NEURO DEVELOPMENTAL CONSEQUENCES OF NEONATAL HYPOGLYCEMIA

Orhideja Stomnaroska¹, Valentina Dukovska², Dragan Danilovski³

¹ University Clinic for Gynecology and Obstetrics, Medical Faculty, Skopje, RN Macedonia
² University Clinic for Pediatrics, Medical Faculty, Skopje, RN Macedonia
³ Institute for Epidemiology and Biostatistics, Medical Faculty, Skopje, RN Macedonia

Corresponding author: Orhideja Stomnaroska, University Clinic for Gynecology and Obstetrics, Medical Faculty Skopje, Vodnjanska BB, 1000 Skopje, Macedonia; e-mail: stomnaroskao@yahoo.com

ABSTRACT

Neonatal hypoglycemia (HG) can cause neurologic damage, epilepsy, mental retardation, behavioral and personality disorders and death. The longest the HG lasts and the greatest the glucose nadir the consequences are more pronounced. Comorbidities are rather important in development of neurological damage. Hypoxemia and ischemia can cause permanent brain damage. Small for gestational age (SGA), large for gestational age (LGA), intrauterine growth restriction, gestational age below the 37th week, low Apgar score, sepsis, children whose mothers have toxemia, diabetes or chorioamnionitis are all newborns with increased HG risk.

Comparing 34 patients with NH and 34 children without NH with similar GA, BW, BL, the Apgar score, we found statistically significant differences in motor and mental development using the Griffith scale. Children with neonatal HG fared significantly worse than those without neonatal HG. Therefore, CBG measurements and early recognition of neonatal HG is of significant importance in preventing motor and mental damage in children. A larger and well-balanced cohort of patients followed for a longer period is also necessary to clarify and discern in detail the importance of neonatal HG and other perinatal factors in neurodevelopmental damage.

Keywords: neonatal hypoglycemia, neurodevelopmental damage, Griffith scale

INTRODUCTION

Hypoglycemia (HG) in newborns can cause mental retardation, epilepsy, neurologic damage, behavioral and personality disorders and death [1, 2]. The longest the HG lasts the consequences are more severe. The same goes for the lowest glucose values measured. Although the discussion on the concentration of blood glucose as cutoff value for HG are long and will last even longer, the authoritative definition of HG in newborn is plasma values below 1.65 mmol/L in the first 24 hours of life and lower than 2.5 mmol/L thereafter [2]. Comorbidities are rather important in development of neurological damage. Hypoxemia and ischemia can cause permanent brain damage. Several groups of newborns have a high risk of developing neonatal HG. Small for gestational age (SGA), large for gestational age
The statistical analysis was performed through Excel and SPSS with standard descriptive and analytical methods. The paired samples statistics and the paired samples test (T-test) assessed the differences on the Griffith scale.

RESULTS

In the 30 newborn babies of the HG group the gestational week was 31.87+/− 2.85, the birth weight 1573.75+/−435.87 (gram), and capillary blood glucose 1.23+/−0.39 (mmol/l). The control group of newborn babies without HG had similar values in gestational age (32.07 +/-3.09 weeks), and birth weight (1527+/−492.37g). Blood glucose levels were 5.7+/10.7 for the group of babies without HG, and 1.23+/-0.39 for the group with HG. HG was non-repetitive and lasted 10-20 minutes. It was treated with 5% dextrose in recommended speed and doses. There was no difference in the Apgar score and co-morbidity. No hypoxic-ischaemic syndrome, pneumonia, sepsis or maternal disease of interest were found in both groups. Ultrasound of the brain was normal in all subjects investigated. The age of the test performed was 11.3 months and 12.2 months, respectively.

Table 1. Patient demographics

| No Hypoglycemia (n=34) | Hypoglycemia (n=34) |
|-----------------------|---------------------|
| Gestational age (weeks, mean ± SD) | 31.87+/− 2.85 | 32.07+/−3.09 |
| Birth weight (g, mean ± SD) | 1573.75+/−435.87 | 1527+/−492.37 |
| Male sex (n,% | 18 (52.94%) | 19 |
| Apgar score at 5 minutes (median) | 5 (4−7) | 5 (4−8) |
| Neonatal seizures (n,% | 18 (52.94%) | 21 (61.76%) |
| CPAP (n,% | 1 (3.4%) | 3 (4.2%) |
| Intubation (n,% | 1 (3.4%) | 2 (6.8%) |
| Capillary blood glucose (CBG, mmol/l, nadir (duration) | 5.7+/10.7 (0) | 1.23+/−0.39 (10-15 minutes, nonrepetitive) |
The statistical analysis (Table 2) demonstrated a significant difference between two groups in regard of achievements of the Griffith scale (p=0.000).

Table 2. Griffith developmental scale for infants and children from birth to the age of two years

| T-Test | Paired Samples Statistics |
|--------|---------------------------|
|        | Mean | N | Std. Deviation | Std. Error Mean |
| Pair 1 | Griffith (k) | 91.56 | 34 | 16.343 | 2.803 |
|        | Griffith | 77.88 | 34 | 16.233 | 2.784 |

| Paired Samples Test |
|---------------------|
|        | Paired Differences |
|        | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | Lower | Upper | t | df | Sig. (2-tailed) |
| Pair 1 | Griffith (k) - Griffith | 13.676 | 11.012 | 1.888 | 9.834 | 17.519 | 7.242 | 33 | .000 |

The difference is statistically highly significant between Griffith controls (k) and Griffith developmental scale for children with neonatal HG (p = 0.000).

DISCUSSION

HG is the most frequent metabolic problem in neonates. Its frequency is estimated to 1.3-3/1000 newborns, in 50-80% of children in neonatal intensive care units (9-14). The nadir CBG witch causes brain damage is not established. The lowest levels of HG, repetitive HG and the longest duration of HG are found to have the most detrimental outcome (2, 15). Histological alterations that are HG consequences are atrophic zones, reduced myelination of the cerebral white matter and atrophy of the cerebral cortex (2). Hypoxic-ischaemic syndrome, neonatal pneumonia, sepsis can accentuate the brain damage (10, 16). Low birth weight, especially very low birth weight, children with low Apgar score, premature new-borns prematurely are all at increased risk of HG and brain damage.

Whether the transitory HG ends in brain damage is difficult to say, as proper clinical studies are missing (17-19). An additional difficulty is that risk factors and comorbidities are difficult to be accounted for (20). A report on 1400 appropriate for gestational age (AGA) and late preterm babies have shown that the children at the age of 10 years and neonatal CBG under 40 mg% have a reduction of school achievement in mathematics and literacy by 50%. (21). Similar outcomes were observed with CBG of 35 mg% and 45 mg% (21). Interestingly the probability of normal development at the age of four years was 50%if CBG was under 30 mg% in the first 72 hours of life (17, 22). It is of note that aging increases cognitive damage.

In all the studies that assess the neurocognitive damage of NH the main issue is to eliminate prenatal, perinatal and socio-economic factors (24-26). In addition, the timing and number of CBG measurements are important confounding factor. Often, at early age it is difficult or impossible to exclude other causes of mental retardation.

Comparing 30 patients with NH and 34 children without NH with similar GA, BW, BL, the Apgar score, we found a statistically significant differences in cumulative motor and mental development. Children with neonatal HG had significantly worse achievements on the Griffith scale than those without neonatal HG.

Therefore, it is very important to early detect and treat neonatal HG. CBG measurements and early recognition of neonatal HG is of significant importance in preventing motor and mental damage in children. A larger and well-balanced cohort of patients followed for a longer period is also necessary to clarify and discern the importance of neonatal HG and other perinatal factors in neurodevelopmental damage.

REFERENCES

1. Faustino EV, Bogue CW. Relationship between hypoglycemia and mortality in critically ill children. Pediatr Crit Care Med 2010; 11(6): 690–698.
2. Adamkin DH. Update on neonatal hypoglycemia. Arch Perinat Med 2005; 11(3): 13–15.
3. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed. 2013; 98: 2–6.
4. Boardman JP, Hawdon JM. Hypoglycaemia and hypoxic-ischaemic encephalopathy. Developmental Medicine and Child Neurology 2015; 57 (Suppl. 3): 29–33.
5. WHO ref. number WHO/CHD/97.1/WHO/ MSM/97. Hypoglycaemia in the newborn. Geneva: World Health Organization. 1997, 4, 19.
6. Luiz DM, Foxcroft CD, Stewart R. The construct validity of the Griffiths scales of mental development. Child Care Health Dev2001; 27: 73–83.
7. Ivens J, Martin N. A common metric for the Griffiths Scales Arch Dis Child 2002; 87: 109–110.
8. Griffiths R. The abilities of young children. High Wycombe, UK: The Test Agency Ltd, 1984.
9. Stomnaroska O. Neonatal hypoglycaemia in children with high and normal risk: incidence, etiology, therapeutics and prognosis. Doctotal thesis, Medical Faculty Skopje, University Sts Cyril and Methodius, 2017.
10. Adamkin DH. Neonatal hypoglycemia. Curr Opin Pediatr. 2016; 28: 150–5.
11. Ishiguro A, Namai Y, Ito YM. Managing “healthy” late preterm infants. Pediatr Int. 2009; 51(5): 720–725.
12. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr. 2012; 161: 787–791. doi: 10.1016/j.jpeds.2012.05.022.
13. Zhou W, Yu J, Wu Y, Zhang H. Hypoglycemia incidence and risk factors assessment in hospitalized neonates. J Matern Fetal Neonatal Med. 2014 Oct 13: 1–4.
14. Sabzehei MK, Basiri B, Bazmamoun H. The Etiology, Clinical Type, and Short Outcome of Seizures in NewbornsHospitalized in Besat Hospital/Hamadan/ Iran. Iran J Child Neurol. 2014 Spring;8(2): 24–8.
15. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, ET AL. Early insulin therapy in very-low-birth-weight infants. N Engl J Med. 2008; 359: 1873–1884.
16. Duning T, van den Heuvel I, Dickmann A, ET AL. Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. Diabetes Care. 2010; 33(3): 639–644.
17. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics. 2006; 117: 2231–2243.
18. Burns CM, Rutherford MA, Boardman JP, ET AL. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycaemia. Pediatrics. 2008; 122(1): 65–74.
19. Kaiser JR, Bia S, Gibson N, et al. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study [published online August 24, 2015]. JAMA Pediatr. 1631.
20. Pilides RS, CornblathM, Warren I, et al. A prospective controlled study of neonatal hypoglycemia. Pediatrics. 1974; 54(1): 5–14.
21. McKinlay CJ, Alsweiler JM, Ansell JM, ET AL. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med. 2015; 373: 1507–1518.
22. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. BMJ. 1988; 297(6659): 1304–1308.
23. McKinlay CJD, Harding JE. Revisiting transitional neonatal hypoglycemia, only time will tell. JAMA Pediatrics. 2015E1–2.
24. Burns CM, Rutherford MA, Boardman JP, Cowan FM Patterns of Cerebral Injury and Neurodevelopmental Outcomes After Symptomatic Neonatal Hypoglycemia. Pediatrics 2008; 122(1): 65–74.
25. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia Is Associated With Increased Risk for Brain Injury and Adverse Neurodevelopmental Outcome in Neonates at Risk for Encephalopathy. 2012; 161(1): 88–93.
26. McKinlay CJD, Alsweiler JM, Anstice NS, et al. Children With Hypoglycemia and Their Later Development (CHYLD) Study Team. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. JAMA Pediatr 2017; 171(10): 972–983.
Резиме

НЕВРОРАЗВОЈНИ ПОСЛЕДИЦИ ОД НЕОНАТАЛНА ХИПОГЛИКЕМИЈА

Орхидеја Стомароска1, Валентина Дуковска2, Драган Даниловски3

1 Универзитетска клиника за гинекологија и акушерство, Медицински факултет, Скопје, РС Македонија
2 Универзитетска клиника за педијатрија, Медицински факултет, Скопје, РС Македонија
3 Институт за епидемиологија и биостатистика, Медицински факултет, Скопје, РС Македонија

Неонаталната хипогликемија (ХГ) може да предизвика невролошко оштетување, епилепсија, ментална ретардација, промени во однесувањето и во личноста. Долгите и длабоки ХГ се особено штетни.

Важен фактор во настанокот на оштетувањата имаат и коморбидитетите. Хипоксемијата и исхемијата може да предизвикаат дополнителни оштетувања. Малите за гестацијска возраст (small for gestational age – SGA), големите за гестацијска возраст, интраутерине-заостанувањето на растот и развитокот, гестацијската возраст под 37-мата недела, нискиот Апгар, сепсата, децата на мајки со дијабет, токсемијата, хориоамионитисот го зголемуваат ризикот за оштетувања доколку се здружени со ХГ.

Споредивме 34 пациенти со неонатална ХГ и 34 пациенти со неонатална без ХГ кај деца со слична гестацијска возраст, телесна тежина и должина, Апгар скор. Притоа, најдовне статистички сигнifikантна разлика во моторната и во менталната развиеност на Грифитовата скала. Оттаму, потребно е рано препознавање на неонаталната ХГ и рана терапија би превенирале настанок на невролошките и ментален дефицит кај овие деца.

Ключни зборови: неонатална хипогликемија, неуролошки дефицит, Грифитова скала
