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Early functional and morphological brain disturbances in late-onset intrauterine growth restriction

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ABSTRACT

Aims: To determine whether the brain disturbances develop in late-onset intrauterine growth restriction (IUGR) before blood flow redistribution towards the fetal brain (detected by Doppler measurements in the middle cerebral artery and umbilical artery). Further, to evaluate predictive values of Doppler arterial indices and umbilical cord blood gases and pH for early functional and/or morphological brain disturbances in late-onset IUGR.
Study design: This cohort study included 60 singleton term pregnancies with placental insufficiency caused late-onset IUGR (IUGR occurring after 34 gestational weeks). Umbilical artery resistance index (URI), middle cerebral artery resistance index (CRI), and cerebroumbilical (C/U) ratio (CRI/URI) were monitored once weekly. Umbilical blood cord samples (arterial and venous) were collected for the analysis of pO_2, pCO_2 and pH. Morphological neurological outcome was evaluated by cranial ultrasound (cUS), whereas functional neurological outcome by Amiel-Tison Neurological Assessment at Term (ATNAT).
Results: 50 fetuses had C/U ratio > 1, and 10 had C/U ratio ≤ 1; among these 10 fetuses, 9 had abnormal neonatal cUS findings and all 10 had non-optimal ATNAT. However, the total number of abnormal neurological findings was much higher. 32 neonates had abnormal cUS (53.37%), and 42 (70.00%) had non-optimal ATNAT. Furthermore, Doppler indices had higher predictive validity for early brain disturbances than umbilical cord blood gases and pH. C/U ratio had the highest predictive validity with threshold for adverse neurological outcome at value 1.13 (ROC analysis), i.e., 1.18 (*party* machine learning algorithm).
Conclusion: Adverse neurological outcome at average values of C/U ratios > 1 confirmed that early functional and/or structural brain disturbances in late-onset IUGR develop even before activation of fetal cardiovascular compensatory mechanisms, i.e., before Doppler signs of blood flow redistribution between the fetal brain and the placenta.

1. Introduction

Intrauterine growth restriction (IUGR) due to placental insufficiency represents an important problem of modern perinatology. According to various studies the risk of perinatal mortality is increased at least 10–20 times in IUGR children compared to children with normal intrauterine growth [1,2]. In addition, IUGR is the risk factor for neurological disorders, ranging from minimal cerebral dysfunction, behavioral disorders, learning disabilities, dyslexia, vision and hearing impairment, mental retardation to cerebral palsy [3–5].

At the moment there is no common consistent management approach to IUGR [6]. To find a better criterion for prediction of perinatal outcome in IUGR children researchers have tried to combine individual Doppler parameters of the fetal and placental circulation. One of the combinations of Doppler parameters is cerebroumbilical (C/U) ratio, which takes into account placental insufficiently responsible for IUGR and hypoxia, and cerebral response to hypoxia. During normal pregnancy, from the 14th to the 40th gestational week, values of C/U ratio range from 1 to 1.45 [7]. Values of C/U ratio < 1 correspond with redistribution of blood flow towards the brain in response to fetal hypoxia due to placental insufficiently, indicating activation of cardiovascular compensatory mechanisms [8]. Experimental data have also shown that reduction of C/U ratio < 1 is proportional to the decrease of fetal pO_2 and degree of hypoxia [9]. However, our studies have shown that redistribution of blood flow is not entirely a protective phenomenon, because in chronic hypoxia neurologic damage can develop despite the fetal blood flow redistribution and increased brain perfusion or brain sparing effect [10,11].

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Specific clinical problem represents late-onset IUGR caused by a milder degree of placental insufficiency, usually presenting after the 34th week of gestation with very subtle Doppler abnormalities, therefore often unrecognized or inadequately supervised [12]. Based on our results and recent findings, our assumption is that in late-onset IUGR there is a possibility of development of early neurologic disturbances, functional and/or morphological, even before activation of cardiovascular compensatory mechanisms, and clinically detectable signs of hypoxia by C/U ratio [10,11,13]. In addition, the brain sparing effect in this population could be a sign of progression of neurological damage.

The aim of this study is to determine whether the brain disturbances develop in late-onset IUGR before blood flow redistribution towards the fetal brain, detected by Doppler measurements in the middle cerebral artery and umbilical artery. Further, to evaluate predictive values of Doppler arterial indices and umbilical cord blood gases and pH for early functional and/or morphological neurological outcome in late-onset IUGR.

2. Materials and methods

This cohort study included 60 singleton pregnancies complicated with late-onset IUGR which occurred after the 34th week of gestation. The patients were enrolled prospectively. Accurate gestation age was determined with ultrasound in early pregnancy and all fetuses had normal growth on regular ultrasound examinations before the 34th week of gestation. IUGR was defined by the estimated fetal weight below the 10th percentile for gestational age based on ultrasound biometry, and by increased umbilical artery resistance index (URI) for the gestational age [14,15]. Further, the study included only neonates whose gestational age at birth was ≥37 weeks.

Exclusion criteria were: fetuses with anomalies and/or chromosomal disorders identified during pregnancy or after birth, pregnant women with chronic preconception diseases (cardiac, nephrologic, systemic, hematologic) or diseases during pregnancy (pre-eclampsia, infection), and addictions (alcoholism, drug addiction, smoking).

The study was conducted after approval of relevant ethics committees (Ethics Committee of the University of Zagreb School of Medicine, and Ethics Committee of the Clinical Hospital Center "Sestre milosrdnice") and with signed informed consent of pregnant women.

Standardized clinical approach, based on gestational age, ultrasound findings, and cardiotocography was applied in delivery decision, independently of this study.

Ultrasonic Doppler measurements were obtained using ultrasound device Aloka, ProSound Alpha 10 with transabdominal transducer, frequency 2–6 MHz (with the possibility of automatic adjustment), and the maximum output power of device below the permitted limit for the use in fetal medicine [16]. Pourcelot resistance index was used for the assessment of fetal hemodynamics [17]. Cerebral artery resistance index (CRI) was obtained from Doppler flow records of the middle cerebral artery, while the URI was obtained from the Doppler recording of blood flow through the umbilical artery. From these measurements the cerebroumbilical ratio was calculated (C/U ratio, also called CRI/URI). The above Doppler measurements were performed once a week. Values with the highest deviation from the normal were used in the statistical analysis.

After delivery the fetal blood samples were collected from the umbilical artery and vein. Gas analysis: partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and pH of umbilical cord blood were determined using standard biochemical analysis.

Early neurological outcome included morphological assessment by ultrasound scan of the brain and functional assessment by The Amiel-Tison Neurological Assessment at Term (ATNAT) [18]. Brain ultrasonic examination and ATNAT were carried out independently by two experienced neonatologists.

Siemens sonoline G40 with a probe of 7.5 MHz was used for ultrasound examination of the brain. Assessment was done through the large fontanel. Periventricular leukomalacia (PVL) was classified using the Pidcock classification, and peri/intraventricular hemorrhage (PIVH) using Volpe classification [19,20]. Examinations were carried out the 1st, 3rd and 7th days after birth. Ultrasound findings with the most prominent changes were taken into account in processing results.

ATNAT was performed within 48 h from birth. In case of discrepancy in the individual test reevaluation was performed (usually 48 h after the first test and by the end of the 1st week of life). Final neurological assessment was based on a synthesis of the responses in individual tests. The function of the central nervous system was considered normal if all the elements obtained optimal response. Neurological disturbances were graded as mild, moderate or severe [18].

Parameters analyzed in relation to neurological outcome were: URI, CRI, C/U ratio, birth weight (BW), pO_2 of the umbilical vein, pCO_2 of the umbilical vein, pH of the umbilical venous blood, pO_2 of the umbilical arterial blood, pCO_2 of the umbilical arterial blood, and pH of the umbilical arterial blood.

Differences in study parameters between the groups were analyzed using a two-group multivariate permutation test, which represents a modern, nonparametric, and robust approach to multivariate comparison of two groups with a large number of variables [21]. To find the variable that would best differentiate between children with and without negative neurological outcome, the Receiver Operating Characteristic (ROC) analysis was used [22,23]. ROC analysis determines the optimal cut-off value for discrimination between two groups by finding the maximal value of the Youden index (J). J is defined as [SEi − SPi − 1], where SEi and SPi are sensitivity and specificity over all possible threshold values. The results of two-group multivariate permutation tests and ROC analysis were supplemented by a party machine learning algorithm which builds a classification tree by finding subgroups with maximal difference in chi-square test statistics [24]. All applied tests were two-way, and p values were considered statistically significant if they were less than or equal to 0.05. Data were analyzed using R software (version 2.12.2) [25].

3. Results

Of the 60 fetuses, 24 were male (40.0%) and 36 female (60.0%). No difference between the male and female genders was found in any of the observed parameters (two-group multivariate permutation test, $p > 0.05$). All neonates were delivered at term. Gestational age was lower if Caesarian section was the mode of the delivery, compared to vaginal birth, but the difference was not statistically significant ($p = 0.4094$, two-group permutation test).

Fifty fetuses had C/U ratio > 1. Ten fetuses had C/U ratio ≤ 1. In this group 9 neonates had abnormal cUS findings, and all 10 had non-optimal ATNAT. Nevertheless, the total number of neonates with abnormal neurological findings, functional and/or morphological, in the study was much higher. Of the 60 neonates in the research, 32 neonates (53.37%) had abnormal ultrasound scan findings and 42 neonates (70.00%) had abnormal functional neurological status. According to cUS results, 23 neonates (38.33%) had PIVH, and 9 (15.0%) had PVL. Intracranial bleeding was mild, first or second degree. In the group of neonates with a non-optimal ATNAT finding, 23 (54.76%) had mild, and 19 (45.24%) moderate changes. There were no severe neurological disturbances.

Differences in the gestational age between neonates with optimal and non-optimal ATNAT outcome were not statistically significant, although neonates with non-optimal result had somewhat higher gestational age at the delivery — about 5–6 days (0.8 weeks).

Median for optimal findings was 37.6 weeks, and for pathological 38.4 weeks ($p = 0.072$ in the Mann–Whitney U-test, and $p = 0.057$ in the t-test for independent samples).

An analysis of parameters using cUS results found the following variables to be statistically significant: BW, venous pO_2, venous pH, arterial pO_2, arterial pH, URI, and C/U ratio (Table 1).