F80, F81, F82, F83
Autism spectrum disorders	F84
Disorders of psychological development	F88
Attention-deficit/hyperactivity disorders	F90
Tics, stereotypic behavior, stuttering	F95, F98.4, F98.5
Myoclonus, epilepsy and recurrent seizures, status epilepticus	G25.3, G40, G41
Abnormalities of gait and movement, other lack of coordination	R26, R27
Dyslexia and alexia, other symbolic dysfunctions	R48.0, R48.8
Seizures including febrile seizures	R56
Any developmental delay	F70, F71, F72, F73, F78, F79 F80.0, F80.1, F80.2, F80.8, F80.9, F81.0, F81.1, F81.2, F81.3, F81.8, F81.9, F82, F83, R26, R27 R48.0, R48.8
Motor developmental delay	F82, R26, R27
Cognitive developmental delay	F70, F71, F72, F73, F78, F79, F80.0, F80.1, F80.2, F80.8, F80.9, F81.0, F81.1, F81.2, F81.3, F81.8, F81.9, F83, R48.0, R48.8

A P value < 0.05 was considered statistically significant. For statistical analyses, SAS version 9.4 was used. The study was approved by the institutional ethical committee.

Results

Out of 170 children, 120 (70.6%) had recurring or multiple episodes of hypoglycemia in their neonatal period and rest 50 children had a single severe episode of hypoglycemia. It was seen that 68 (40.0%) children were diagnosed with hyperbilirubinemia and 18 (10.6%) with Hypoxic-Ischaemic Encephalopathy (HIE).

The mean age of children was 3.2 years (SD 0.5 years), with a mean birth weight of 1824 grams (SD 504 grams). One hundred and fifteen children (67.6%) were premature or small for date. Their mean blood glucose level at 28 days was 44 gm/dl (SD 13 gm/dl).

For analysis, the study population was divided into two groups: one group consisted of children who suffered from 5 or more episodes of hypoglycemia in neonatal period (n=42) and the second group consisted those who suffered with less than 5 episodes (n=128). This division, though arbitrary, was made as some of the outcomes were significantly different in the two groups. It was noted that children having 5 or more episodes had more complications and interest of outcome (any neurological outcome like intellectual disabilities, autism spectrum disorders, disorders of psychological development, attention deficit/ hyperactivity disorder, tics, stereotype behavior, stuttering, myoclonus, epilepsy and recurrent seizures, status epilepticus, abnormalities of gait and movement, other lack of coordination, dyslexia and alexia, other symbolic dysfunctions, seizures including febrile seizures, any motor/ cognitive developmental delay) as compared to the children with lower number of hypoglycemic episodes. Maternal, delivery and infant characteristics have been depicted in Table 2. It was noted that the group having 5 or more hypoglycemic episodes had a higher proportion of premature or small for date children as compared to the other group (76.2% Vs 60.9%), and the difference is statistically significant. The neurologic sequalae reported in study population has been depicted in Table 3, with seizures as presenting symptom to be the most common neurological finding in these children.

Table 2: *Maternal, delivery and infant characteristics.*

Characteristics		Group with 5 or more hypoglycemic episodes (n=42) Number (%)	Group with less than 5 hypoglycemic episodes (n=128) Number (%)	Significant difference present
Maternal age	<30 years	28 (66.6)	77 (60.1)	No
	>30 years	14 (33.4)	51 (39.9)	
Maternal BMI	<25	20 (47.6)	68 (53.1)	No
	>25	22 (52.4)	60 (46.9)	
Prematurity or Small for gestational age	Yes	32 (76.2)	78 (60.9)	Yes
	No	10 (23.8)	50 (39.1)	
Infant sex	Male	22 (52.4)	58 (45.3)	No
	Female	20 (47.6)	70 (54.7)	

The odds of developing an abnormal neurodevelopmental outcome was 3.5 times more in children who suffered from 5 or more episodes of hypoglycemia as compare to children who suffered from leaser or one episode of hypoglycemia. In adjusted regression analyses, the odds ratio (OR) of any neurological or neurodevelopmental outcome was 1.48 (95% confidence interval: 1.17–1.88) in group with 5 or more hypoglycemic episodes as compared to the other group. The adjusted risk of any developmental delay was more than doubled (OR 2.53 [1.71–3.73]), the adjusted risk of motor developmental delay was almost doubled (OR: 1.91 [1.06–3.44]) and the adjusted risk of cognitive developmental delay was almost tripled (OR 2.85 [1.70–4.76]) in the group that had more than 5 hypoglycemic episodes in neonatal period (Table 4).

Discussion

The general assumption is that asymptomatic infants with transient hypoglycemia are at very low risk of neurologic complications [10,11] and this is supported by some studies [12,13]. However, there are indications that even moderate neonatal hypoglycemia may be associated with structural brain abnormalities [14,15], impaired neurodevelopment [16], impaired executive function and visual motor function [17] and poor school performances [18].

In the current study it was noted that the proportion of children manifesting any one or more adverse neurological outcomes (enlisted in methods section) was very high (70%). The proportion of children manifesting these

Table 3: *Neurologic sequalae and hypoglycemic findings in 170 children.*

Findings		No. of Patients (%)
Neurologic sequalae	Seizures as presenting symptoms	119 (70.0)
	Any neurological outcome	112 (65.9)
	Motor and/ or psycho-developmental delay	111 (65.3)
	Visual impairment	82 (48.2)
	Microcephaly	63 (37.0)
	Any other anomaly	34 (26.6)
Hypoglycemic findings	Blood glucose level when hypoglycemia first detected	Median – 7 mg/dl (Range 2-26 mg/dl)
	Postnatal time (hours) when hypoglycemia first detected	Median – 48 hours (Range 1-72 hours)
	Recurrent episodes	N (%): 120 (70.6)

Table 4: *Risks of adverse neurodevelopmental outcomes in the two groups.*

Outcomes	Less than 5 hypoglycemic episodes (N=128)			5 or more hypoglycemic episodes (N=42)		
	n	Adjusted Odd's Ratio*	95% confidence intervals	n	Adjusted Odd's Ratio*	p-Value (95% confidence intervals)
Any neurological or neurodevelopmental outcome	76	1.00	(Reference)	36	1.48	0.03 (1.17–1.88)
Any developmental delay	55	1.00	(Reference)	56	2.53	<0.001 (1.71–3.73)
Motor developmental delay	26	1.00	(Reference)	25	1.91	0.002 (1.06–3.44)
Cognitive developmental delay	29	1.00	(Reference)	31	2.85	<0.001 (1.70–4.76)

*Adjusted for mode of delivery, birth weight for gestational age, gestational age, sex, Apgar score and birth year

outcomes were not that high in other studies [10,12,15]. The reason for the same is that our study was a hospital based study and consisted of children visiting the hospital due to some neurological adverse event or developmental delay. Children who did not develop any sequalae due to hypoglycemia are least likely to visit the hospital. It is also noteworthy that majority of the study sample was premature or small for date, which in itself is a predisposing factor for developmental delay. Also, the diagnostic criteria vary between studies that could lead to this incongruency.

However, in the current study we found that recurrent episodes of hypoglycemia were strongly correlated with persistent neurodevelopmental and physical growth deficits until 5 years of age. Other studies have also reported congruent findings to our study [12,19-22]. In our study, it was reported that prematurity or being small for date is associated with having 5 or more hypoglycemic episodes. In another study of moderately preterm infants, hypoglycemia was identified as the only neonatal morbidity that could predict an impaired neurodevelopment as reported by parents at 4 years of age [23]. The authors argued for a causal association and suggested intensified monitoring of glucose levels in moderately preterm infants. Two other studies have failed to associate moderate hypoglycemia to impaired neurodevelopmental outcomes [12,24].

In the current study it was found that 40% of the children had jaundice. Jaundice in neonates can be of various kinds: physiologic jaundice, breastfeeding failure jaundice, breast milk jaundice, jaundice from hemolysis, and jaundice caused by poor liver function. Also, genetic disorders or enzymatic deficiencies like galactose-1-phosphate uridyl transferase deficiency, 1-phosphofructaldolase deficiency (hereditary fructose intolerance), and fumaryl acetoacetate hydrolyase deficiency (Tyrosinemia) manifest as hyperbilirubinemia and many such neonates suffer from hypoglycemia. In this case, all the neonates had unconjugated hyperbilirubinemia. One of the main reasons is that the hepatobiliary system is immature. Hepatocytes haven't yet expressed the genes related to the formation of glycosyltransferase with full power. (The hepatocytes have undersupplied the glycosyltransferase). Newborn babies have a little extra load of unconjugated bilirubin to the liver. There is a significant impairment of conjugating power of the newborn's liver. However, in this study, the main problem identified was hypoglycemia and not hyperbilirubinemia. Discussion over the same is out of the scope in this paper.

Recurrent hypoglycemia also was a more predictable factor for long-term effects than the severity of a single hypoglycemic episode. Therefore repetitive blood glucose monitoring and rapid treatment even for mild hypoglycemia are recommended for small-for-gestational-age infants in the neonatal period.

In the current study, seizure was reported as the most common neurological sequalae in the study population. Seizures are usually the first presenting symptom of profound hypoglycemia (bgl<25 g/dl).[8] Seizures that are associated with hypoglycemia have a worse prognosis than hypoglycemia without seizures.[25] Visual impairment, another common symptom reported in the current study, is reportedly due to injury of the occipital lobes [8].

There are several limitations to the study. Firstly, due to lack of time and resources we conducted a retrospective study. However, a prospective cohort model is more suitable to these kinds of cause-effect studies. We excluded children whose hospital records did not show the desired outcome (hypoglycemia). Diagnosis status is a blunt instrument and there may be missed cases of moderate hypoglycemia where the diagnosis was not entered by the doctor at discharge. Like any other retrospective study, this study is susceptible to detection bias or selection bias (as is evidenced from the over representation of the outcome of interest in the study population). Despite of the limitations, our study contributes to the pool of evidence by providing data on a disputed and under-studied subject.

Conclusion

Hypoglycemia is a heterogeneous disorder with many possible etiologies, and a multidisciplinary approach is ideal in caring for these infants and children with this condition. We conclude that moderate neonatal hypoglycemia is associated with increased risks of impaired neurodevelopment in pre-school children. However, larger prospective studies are needed to substantiate the claims.

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References

1. Gandhi K. Approach to hypoglycemia in infants and children. Transl Pediatr 2017; 6:408-420.
2. Stanley CA. Perspective on the Genetics and Diagnosis of Congenital Hyperinsulinism Disorders. J Clin Endocrinol Metab 2016; 101: 815-826.
3. Kappy MS, Geffner ME, Allen DB. Pediatric Practice: Endocrinology. 2nd Edition. McGraw-Hill Education/ Medical 2014.
4. Thornton PS, Stanley CA, De Leon DD. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr 2015; 167: 238-245.
5. Lteif AN, Schwenk WF. Hypoglycemia in Infants and Children. Endocrinol Metab Clin North Am 1999; 28: 619-646.
6. Sperling MA. Editor. Pediatric Endocrinology. 3rd edition. Philadelphia: Elsevier/Saunders, 2008.
7. Cornblath M, Hawdon JM, Williams AF. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000; 105: 1141-1145.

8. Alkalay AL, Sarnat HB, Flores-Sarnat L, Simmons CF. Neurologic aspects of neonatal hypoglycemia. Isr Med Assoc J 2005; 7: 188-192.
9. Volpe I. Hypoglycemia and brain injury. In: Neurology of the newborn. 4th Edn. Philadelphia, WB Saunders. 2001:497-520.
10. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed 2013; 98: 2-6.
11. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000; 105: 1141–1145.
12. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015; 373: 1507-1518.
13. Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012; 130: e1497–e1503.
14. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008; 122: 65-74.
15. Kinnala A, Rikalainen H, Lapinleimu H, Parkkola R, Kormano M, Kero P. Cerebral magnetic resonance imaging and ultrasonography findings after neonatal hypoglycemia. Pediatrics 1999; 103: 724–729.
16. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988; 297: 1304–1308.
17. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatr 2017; 171: 972–983.
18. Kaiser JR, Bai S, Gibson N, Holland G, Lin TM, Swearingen CJ. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. JAMA Pediatr 2015; 169: 913-921.
19. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatr 2017; 171: 972-983.
20. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008; 122: 65-74.
21. Kinnala A, Rikalainen H, Lapinleimu H, Parkkola R, Kormano M, Kero P. Cerebral magnetic resonance imaging and ultrasonography findings after neonatal hypoglycemia. Pediatrics 1999; 103: 724–729.
22. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988; 297: 1304–1308.
23. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 2012; 130: e265–e272.
24. Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012; 130: e1497–e1503.
25. Greery RDG. Hypoglycemia in the newborn: diagnosis, treatment and prognosis. Dev Med Child Neurol 1966; 8: 764-754.

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