Correlation between Hypoglycemia and Positive Rate of Inborn Error of Metabolism in Neonatal Intensive Care Unit

Wen-jun Tu*[1], MD; Jian He[2], MD and Ying Li[3], MD

1. Department of Clinical laboratory, China Rehabilitation Research Center, Beijing, China
2. Center for Clinical Laboratory Development, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China
3. Department of Pediatrics, Beijing Haidian Maternal & Child Health Hospital, Beijing, China

Abstract

Objective: To investigate the correlation between hypoglycemia and positive rate of inborn error of metabolism (IEM) in neonatal intensive care unit.

Methods: 160 patients from a neonatal intensive care unit were enrolled. Blood glucose was measured by Roche Modular chemistry. The dry blood on filter papers, collected from 160 patients, was tested by tandem mass spectrometry to detect 35 inborn errors of metabolism. Clinical follow-up of all the patients was at least in an interval of 12 months. The mean observation period was 13.5 months per child**.**

Findings: Based on the ROC curve, the optimal cut-off value of hypoglycemia as an indicator for screening for IEMs was projected to be 2.8 mmol/L, which yielded a sensitivity of 71.4% and a specificity of 76.5%. The patients were divided into two groups: hypoglycemia group (48 cases) and the control group (112 cases). 5(10.4%) of the 48 patients in the hypoglycemia group were positive, while only 2(1.8%) of the 112 patients in the control group were positive. The difference of the positive rate in the screening for IEMs between the two groups was significant (χ^2=4.10, *P*<0.05); the relative risk (RR) was 5.83 (95% CI: 1.06-32.12).

Conclusion: The risk of patients with hypoglycemia suffering from IEMs was significantly higher than that of the non-hypoglycemia patients in NICU, based on cut-off value of 2.8mmol/L.

Iranian Journal of Pediatrics, Volume 22 (Number 1), March 2011, Pages: 113-116

Key Words: Neonatal Intensive Care Units; Hypoglycemia; Inborn Errors of Metabolism; Tandem Mass Spectrometry

Introduction

Inborn errors of metabolism (IEMs) are a group of highly heterogeneous inherited diseases. Although relatively rare in the population in neonatal intensive care unit (NICU), these disorders are being increasingly identified and are responsible for significant morbidity and mortality [1-2]. For most of these disorders, the early symptoms and signs are non-specific. Newborn screening is important for those disorders. In the present study, we investigate the correlation between hypoglycemia and positive rate of IEM in NICU, and discuss the feasibility of the hypoglycemia as an indicator for screening high risk patients with IEMs in NICUs.

* **Corresponding Author;**
Address: حگـ، فجـگـگـک حـگـ؛ تهـک، مـفـلهـلعـم ،گـففـک ۶۸۰۰۱ خـدـبـ خـدـک
E-mail: م کهـ۸۳۸۷۱ ۱۶۳ کهـگـک

Subjects and Methods

All specimens used in this study were received from the neonatal intensive care unit, Beijing Haidian Maternal and Child Health Hospital between May 1, 2009, and August 31, 2009. All the patients who were eligible to participate in this study were born in this hospital and aged >24 hours, protein-containing feedings have been started, blood glucose was monitored. During this period, 4021 babies were born in our hospital, and 452 babies admitted to NICU, of which 205 neonates satisfied requirement. 160 (89 male and 71 female) patients were approved to enroll. The rate of participation was 78.05%. The median age was 4 days (1 to 11 days). The median gestation was 36 weeks (31 to 39 weeks). The median birth weight was 2780g（1450g to 4760g）. These patients were generally characterized by prematurity, low birth weight, respiratory disorder, feeding difficulties with vomiting, lethargy progressing to coma, failure to thrive, jaundice. Laboratory tests showed metabolic acidosis, hypoglycemia, hepatic failure, hyperammonemia. Consent forms were signed by the children's parents before collection of specimens.

We drew off vein blood to test blood glucose by Roche Modular chemistry and collected the filter paper samples by pricking the heels of the patients to get enough blood to fill a few circles on S&S Grade 903 filter paper as soon as the patients were admitted to NICU. The dry blood on filter papers was tested by Liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect 35 inborn errors of metabolism. The specimen was extracted out of the dry blood on filter paper, derivatized before injected into LC-MS/MS. The diagnosis of IEMs was further confirmed through clinical symptoms, by gas chromatography-mass spectrometry. Clinical follow-up of all the patients was at least in an interval 12 months. The mean observation period was 13.5 months per child.
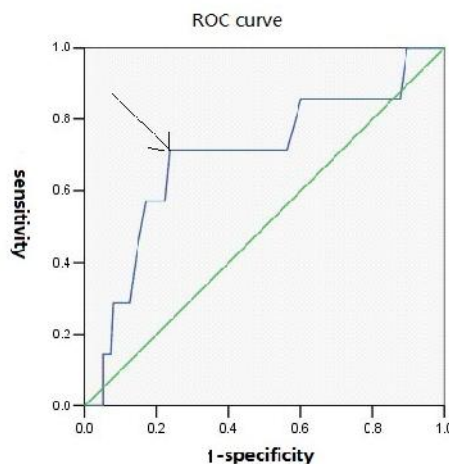
Findings

Based on the ROC curve, the optimal cut-off value of hypoglycemia as an indicator for screening for

IEM was projected to be 2.8mmol/L which yielded a sensitivity of 71.4% and a specificity of 76.5% (Fig 1). Using the blood glucose cut off level of 2.8mmol/L, the patients were divided into two groups: hypoglycemia group (48 cases) and the control group (112 cases). The average blood glucose level of the hypoglycemia group and the control group were 2.05±0.45mmol/L and (4.17±1.30) mmol/L, respectively.

A total of 5(10.4%) out of 48 patients in the hypoglycemia group were positive in the screening for IEMs including four with methylmalonic academia (MMA) and one with tyrosinemia, while only 2(1.8%) out of the 112 patients in the control group were positive including one with methylmalonic acidemia and one with maple syrup urine disease (MSUD). The difference of the positive rate in the screening for IEMs between the hypoglycemia group and the control group was significant (χ^2=4.10, $P<0.05$); the relative risk (RR) was 5.83 (95% CI: 1.06-32.12).

Discussion

Approximately one half of all the flagged infants were from the 5% of newborns who required neonatal intensive care or had birth weights <1500 g in the New England Newborn Screening

Fig. 1: The ROC curve of the hypoglycemia is used as an indicator for screening of IEMs in NICU. The arrow denotes the point of cut-off value, 2.8mmol/L

Program reported by Zytkovicz et al[3]. For this study, enrollments are the patients whose blood glucose was monitored in one NICU. There are many causes of hypoglycemia in neonates. IEMs should be suspected if the neonate has recurrent severe hypoglycaemia [4]. In this study, 7 patients were diagnosed as IEMs, 5 suffered from hypoglycemia. The optimal cut-off value of hypoglycemia as an indicator for screening for IEMs in our study was projected to be 2.8mmol/L, according to the ROC curve. This figure is quite similar to other reports in the literature[5]: 2.2∼2.8mmol/L, and consistent with the principles of clinical intervention, indicating that this threshold is feasible.

The positive rate of IEMs in the hypoglycemia group was 10.4%, significantly higher than the non-hypoglycemia group's rate (1.8%) and all enrollment's rate (4.4%). In our hospital, the incidence of 35 IEMs among the normal newborn babies was 1:4300, while it was 1.1% among the babies admitted to NICU. All of those results came from a small sample's observational study, thus, it maybe higher than the actual data. Up to now, expanded newborn screening for inborn errors of metabolism in the general population had been carried out in most developed countries [6-10]. Unfortunately, few of the developing countries carried out this expanded Newborn Screening Program. In the mainland of China, the technology of LC-MS/MS was primarily used to screen high risk children with IEMs [11-12]. It was unrealistic to carry out expanded Newborn Screening Program in the general population in mainland of China. From this study, we could see that most of patients with IEMs suffered from hypoglycemia; hypoglycemia could be considered to be used as an indicator for screening of IEMs in NICU. We recommend that the patients with hypoglycemia in NICU be channeled to expanded Newborn Screening Program. It was more targeted and cost-effective compared with screening in the general population.

In this study, the cut-off value of hypoglycemia was based on the ROC curve rather than literature's report. In addition, for the general population such studies would require enormous numbers to obtain meaningful results.

Our work was just a small sample's prospective study, a large multicentric approach would be necessary to validate our conclusions in future researches.

Conclusion

The risk of patients with hypoglycemia suffering from IEMs was significantly higher than that of the non-hypoglycemia patients in NICU, based on cut-off value of 2.8mmol/L. We assume that hypoglycemia can be considered to be used as an indicator for screening of IEMs in NICU. Next step, a large multicentric approach would be necessary to validate our conclusions.

Acknowledgment

References

1. Jouvet P, Touati G, Lesage F, et al. Impact of inborn errors of metabolism on admission and mortality in a pediatric intensive care unit. *Eur J Pediatr* 2007;166(5):461-5.

2. Campeau PM, Scriver CR, Mitchell JJ. A 25-year longitudinal analysis of treatment efficacy in inborn errors of metabolism. *Mol Genet Metab* 2008;95(1):11-6.

3. Zytkovicz TH, Fitzgerald EF, Marsden D, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem* 2001;47(11):1945-55.

4. Leonard JV, Morris AA. Diagnosis and early management of inborn errors of metabolism presenting around the time of birth. *Acta Paediatr* 2006;95(1):6-14.

5. Cornblath M, Schwartz R, Aynsley-Green A. Hypoglycemia in infancy: the need for a ration-al definition. *Pediatrics* 1990;85(5):834-7.

6. Wilcken B, Wiley V, Hammond J, et al. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *New Engl J Med* 2003;348(23):2304-12.

7. Schulze A, Lindner M, Kohlmüller D, et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome and implications. *Pediatrics* 2003;111(6):1399-406.

8. Frazier DM, Millington DS, McCandles SE, et al. The tandem mass spectrometry newborn screening experience in North Carolina: 1997–2005. *J Inherit Metab Dis* 2006;29(1):76–85.

9. Loukas YL, Soumelas GS, Dotsikas Y, et al. Expanded newborn screening in Greece: 30 months of experience. *J Inherit Metab Dis* 2010 Aug 19. [Epub ahead of print]

10. Lee HC, Mak CM, Lam CW, et al. Analysis of inborn errors of metabolism: disease spectrum for expanded newborn screening in Hong Kong. *Chin Med J* (Engl) 2011;124(7):983-9.

11. Sun W, Wang Y, Yang Y, et al. The screening of inborn errors of metabolism in sick Chinese infants by tandem mass spectrometry and gas chromatography/mass spectrometry. *Clin Chim Acta* 2011;412(13-14):1270-4.

12. Tu WJ, Song XT, Fang D, et al. Application of liquid chromatography-tandem mass spectro-metry (LC-MS/MS) in screening of high risk children with inherited metabolic diseases in northern China. *J Pediatr Endocrinol Metab* 2010;23(12):1245-52.