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Original Scientific Paper

HIGHER FREQUENCY OF GERMINAL MATRIX-INTRAVENTRICULAR HEMORRHAGE IN MODERATE AND LATE PRETERM AND EARLY TERM NEONATES WITH INTRAUTERINE GROWTH RESTRICTION COMPARED TO HEALTHY ONES

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SUMMARY – Germinal matrix-intraventricular brain hemorrhage is mostly found in preterm neonates, but may also occur in term neonates. The aim of this study was to analyze the prevalence and severity of this type of hemorrhage in moderate and late preterm and early term neonates with intrauterine growth restriction. In the prospective analysis, 100 newborns were examined, i.e. 70 with intrauterine growth restriction and 30 as a control group. Study subjects were neonates from 32 0/7 to 38 6/7 gestational weeks. Body weight, body length, head circumference and ponderal index at birth were analyzed. Hemorrhage was assessed by cranial ultrasound using Papile classification. Out of 70 neonates with intrauterine growth restriction, germinal matrix-intraventricular hemorrhage was not found in 36 (51.43%) neonates, 31 (44.29%) had hemorrhage grade 1, and three (4.29%) had hemorrhage grade 2, which was statistically significant ($p<0.001$) in relation to the control group. There were no neonates with hemorrhage grade 3 or 4. The predominant type of germinal matrix-intraventricular hemorrhage in the intrauterine growth restriction group was hemorrhage grade 1. Germinal matrix-intraventricular hemorrhage was more often present in the intrauterine growth restricted neonates than in the control group.

Key words: *Neonates; Growth restriction; Germinal matrix–intraventricular hemorrhage; Cranial ultrasound*

Introduction

Intrauterine growth restriction (IUGR) represents fetal growth below the normal for the growth potential. When IUGR is not detected during pregnancy, it can be detected only at birth[1]. It is important because a large number of acute and chronic complications put IUGR at the very top of mortality causes and fetal and neonatal morbidity, as well as childhood developmental disorders, which can result from deficiency of only one individual nutritional element and lead to diseases in adulthood[2,3].

Moderate preterm, late preterm and early term neonates represent a group of newborns for whom recent research has shown an increased risk of short-term perinatal morbidity and long-term developmental difficulties[4,5].

Germinal matrix-intraventricular hemorrhage (GMH-IVH) is cerebral hemorrhage that typically occurs in premature babies. The underlying pathogenetic mechanisms that lead to this type of hemorrhage are the fragility of the vasculature and fluctuation of the cerebral blood flow in the germinal matrix[6]. Although a less severe hemorrhage can be asymptomatic, it is considered that they also carry an increased risk of

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Table 1. Characteristics of study subjects according to groups

Neonates		IUGR n=70	Control group n=30	p-value
Gender:	male	39 (55.71%)	15 (50.00%)	0.6011
	female	31 (44.29%)	15 (50.00%)	
Body weight (g)		1892.13±457.36 (1825)	2189.67±529.24 (2075)	0.0065
Body length (cm)		44.94±3.66 (45.00)	44.92±3.30 (44.50)	0.7914
Head circumference (cm)		30.45±2.21 (30.00)	30.77±1.90 (31.00)	0.4015
Ponderal index		2.01±0.27 (2.00)	2.28±0.17 (2.27)	0.0000
Moderate and late preterm		44 (62.86%)	24 (80.00%)	0.0938
Early term		26 (37.14%)	6 (20.00%)	
Mode of delivery:	vaginal	33 (47.14%)	15 (50.00%)	0.7943
	cesarean section	37 (52.86%)	15 (50.00%)	

IUGR = intrauterine growth restriction; continuous variables are expressed as mean ± standard deviation and median; categorical variables are expressed as absolute number (n) and percentage (%).

disability[7]. Rarely, GMH-IVH can also occur in term neonates and carries a risk of adverse neurodevelopmental delay[8].

Cranial sonography is a diagnostic method that is widely used in neonatology for the assessment of brain morphology and cerebral circulation, as well as for detection of a large number of cerebral lesions.

The main aim of the study was to analyze the prevalence and severity of GMH-IVH in moderate preterm and late preterm neonates, as well as early term neonates with IUGR, by use of cranial ultrasound.

Subjects and Methods

This study was performed at the Institute of Neonatology, Belgrade, Serbia, from June 24, 2013 to August 24, 2014. All moderate preterm (32 0/7-33 6/7 weeks of gestational age), late preterm (34 0/7-36 6/7 weeks of gestational age) and early term (37 0/7-38 6/7 weeks of gestational age) neonates with IUGR (birth weight and/or ponderal index below the 10th percentile) admitted to the admission unit (out of the intensive care unit) were analyzed. Thirty neonates with appropriate intrauterine growth (both birth weight and ponderal index between the 10th and 90th percentile) were included as control group. Neonates were analyzed in the order of admission to the unit.

The criteria for exclusion from the study related to both study group and control group were as follows: neonates with Apgar score 0-3, hemodynamically unstable neonates, neonates with congenital anomalies that indicate chromosomal defects, mother's eclampsia, neonates transferred from the admission unit to the intensive care unit, as well as those who received blood products before ultrasound examinations, and twins.

Gender, gestational weeks, body weight, body length, head circumference and ponderal index at birth, as well as the mode of delivery were collected from medical documentation. Body weight, body length and head circumference assessments were performed using Fenton growth curves, while ponderal index was based on the Lubchenco graphic[9,10].

Ultrasound examinations of the brain were performed on the MySonoU6 (Samsung Medison, Seoul, South Korea) ultrasound apparatus, 7.5 MHZ probe, in the first 72 hours of life and from the 7th to 10th day of life. The anterior fontanelle was used as an ultrasound window. Photographic record was obtained in all patients. The presence and degree of GMH-IVH were evaluated using the Papile classification[11].

This study was approved by the Ethics Committee of the Institute of Neonatology in Belgrade.

Statistical analysis

Statistical data processing was performed by Statistical Package for the Social Sciences Program, version 15.0. Continuous variables were expressed as mean ± standard deviation and median. Categorical variables were expressed as absolute number (n) and percentage (%). Depending on the normality of data

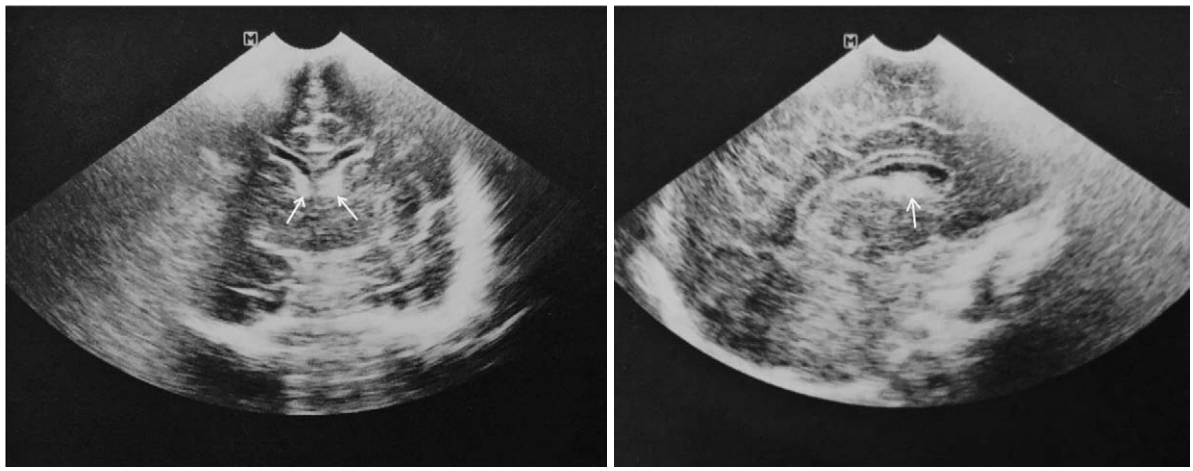

Fig. 1. Germinal matrix-intraventricular hemorrhage grade 1 (coronal section – looks like cat eyes, and sagittal section – looks like a snake).

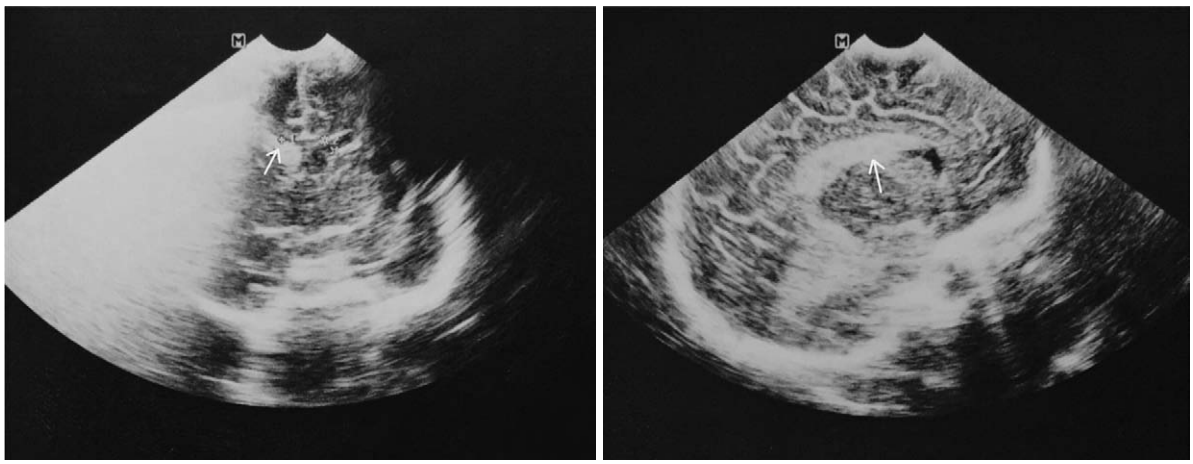

Fig. 2. Germinal matrix-intraventricular hemorrhage grade 2 (coronal and sagittal sections).

distribution, continuous variables were compared by independent samples t-test or Mann-Whitney test. Categorical variables were compared using the χ^2-test. The value of $p<0.05$ was considered statistically significant.

Results

During the study period, a total of 292 moderate preterm, late preterm and early term neonates were admitted to the admission unit. Among these 292 neonates, 108 were IUGR neonates. Thirty-eight IUGR neonates were excluded from the study. Seventy IUGR neonates and 30 control group neonates had complete ultrasound examination and their characteristics are summarized in Table 1.

In the IUGR group of 70 neonates, 36 (51.43%) did not have GMH-IVH, 31 (44.29%) had GMH-IVH grade 1, and three (4.29%) had GMH-IVH grade 2 (Figs. 1 and 2). None of the subjects showed GMH-IVH grade 3 or 4.

In the control group of 30 neonates, 27 (90%) did not have GMH-IVH, three (10%) had GMH-IVH grade 1, while there were no GMH-IVH grade 2, 3 or 4.

Pearson's χ^2-test showed the presence of GMH-IVH in total (both grade 1 and grade 2) to be statistically significantly more common ($p<0.001$) in the IUGR group as compared to the control group (Fig. 3).

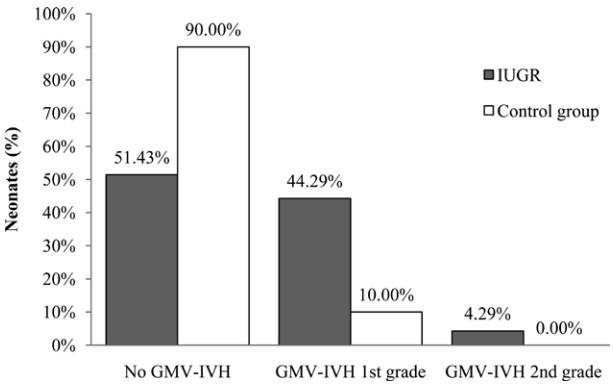

Fig. 3. GMH-IVH in IUGR and control group (p<0.001).

GMH-IVH = germinal matrix-intraventricular hemorrhage; IUGR = intrauterine growth restriction

Discussion

Studies on the possible pathophysiological events in fetal brain with IUGR are extremely rare. One of them is the study by Cohen *et al.*[12], stating that in cases of fetal nutritional deprivation or chronic fetal hypoxemia, there is a 'brain-sparing' phenomenon which involves adaptation of fetal circulation to preserve the nutritional factors and oxygen for the brain. Prolonged 'brain-sparing' in cases of IUGR leads to vascular remodeling of the fetus with cerebral vasculature that becomes fragile, and it is believed that these changes persist even postnatally[12].

There has been a declining trend in birth rates in developed countries, but an increase in the birth of children above 40 gestational weeks. Children born at late preterm and early term experience higher rates of infant morbidity and mortality, as well as higher risks of childhood disabilities. Shapiro-Mendoza and Lackritz point to the fact that morbidity of newborns is doubled for every week less than 38 gestational weeks[13].

The exact incidence of moderate preterm, late preterm and early-term neonates, IUGR, as well as GMH-IVH in Serbia is unknown, and so are their early and late complications. There are only a few studies in the world related to IUGR and moderate preterm, late preterm and early term neonates, next to the studies on the incidence and severity of GMH-IVH in these IUGR neonates, which are sporadic and can vary greatly[4].

Initial sonogram in this study was performed during the first 3 days of life. The second scan was performed from the 7th to 10th day of life to confirm suspicious findings and because more than 90% of GMH-IVH is manifested on cranial ultrasound during that period.

The incidence of GMH-IVH grade 1 in neonates with IUGR was high in this study (44.29%) and it was much more frequent as compared with control group. The incidence of this type of hemorrhage was also higher than reported in the published studies, which were not of identical design but addressed a similar problem. Some of these retrospective studies[14-16], as well as our examination, have shown that neonates with IUGR are at a higher risk of periventricular-intraventricular hemorrhage. Opposite to them, Ballardini *et al.* did not find statistical significance with IUGR, emphasizing that the study was retrospective too[17].

A large percentage of low grade hemorrhage, GMH-IVH grade 1, was present in our IUGR subjects. Kim *et al.* state that, despite regression, germinal matrix is still present in term neonates[18]. It is possible that it is more pronounced in IUGR neonates, and this is one of the possible explanations for the high incidence of GMH-IVH in our subjects. Examining this problem also among term neonates in their retrospective studies, Chinta[19] and Hernández *et al.*[20] suggest implementation of a multicenter study.

Another explanation for the higher occurrence of this type of hemorrhage in our subjects relative to data from other studies can be found in the previously mentioned study conducted by Ballardini *et al.*, where they state that cranial ultrasound is not routinely performed in all gestational weeks[17]. The American Academy of Neurology and Practice Committee of Child Neurology and the Guideline of the Canadian Pediatric Society recommend cranial ultrasound as routine screening on all newborns born before 30 and 32 gestational weeks, respectively[21,22]. Meijler states that cranial ultrasound should be done in each neonate in the neonatal unit[23]. However, later studies also include less than 40% of infants born in later gestation[17]. Also, many of these studies are retrospective.

Cohen *et al.* conclude that studies on IUGR and altered cerebral hemodynamics, as well as the clinical consequences of these disorders are extremely scarce, and that monitoring and action strategy related to IUGR of fetuses and neonates are insufficiently defined. They also state that the existing literature on this topic shows many controversies and that an interna-

tional initiative to address these issues would be of great importance for improvement of care of these neonates[12].

Conclusion

The predominant type of GMH-IVH in the groups of moderate preterm, late preterm and early term neonates with IUGR was hemorrhage grade 1. In the neonates with IUGR, GMH-IVH in total was more frequent as compared to the control group. Given that both IUGR and less pronounced asymptomatic forms of GMH-IVH are associated with increased mortality, morbidity and developmental disorders, it is very important to detect these disorders early due to their early prevention, treatment, and early rehabilitation. Therefore, it is advisable for every neonate with IUGR to undergo cranial ultrasound during the first days of life. The scarcity of this topic in the literature, the clinical consequences of these disorders, as well as the controversies associated with it impose the need for a wider study of these problems.

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Sažetak

VEĆA UČESTALOST PERIVENTRIKULSKOG-INTRAVENTRIKULSKOG KRVARENJA KOD UMJERENE I KASNE NEDONOŠČADI I RANE TERMINSKE NOVOROĐENČADI S INTRAUTERINIM ZASTOJEM U RASTU U ODNOSU NA ZDRAVU NOVOROĐENČAD

R. Mileusnić-Milenović

Periventrikulsko-intraventrikulsko krvarenje u mozgu uglavnom se nalazi u nedonoščadi, ali se također može pojaviti kod djece rođene u terminu. Cilj ovog istraživanja bio je analizirati učestalost i ozbiljnost ovog tipa krvarenja kod umjerene i kasne nedonoščadi i rane terminske novorođenčadi s intrauterinim zastojem u rastu. U prospektivnoj analizi ispitano je 100 novorođenčadi: 70 s intrauterinim zastojem u rastu i 30 kao kontrolna skupina. Ispitanici su bili novorođenčad od 32 0/7 do 38 6/7 tjedana gestacije. Analizirana je tjelesna težina, duljina tijela, opseg glave i ponderalni indeks pri rođenju. Krvarenje je određeno klasifikacijom Papile, uz pomoć ultrazvučne pretrage mozga. U 36 (51,43%) od 70 novorođenčadi s intrauterinim zastojem u rastu nije pronađeno periventrikulsko-intraventrikulsko krvarenje, 31 (44,29%) je imalo krvarenje 1. stupnja, dok ih je 3 (4,29%) imalo krvarenje 2. stupnja, što je bilo statistički značajno ($p<0,001$) u odnosu na kontrolnu skupinu. Nije bilo novorođenčadi s krvarenjem 3. ili 4. stupnja. Dominantni tip periventrikulskog-intraventrikulskog krvarenja u skupinama umjerene i kasne nedonoščadi i rane terminske novorođenčadi s intrauterinim zastojem u rastu bilo je krvarenje 1. stupnja. U novorođenčadi s intrauterinim zastojem u rastu periventrikulsko-intraventrikulsko krvarenje zabilježeno je češće u odnosu na kontrolnu skupinu.

Ključne riječi: *Novorođenčad; Zastoj u rastu; Periventrikulsko-intraventrikulsko krvarenje; Ultrazvuk mozga*