Identifying risk effectors involved in neonatal hypoglycemia occurrence

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Abstract

Hypoglycemia is a common metabolic condition in neonatal period, but severe and persistent hypoglycemia can cause neurological damage and brain injury. The aim of this study was to analyze the risk factors of neonatal hypoglycemia in clinic. A total of 135 neonatal hypoglycemia infants and 135 healthy infants were included in this study. The differences in birth weight between neonatal hypoglycemia group and healthy control group were analyzed via t test. The associations between neonatal blood sugar level and relevant characteristic factors were explored using χ² test. Binary logistic regression analysis was used to analyze risk factors related to the incidence of neonatal hypoglycemia. The results showed that the average birth weight was matched in neonatal hypoglycemia group and healthy control group. Neonatal blood sugar level of the infants was significantly associated with born term, birth weight, feed, GDM and hypothermia (all \( P < 0.05 \)). Besides, logistic regression analysis showed that babies’ born term (OR=2.715, 95%CI: 1.311-5.625), birth weight (OR=1.910, 95%CI: 1.234-2.955), improper feeding (OR=3.165, 95%CI: 1.295-7.736) and mother’s GDM (OR=2.184, 95%CI: 1.153-4.134) were high risk factors for neonatal hypoglycemia. The incidence of hypoglycemia in infants was significantly associated with various clinical factors. And monitoring these risk factors is one of important measures to reduce long-term neurological damage caused by neonatal hypoglycemia.

Keywords: Hypoglycemia; Risk factor; Clinical analysis; Neonatal
Introduction

Hypoglycemia is a common and life threatening complication of several diseases, such as severe malaria, bacterial sepsis, severe malnutrition and neonatal illness [1, 2]. As a common metabolic condition in neonatal period, hypoglycemia reflects the process of physiological glucose metabolism and is transient in most cases [3]. The majority of neonatal hypoglycemia symptoms are hidden, and refractory hypoglycemia can lead to more severe neurological damage, and even sudden death [4-6]. Hypoglycemia usually occur within 1-2 days after birth, especially in 6-12 hours, with most of the cases being asymptomatic. In recent years, the incidence of neonatal hypoglycemia has shown an increasing trend along with the increase in birth rate and advanced technique for hypoglycemia detection. Severe and prolonged hypoglycemia can result in metal retardation, neurological deficits and recurrent seizures. In developing world, hypoglycemia remains a killer among children due to the lack of understanding on this problem.

Accumulated studies have shown that pregnancy complications, such as pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM) and intrahepatic cholestasis (ICP), could affect perinatal situations [7-13]. Glucose plays important roles in brain metabolism and brain development in newborns. The clinical symptoms of newborns with neonatal hypoglycemia contain hypotonia, low reaction, pale, sweating, feeding difficulties and low temperature, and are often accompanied by mild to moderate disturbance of consciousness, lethargy, tremors and irritability. With the aggravation of hypoglycemia severity, newborns may show coma, epilepsy and other neurological symptoms [5]. Severe neonatal hypoglycemia can lead to poor outcome. Therefore, it is of great importance to identify factors associated with hypoglycemia so as to improve the outcomes of hypoglycemic children.

In this study, we aimed to explore clinical factors associated with the incidence of neonatal hypoglycemia. Moreover, binary logistic regression analysis was used to analyze high risk factors for neonatal hypoglycemia.

Materials and methods
Study populations and general parameters

Born between October 2015 and November 2016 in Guizhou Provincial People’s Hospital, a total of 135 newborns with neonatal hypoglycemia were collected in the study, and according to 1:1 proportion, 135 healthy newborns with normal blood sugar level were randomly selected during the same period in hospital as control group. The infants in the two groups were all with gestational age ranged from 35 weeks to 42 weeks and their birth weights were between 2,000 and 4,900 g.

Usually, blood glucose less than 2.6mmol/L is an indicator for clinical intervention and treatment. In our study, venous or peripheral blood glucose less than 2.2 mmol/L (40mg/dL) was considered as hypoglycemia. After 48-72h of birth, the diagnosis of newborns is still with hypoglycemia was considered as persistent hypoglycemia. All the newborns with hypoglycemia were regularly monitored for blood glucose, and timely treatments were performed for the cases. The main symptoms of hypoglycemia among the newborns included hypotonia, low reaction, less cry, low temperature, pale, sweating, apnea and irritability, and these symptoms would disappear after blood glucose got back to normal level, and no sever complications, such as infection or neonatal hyperbilirubinemia, were observed.

Newborns with congenital metabolic diseases, endocrine disorders or hyperinsullinemia, and those with incomplete clinical data or without information from regular monitoring of blood glucose were excluded from our study.

This study protocol was approved by the Medical Ethics Committee of Guizhou Provincial People’s Hospital. Written informed consent for sample collection was obtained before the study.

Blood glucose determination and treatment

2-3 mL of femoral vein blood was obtained from each of the newborns within 1-2 hour after birth. The blood glucose levels were measured using automatic biochemical analyzer (Backman, USA ). Then the glucose levels of heel peripheral blood were monitored using micro blood glucose instrument (JNJ, USA) according to the situation.

The newborns with symptomatic hypoglycemia were immediately given 10% glucose at a
dose of 2 ml/kg through intravenous injection, and then through infusion at a dose of 6-8 mg/(kg.min), thus maintaining blood glucose at 4.4-5.5 mmol/L. For asymptomatic hypoglycemia newborns, the first choice was feeding as soon as possible. If they were not able to suck, intravenous glucose infusion would be adopted for the treatment. Blood glucose levels were monitored once an hour, accompanied by the treatment of primary disease. Such monitoring would be stopped 48 ~ 72 h after blood glucose achieving normal levels.

Statistical analysis
Data were expressed as mean ± standard deviation (SD). Statistical analyses were carried out using the software of SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). The differences in birth weight between neonatal hypoglycemia group and healthy control group were analyzed with t test. The associations between neonatal blood sugar level and relevant factors were analyzed using χ² test. Binary logistic regression analysis was used to analyze risk factors related to the incidence of neonatal hypoglycemia. P value less than 0.05 was considered to be statistically significant.

Results
The characteristics of infants in this study
135 newborns with neonatal hypoglycemia were collected as cases and 135 healthy babies as controls. The average birth weight was 3329.58±630.41 g in neonatal hypoglycemia group, ranging from 2160 to 4800 g, while 3277.07±464.87 g in the control group, ranging from 2000 to 4430 g. The average birth weight in the two groups was matched. The characteristics of the newborns were listed in Table 1, including gender, term, body weight, feeding, GDM, gestational hypertension and body temperature.

Relationship between blood glucose levels and clinical parameters
In the present study, we analyzed the clinical characteristics both in neonatal hypoglycemia group and normal control group. As shown in Table 1, neonatal blood sugar level were
significantly associated with term ($P=0.005$), birth weight ($P<0.001$), feeding ($P=0.007$), mother’s GDM ($P=0.006$) and hypothermia ($P=0.010$). However, no significant association was found with gender or gestational hypertension (all $P>0.05$).

Risk factors related to the incidence of neonatal hypoglycemia

To analyze risk factors correlated with neonatal hypoglycemia, we used binary logistic regression analysis. As shown in Table 2, born term (OR=2.715, 95%CI: 1.311-5.625), birth weight (OR=1.910, 95%CI: 1.234-2.955), improper feeding (OR=3.165, 95%CI: 1.295-7.736) and mother’s GDM (OR=2.184, 95%CI: 1.153-4.134) were among high risk factors for the incidence of neonatal hypoglycemia (all $P<0.05$).

Discussion

Glucose is the sole energy source for brain development during neonatal period [14]. The level of glucose in brain tissue is related to cerebral blood flow, the quantity and activity of glucose transporters in blood-brain barrier, and the available surface area. Hypoglycemia can harm multiple organs, especially for metabolically active organ, such as the brain, liver and heart [15-18]. Kirchhoff BA et al. analyzed the long-term effects of severe hypoglycemia on brain structure and neural memory impairments in individuals with type 1 diabetes mellitus and suggested that hypoglycemia would produce permanent deleterious effects on brain structure and memory function [15]. Severe and persistent hypoglycemia can cause neurological damage in brain [19]. Blood tests are necessary for approximately 30% of newborns for screening neonatal hypoglycemia, and half of them will develop hypoglycemia [20]. Although clinical guidelines have offered some recommendations announcing that prophylactic measures should be taken for babies at risk of neonatal hypoglycemia, no effective measure for the prevention has been developed beyond early feeding. In the present study, we found that the average birth weight was matched in neonatal hypoglycemia group and healthy control group. The analysis results from $\chi^2$ test showed that neonatal hypoglycemia was significantly associated with born term, birth weight, mother’s GDM and hypothermia. Reportedly, neonatal
hypoglycemia could cause many perinatal conditions. For instance, Montassir H et al. indicated that severe and prolonged neonatal hypoglycemia could cause cerebral lesions and other perinatal syndromes, such as hypoxia, neonatal seizure and pathological jaundice, which would exacerbate hypoglycemic brain injuries [21]. Wong DS et al. reported that selective posterior white matter and pulvinar edema were among the strongest predictors for clinical hypoglycemia, and that injury (36%) or watershed (32%) pattern of injury was rare in severe hypoglycemia [22].

In this study, we also analyzed risk factors related to the incidence of neonatal hypoglycemia, mainly including born term, birth weight, improper feeding and mother’s GDM, and the findings were consistent with those from previous studies. For example, the study by Abu-Salah O et al. showed that late preterm infants had higher risk of morbidity and hospitalization than term infants, and preterm infants might suffer hypoglycemia, septicaemia, feeding difficulties and significant jaundice [23]. Staffler A et al. also demonstrated that preterm infants with very low birth weight were at risk of hypoglycemia [24]. Accumulated evidences have indicated that infants born to women with GDM are at high risk for hyperinsulinism-related hypoglycemia in response to maternal hyperglycemia during pregnancy [25-27]. Hypoglycemia in infants at risk can be attenuated or cured through intervention treatments, such as oral dextrose gel or reasonable feeding [28, 29].

There are still some limitations in our study. Firstly, a large number of study subjects can improve the accuracy of the results, but the sample size in the current study was not large enough. Secondly, clinical parameters involved in the study analyses were limited. Thirdly, premature birth and low birth weight are significantly correlated with neonatal hypoglycemia [30]. However, the gestational age less than 35 weeks and infants with very low birth weight were not included in this study. In such conditions, partly premature and infants of very low birth weight were ignored, thus leading bias to our final results. Therefore, more studies are needed to solve these issues and verify our results based on the large sample size.

In conclusion, the incidence of hypoglycemia in infants was significantly associated with born term, birth weight, improper feeding and mother’s GDM. Due to the limitations of this study, further studies are needed to identify more effective factors for the hypoglycemia diagnosis and treatment so as to prevent brain injury.
Ethical Statement

This study was supported by the Ethics Committee of Guizhou Provincial People's Hospital and also has been carried out in accordance with the World Medical Association Declaration of Helsinki.

The subjects had been informed the objective. Certainly, written consents were signed by every subject in this study.

Authors’ contributions:

Conceived and designed the study strategy: Q.L, T.Z. Designed the experiment: M.Z.
Recruited the participants and collected their information: W.D. Conducted the literature review and selected candidate SNPs: Y.X. Performed the experiments: L.K. Analysis the data: Y.M. Wrote the manuscript: G.S. Prepared the tables and references: G.S.

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References

[1] Nadjm B, Mtove G, Amos B, Hildenwall H, Naijuka A, Mtei F, Todd J and Reyburn H. Blood glucose as a predictor of mortality in children admitted to the hospital with febrile illness in Tanzania. Am J Trop Med Hyg 2013; 89: 232-237.

[2] Houin S and Rozance PJ. 50 years ago in the Journal of pediatrics: The incidence of neonatal hypoglycemia in a nursery for premature infants. J Pediatr 2014; 164: 1485.

[3] Tin W. Defining neonatal hypoglycaemia: a continuing debate. Semin Fetal Neonatal Med 2014; 19: 27-32.

[4] Harris DL, Weston PJ, Battin MR and Harding JE. A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network. J Paediatr Child Health 2014; 50: E55-62.

[5] Fong CY and Harvey AS. Variable outcome for epilepsy after neonatal hypoglycaemia. Dev Med Child Neurol 2014; 56: 1093-1099.

[6] Zhou D, Qian J, Liu CX, Chang H and Sun RP. Repetitive and profound insulin-induced hypoglycemia results in brain damage in newborn rats: an approach to establish an animal model of brain injury induced by neonatal hypoglycemia. Eur J Pediatr 2008; 167: 1169-1174.

[7] Blair E and Watson L. Cerebral palsy and perinatal mortality after pregnancy-induced hypertension across the gestational age spectrum: observations of a reconstructed total population cohort. Dev Med Child Neurol 2016; 58 Suppl 2: 76-81.

[8] Park YH, Lee GM, Yoon JM, Cheon EJ, Ko KO, Lee YH and Lim JW. Effect of early postnatal neutropenia in very low birth weight infants born to mothers with pregnancy-induced hypertension. Korean J Pediatr 2012; 55: 462-469.

[9] Sirimarco MP, Guerra HM, Lisboa EG, Vernini JM, Cassetari BN, de Araujo Costa RA, Rudge MV and de Mattos Paranhos Calderon I. Diagnostic protocol for gestational diabetes mellitus (GDM) (IADPSG/ADA, 2011): influence on the occurrence of GDM and mild gestational hyperglycemia (MGH) and on the perinatal outcomes. Diabetol Metab Syndr 2017; 9: 2.

[10] Palatnik A, Mele L, Landon MB, Reddy UM, Ramin SM, Carpenter MW, Wapner RJ, Varner MW, Rouse DJ, Thorp JM, Jr., Sciscione A, Catalano P, Saade GR, Caritis SN and Sorokin Y. Timing of treatment initiation for mild gestational diabetes mellitus and perinatal outcomes. Am J Obstet Gynecol
Mirzamoradi M, Heidar Z, Faalpoor Z, Naeiji Z and Jamali R. Comparison of glyburide and insulin in women with gestational diabetes mellitus and associated perinatal outcome: a randomized clinical trial. Acta Med Iran 2015; 53: 97-103.

Ekiz A, Kaya B, Avci ME, Polat I, Dikmen S and Yildirim G. Alanine aminotransferase as a predictor of adverse perinatal outcomes in women with intrahepatic cholestasis of pregnancy. Pak J Med Sci 2016; 32: 418-422.

Sargin Oruc A, Seckin B, Ozcan N, Ozyer S, Uzunlar O and Danisman N. Role of postprandial bile acids in prediction of perinatal outcome in intrahepatic cholestasis of pregnancy. J Obstet Gynaecol Res 2014; 40: 1883-1889.

Brekke E, Morken TS and Sonnewald U. Glucose metabolism and astrocyte-neuron interactions in the neonatal brain. Neurochem Int 2015; 82: 33-41.

Kirchhoff BA, Lugar HM, Smith SE, Perantie DC, Kolody BC, Koller JM, Arbelaez AM, Shimony JS and Hershey T. Hypoglycaemia-induced changes in regional brain volume and memory function. Diabet Med 2013; 30: e151-156.

Ennis K, Dottermann H, Stein A and Rao R. Hyperglycemia accentuates and ketonemia attenuates hypoglycemia-induced neuronal injury in the developing rat brain. Pediatr Res 2015; 77: 84-90.

Chung K, Bang S, Kim Y and Chang H. Intraoperative severe hypoglycemia indicative of post-hepatectomy liver failure. J Anesth 2016; 30: 148-151.

Kobayashi C, Sasaki H, Kosuge K, Miyakita Y, Hayakawa M, Suzuki A, Abe E, Suzuki K and Aizawa Y. Severe starvation hypoglycemia and congestive heart failure induced by thyroid crisis, with accidentally induced severe liver dysfunction and disseminated intravascular coagulation. Intern Med 2005; 44: 234-239.

Boardman JP, Wusthoff CJ and Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed 2013; 98: 2-6.

Harris DL, Weston PJ and Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr 2012; 161: 787-791.

Montassir H, Maegaki Y, Ogura K, Kurozawa Y, Nagata I, Kanzaki S and Ohno K. Associated factors in neonatal hypoglycemic brain injury. Brain Dev 2009; 31: 649-656.

Wong DS, Poskitt KJ, Chau V, Miller SP, Roland E, Hill A and Tam EW. Brain injury patterns in
hypoglycemia in neonatal encephalopathy. AJNR Am J Neuroradiol 2013; 34: 1456-1461.

[23] Abu-Salah O. Unfavourable outcomes associated with late preterm birth: observations from Jordan. J Pak Med Assoc 2011; 61: 769-772.

[24] Staffler A, Klemme M, Mola-Schenzle E, Mittal R, Schulze A and Flemmer AW. Very low birth weight preterm infants are at risk for hypoglycemia once on total enteral nutrition. J Matern Fetal Neonatal Med 2013; 26: 1337-1341.

[25] Youngwanichsettha S and Phumdoung S. Association between neonatal hypoglycaemia and prediabetes in postpartum women with a history of gestational diabetes. J Clin Nurs 2014; 23: 2181-2185.

[26] Flores-le Roux JA, Sagarra E, Benaiges D, Hernandez-Rivas E, Chillaron JJ, Puig de Dou J, Mur A, Lopez-Vilchez MA and Pedro-Botet J. A prospective evaluation of neonatal hypoglycaemia in infants of women with gestational diabetes mellitus. Diabetes Res Clin Pract 2012; 97: 217-222.

[27] Rahmani A and Afandi B. Improving neonatal complications with a structured multidisciplinary approach to gestational diabetes mellitus management. J Neonatal Perinatal Med 2015; 8: 359-362.

[28] Weston PJ, Harris DL, Battin M, Brown J, Hegarty JE and Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database Syst Rev 2016; CD011027.

[29] Harding JE, Hegarty JE, Crowther CA, Edlin R, Gamble G and Alsweiler JM. Randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): study protocol. BMC Pediatr 2015; 15: 120.

[30] Stomnaroska O, Petkovska E, Jancevska S and Danilovski D. Neonatal Hypoglycemia: Risk Factors and Outcomes. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2017; 38: 97-101.
| Parameters                               | Case number | Neonatal blood sugar level | $\chi^2$ | $P$    |
|-----------------------------------------|-------------|-----------------------------|----------|--------|
| Gender                                  |             |                             |          |        |
| Boy                                     | 145         | normal 74                   | 0.134    | 0.714  |
| Girl                                    | 125         | hypoglycemia 71             |          |        |
| Term                                    |             |                             |          |        |
| Full-term                               | 227         | normal 122                  | 7.994    | 0.005  |
| Premature                               | 43          | hypoglycemia 105            |          |        |
| Birth weight                            |             |                             |          |        |
| Normal                                  | 213         | normal 118                  | 15.503   | <0.001 |
| LBW                                     | 28          | hypoglycemia 95             |          |        |
| Macrosomia                              | 29          | normal 5                    |          |        |
| Feed                                    |             |                             |          |        |
| Normal                                  | 240         | normal 127                  | 7.350    | 0.007  |
| Improper                                | 30          | hypoglycemia 22             |          |        |
| GDM                                     |             |                             |          |        |
| No                                      | 209         | normal 114                  | 7.645    | 0.006  |
| Yes                                     | 61          | hypoglycemia 40             |          |        |
| Gestational hypertension                |             |                             | 0.567    | 0.451  |
| No                                      | 238         | normal 121                  |          |        |
| Yes                                     | 32          | hypoglycemia 18             |          |        |
| Body temperature                        |             |                             | 6.595    | 0.010  |
| Normal                                  | 236         | normal 125                  |          |        |
| Hypothermia                              | 34          | hypoglycemia 24             |          |        |

Notes: LBW: low birth weight; GDM, gestational diabetes mellitus.
Table 2. Binary logistic regression analysis of factors contributing to neonatal hypoglycemia

| Variables  | $\beta$ | Wald  | $P$  | OR   | 95%CI          |
|------------|--------|-------|------|------|---------------|
| Term       | 0.999  | 7.229 | 0.007| 2.715| 1.311-5.625   |
| Birth weight | 0.647  | 8.440 | 0.004| 1.910| 1.234-2.955   |
| Feed       | 1.152  | 6.381 | 0.012| 3.165| 1.295-7.736   |
| GDM        | 0.781  | 5.751 | 0.016| 2.184| 1.153-4.134   |

Notes: GDM, gestational diabetes mellitus; OR: Odds Ratio; 95% CI: 95% confidence interval. A two-sided $P$ value of less than 0.05 was considered statistically significant.
