

## NEURO DEVELOPMENTAL CONSEQUENCES OF NEONATAL HYPOGLYCEMIA

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### 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), intra-uterine growth restriction, gestational age bellow 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 authori-

tative definition of HG in newborn is plasma values bellow 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

(LGA), intrauterine growth restriction, gestational age below the 37<sup>th</sup> week, low Apgar score, sepsis, children whose mothers have toxemia, diabetes or chorioamnionitis [3–5].

We undertook to investigate the neurological and developmental outcomes in children with neonatal HG.

## PATIENTS AND METHODS

We investigated newborns at the Clinic for Gynecology and Obstetrics (~4000 deliveries yearly) excluding children with congenital malformations and polycythemia. The study is approved by the institutional ethics committee. We recorded the gestational age, weight and length, delivery mode, the Apgar score, children with infections (sepsis, pneumonia...), children with hypoxic ischemic syndrome, children whose mothers have toxemia, diabetes, addictions, or chorioamnionitis. We also recorded the timing, duration and plasma glucose concentrations.

Capillary blood glucose was analyzed using ABL700 analyzation (Radiometer Medical A/S, Copenhagen, Denmark) with the glucose oxidase method, or with Elite XL (Bayer, Tarrytown, New York, N.Y., USA). The values for HG are as above mentioned.

The follow-up of the motor and mental development in the following year was done with physical examination and using the Griffith scale of psychomotor development for children aged 0-2 years (6-9). The scale is widely used in psychology and pediatrics. The scale measures five fields. The subscale A measures the rough motor activity, and the ability to keep balance, coordination and movement control. This part includes ability to walk, run and climb. The part B of the scale measures the abilities to be independent, to recognize the mother, to follow people with glance, the ability to hold a spoon, hearing and use a combination of words. This subsection also looks at the ability to eat by itself, to open door and to assist dressing and undressing. The scale part C assesses hearing, receptive and expressive language. The scale part D measures hand-eye coordination, fine motor movements, manual dexterity and visual monitoring skills. The subscale E assesses the capability to understand through performance tests that looks at the ways motor activities is used in new situations. A prepared kit of 29 pieces serves as a tool for the Griffith scale.

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-morbidities. 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)
<b>Gestational age (weeks, mean ± SD)</b>	31.87+/- 2.85	32.07+/-3.09
<b>Birth weight (g, mean ± SD)</b>	1573.75+/-435.87	1527+/-492.37
<b>Male sex (n,%)</b>	18 (52.94%)	19
<b>Apgar score at 5 minutes (median)</b>	5 (4–7)	5 (4–8)
<b>Neonatal seizures (n,%)</b>	18 (52.94%)	21 (61.76%)
<b>CPAP (n,%)</b>	1 (3.4%)	3 (4.2%)
<b>Intubation (n,%)</b>	1 (3.4%)	2 (6.8%)
<b>Capillary blood glucose (CBG, mmol/l, nadir) (duration)</b>	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					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 Griffith (k) - Griffith	13,676	11,012	1,888	9,834	17,519	7,242	33	<b>,000</b>

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.

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**Резиме****НЕВРОРАЗВОЈНИ ПОСЛЕДИЦИ  
ОД НЕОНАТАЛНАТА ХИПОГЛИКЕМИЈА****Орхидеја Стомнароска<sup>1</sup>, Валентина Дуковска<sup>2</sup>, Драган Даниловски<sup>3</sup>**<sup>1</sup> Универзитетска клиника за гинекологија и акушерство, Медицински факултет, Скопје, РС Македонија<sup>2</sup> Универзитетска клиника за педијатрија, Медицински факултет, Скопје, РС Македонија<sup>3</sup> 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 гестациска возраст (small for gestational age – SGA), големите за гестациска возраст, интраутерине-заостанувањето на растот и развитокот, гестациската возраст под 37-мата недела, нискиот Апгар, сепсата, децата на мајки со дијабет, токсемијата, хориоамнионитисот го зголемуваат ризиикот за оштетувања доколку се здружени со ХГ.

Споредивме 34 пациенти со неонатална ХГ и 34 пациенти со неонатална без ХГ кај деца со слична гестациска возраст, телесна тежина и должина, Апгар скор. Притоа, најдовме статистички сигнификантна разлика во моторната и во менталната развиеност на Грифитовата скала. Оттamu, потребно е рано препознавање на неонаталната ХГ и рана контрола на гликемијата во неонаталната возраст. Раното откривање на неонаталната ХГ и раната терапија би превенирале настанок на моторни и ментални трајни оштетувања во детската возраст. Потребна е поголема и добро балансирана група деца следени подолг временски период за јасно разграничување на влијанијата на ХГ и на другите коморбидитети на трајниот невролошки и ментален дефицит кај овие деца.

**Клучни зборови:** неонатална хипогликемија, невролошки дефицит, Грифитова скала

