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The impact of neonatal complications on motor function outcome in children born with asymmetric intrauterine growth retardation

Andrea Šimić Klarić[1,2], Zdravko Kolundžić[1], Slavka Galić[1], Marijana Tomić Rajić[1], Damir Matoković[1,2], Ljerka Banožić[1]

The aim of this study was to estimate the impact of neonatal complications on motor outcome in children born with asymmetric intrauterine growth retardation. Study subjects were born at term with birth weight below the 10th percentile for gestational age, parity and gender, mean age six years and four months. They were divided into two groups: group 1 with associated neonatal complications (30 children) and group 2 without such complications (20 children). Group 3 included 50 children matched for chronologic and gestational age, gender and maternal education (control group). Exclusion criteria were central nervous system infections, chromosomopathies, congenital infections, major malformations, severe asphyxia and presence of recognizable genetic syndromes. Touwen neurologic examination was performed for assessment of motor function. Children with neonatal complications had lower results ($p<0.05$) in coordination and visual function compared to intrauterine growth retardation children without neonatal complications. There were also marginally significant differences for posture and fine motor skills. In conclusion, intrauterine growth retardation has negative effect on neurologic development with a synergistic influence of neonatal complications. Neonatal complications correlated negatively with some motor functions. These difficulties could have negative impact on school performance, so it is important to monitor development of intrauterine growth retardation children and enable early therapeutic intervention if necessary.

Keywords: fetal growth retardation; child

INTRODUCTION

Intrauterine growth restriction (IUGR) means the slowing of fetal growth and fetal inability to achieve his/her genetic growth potential due to adverse intrauterine conditions (1, 2). IUGR is most frequently defined by birth weight below the 10th percentile for gestational age, parity and gender, or below or at the 2nd standard deviation for gestational age (3). The incidence is between seven and 10 percent of births (4).

IUGR is one of the most common pregnancy disorders and it is related, directly or indirectly, to 30 percent of intrauterine fetal deaths. IUGR increases neonatal morbidity three times and neonatal mortality 20 times (2, 5). The main pathopsychological mechanism related to IUGR is the presence of chronic hypoxia *in utero* (2).

A child born after asymmetric IUGR has preserved birth length and head circumference but low birth weight. However, this child is more susceptible to perinatal complications because of the prenatal exposure to chronic hypoxia. Fetal adaptations to adverse intrauterine conditions are

[1] General County Hospital, Osječka 106, 34000 Požega, Croatia
[2] School of Medicine, Josip Juraj Strossmayer University, Croatia

Correspondence to:
Andrea Šimić Klarić, MD, PhD, General County Hospital, Osječka 106, 34000 Požega, Croatia, e-mail: andrea.simic-klaric@po.t-com.hr

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growth slowing down, activity decrease, blood flow redistribution and increasing number of red blood cells, which can lead to polycythemia and hyperviscosity. The risk of perinatal asphyxia is increased. Children with IUGR born at term have lower Apgar score and lower umbilical pH (6). They may develop hypoglycemia, hypothermia, perinatal infection, hypocalcemia, meconium-stained amniotic fluid and meconium aspiration. Children with IUGR have an increasing risk of developing perinatal insults and respiratory distress syndrome (7). They more often have selective immune deficiencies, so they are at risk of developing neonatal sepsis. These children have lower IgG concentration, phagocytic index and lower lysosome function as well as neutropenia, which is especially observed in children whose mothers had preeclampsia. Because of that, these children are more susceptible to infections (6).

Children born after IUGR have more coagulation disorders, which increase the risk of hemorrhage, especially pulmonary hemorrhage as well as persistent pulmonary hypertension. Due to prenatal hypoxia of the liver, the level of coagulation factors dependent of vitamin K is decreased and thrombocytopenia is present. Isolated thrombocytopenia is also a sign of some intrauterine viral infections. Sudden infant death syndrome occurs more often in children who were restricted in intrauterine growth (6, 8).

In the umbilical serum of the children born with IUGR, increased interleukin 6, tumor necrosis factor alpha (TNF-α), C-reactive protein, thrombopoietin and interferon gamma levels were found as the result of chronic intrauterine hypoxia (9, 10). Prematurely born children with IUGR have an increased risk of chronic pulmonary disease, necrotizing enterocolitis, retinopathy and lower postnatal growth. The risk of complications is increased in every gestational age (2).

The adverse impact of prenatal growth restriction on brain development and histogenesis consequently results in reduced brain growth potential that is clinically presented as reduced head growth (6, 11). Children with slower postnatal head growth have worse neurocognitive outcome (12). There is no significant difference in the risk of intracranial hemorrhage or periventricular leukomalacia between children with and without IUGR (7).

IUGR directly affects brain growth, leads to pathological development of the endocrine and other systems, and increases susceptibility to hypoxia, perinatal complications and congenital malformations of the central nervous system. An insult that occurs during developmental period can produce important structural and functional effects that lead to later morbidities (13). Consequently to IUGR, numerous minor impairments can develop, like neurocognitive difficulties and language disorders. Major impairments like cerebral palsy can also occur, but rarely (6).

Beside that, neonatal insults alone even without IUGR have a high risk of causing long-term neurodevelopmental impairments. Many neonates survive neonatal complications without neurologic impairment because of the plasticity of the developing brain and improvements in medical care. However, in some newborns these insults result in cognitive and motor impairment as well as in hearing and vision loss (14). Neonatal complications in children born after IUGR could result in future neurodevelopmental delay. More readily visible neurologic sequels develop after perinatal acidosis or labor complications (6).

The aim of this study was to estimate the impact of neonatal complications on motor function outcome in children born with asymmetric IUGR because of their increased susceptibility to neonatal insults.

SUBJECTS

All study subjects were born at term in Maternity Department of General County Hospital in Požega, Croatia, between 2002 and 2004, with birth weight below the 10th percentile for gestational age, parity and gender according to the Croatian percentile curves (15). Gestational age was calculated according to the date of the last menstrual period. Exclusion criteria were central nervous system infections, chromosomopathies, congenital infections, major malformations, severe asphyxia and presence of recognizable genetic syndromes.

Subjects born after asymmetric IUGR were divided into two groups: group 1 consisted of 30 children who had IUGR associated neonatal complications; and group 2 including 20 children free from neonatal insults. Group 3 serving as control group consisted of children born in the same Maternity Department during the 2002-2004 period, with normal birth weight. They were matched to IUGR children for chronologic and gestational age, gender and maternal education. A total of 50 children with IUGR and 50 controls were included in the study. In both groups, there were 28 (56%) girls and 22 (44%) boys. Antenatal ultrasound scan revealed that study subjects had sustained mid-second trimester to third trimester onset IUGR, which we assumed to have been due to placental dysfunction. At the time of examination, children were aged between five years and six months, and seven years. None of the study children had postnatal central nervous system infections or traumatic brain injury.

There were no statistically significant differences between the two groups according to gender (χ^2=0.04; p=0.840), parity (χ^2=8.07; p=0.152), chronologic age (IUGR group median 76 months; interquartile range (IQR) 7.0; control group median 77; IQR 7.0; Mann-Whitney *p*=0.699), gestational age (IUGR group median 277 days; IQR 12.0; control group

median 279; IQR 8.0; Mann-Whitney *p*=0.353) and Apgar score (median for both groups 10.0; IQR 1.0; Mann-Whitney *p*=0.165).

METHODS

Children with IUGR were examined at Department of Pediatrics, General County Hospital in Požega, whereas control group children were examined at a kindergarten in Požega. Both groups were examined by a pediatrician in the presence of the children's parents. The duration of examination and tests was approximately 30 minutes. Neurologic development was evaluated by Touwen neurologic examination (16). The study was approved by the Ethics Review Committee of the General County Hospital in Požega and by the Ethics Review Committee of the School of Medicine, University of Zagreb, Zagreb, Croatia. Informed parental consent was obtained in all cases. Parents received their child's examination report and recommendation for therapeutic or other diagnostic intervention, as necessary. No compensation or travel fees were provided for participation.

Statistical analysis

On statistical analysis, descriptive and inferential statistical methods and the general linear model were used (17). Nonparametric statistical methods were used to compare non-normally distributed variables. The median was calculated as a measure of central tendency and IQR as a measure of variability. The analysis was conducted using SPSS (SPSS Inc., Chicago, USA) with the level of statistical significance set at p<0.05.

RESULTS

The study compared children with IUGR: median gestational age (days) 277; IQR 12.0, median body weight 20.5 kg; IQR 6.0 and median head circumference 50.5 cm; IQR 2.1; and a control group of children born with normal body weight: median gestational age (days) 279; IQR 8.0, median body weight 23.0 kg; IQR 4.0 and median head circumference 52.5 cm; IQR 1.6. All children were born at term.

There were no statistically significant between-group differences according to chronologic age, gestational age, gender, parity, maternal education and Apgar score. In the group of children born after IUGR, the following neonatal complications were recorded: hyperbilirubinemia, hypoxia, electrolyte imbalance, perinatal infections and intracranial hemorrhage (ICH grade I and II). Thirty (60%) children born after IUGR had neonatal complications (Table 1).

Comparison between the two groups of children born after IUGR according to the presence of neonatal complications showed statistically significant differences for coordination and visual function. There were marginally significant differences for posture and fine motor skills (p<0.05 and p<0.1, respectively) (Table 2).

TABLE 1. Neonatal complications in IUGR children

	Number of subjects (n=30)	Percentage of subjects (60%)
Hyperbilirubinemia	11	22%
Perinatal infection	12	24%
Hypoxia	2	4%
Electrolyte imbalance	2	4%
ICH I-II	3	6%

ICH I-II = intracranial hemorrhage grade I and II

TABLE 2. Difference between IUGR children with and without neonatal complications according to motor functions

	Neonatal complications	
Variable	F	P
Sensorimotor function	0.08	0.785
Posture	3.80	0.055
Balance	1.09	0.299
Coordination	5.37	0.023
Fine motor skills	2.85	0.096
Dyskinesia	0.10	0.754
Muscle power	2.25	0.138
Quality of movements	0.39	0.537
Associated movements	0.17	0.680
Visual function	29.26	<0.001
Quantity of movements	0.13	0.716

Distribution of the group of IUGR children with neonatal complications according to specific disorders did not yield statistical significance (p=0.247), probably due to numerous neonatal difficulties that were present in a small portion of the whole sample.

DISCUSSION

Children born after asymmetric IUGR are more susceptible to perinatal complications because of the prenatal exposure to chronic hypoxia. This makes the impact of neonatal complications on their development even more important. Neonatal complications alone are related to a high risk of causing long-term neurodevelopmental impairments. They result in cognitive, motor and sensory function impairments (14).

IUGR has a negative impact on neurocognitive and language development recognizable in preschool age. Slow

postnatal head growth is related to adverse motor, language and cognitive function outcome in children born after asymmetric IUGR (12, 18, 19).

The aim of this study was assessment of the impact of neonatal complications on motor outcome of children with asymmetric IUGR, due to the increasing frequency of neonatal complications in these children. The study assessed neuropsychological development of children born at term, so other reasons for their developmental delay such as prematurity were excluded.

We found that children born after IUGR, who had associated neonatal complications, had achieved lower results in preschool age. Lower outcome was found for visual function, coordination, posture and fine motor skills. Motor outcome of children born after IUGR, but without neonatal complications, was significantly better. A broader research in the same group of children showed that neonatal complications correlated negatively with language comprehension, total expressive language, language structure, content and vocabulary (18).

Many important neurologic sequels after severe perinatal acidosis or delivery complications have been reported in the literature (6). *Fattal-Valevski and Leitner* showed the presence of neonatal complications to be predictive of lower neurodevelopmental outcome in children aged three to six years born with IUGR (4, 11). At the age of three years, children born after IUGR and with neonatal complications had lower IQ (4, 11). This was not confirmed in the present study. In 2006, *Geva et al*. found neonatal complications to be predictive of cognitive impairments in children with IUGR, while it was not proven in control group. The explanation is increased susceptibility of these children to neonatal complications and lower compensation possibility (2).

Systemic intrauterine insult incurred during the neonatal period spreads to the cerebral cortex during childhood, so difficulties can be identified in higher functions, for example fine motor skills. Impairment in higher cortical functions manifests during tasks involving increased neurologic demands.

Visual function is rarely impaired in children with IUGR, but there are studies showing disorders in visual function to be more often apparent. Neonatal insults affect visual functions and result in various visual impairments. So, visual function impairments are more likely associated with neonatal complications than IUGR (20). There are numerous patterns of injury explaining the impact of neonatal complications on neurologic development. Perinatal infections have direct effect on neurons during bacteremia and systemic inflammatory response. Hyperbilirubinemia causes lesions in the subregions of basal ganglia.

However, neonatal complications and IUGR have negative impact on neurologic development. Results show synergistic impact of neonatal complications on neurodevelopmental outcome of children born after asymmetric IUGR. Neonatal complications correlated negatively with motor outcome. Therefore, it is important to act preventively on decreasing neonatal complications in children with perceived slow growth during pregnancy, due to the impact of perinatal complications on neurologic development. Monitoring of children with IUGR who had some difficulties in neonatal period allows for identification of developmental disorders. If it fails to be done, these children will have more often reading, writing and learning difficulties, which leads to lower school performance and academic achievements.

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REFERENCES

1. Seeds JW. Impaired fetal growth: definition and clinical diagnosis. Obstet Gynaecol. 1984;64:303.
2. Rosenberg A. The IUGR newborn. Semin Perinatol. 2008;32:219-24.
3. Roth S, Chang TC, Robson S, Spencer JA, Wyatt JS, Stewart AL. The neurodevelopmental outcome of term infants with different intrauterine growth characteristics. Early Hum Dev. 1999;55:39-50.
4. Fattal-Valevski A, Leitner Y, Kutai M, et al. Neurodevelopmental outcome in children with intrauterine growth restriction. J Child Neurol. 1999;14:724-7.

5. Damodaram M, Story L, Kulinskaya E, Rutherford M, Kumar S. Early adverse perinatal complications in preterm growth-restricted fetuses. Aust M Z J Obstet Gynaecol. 2011;51:204-9. doi: 10.1111/j.1479-828X.2011.01299.x.
6. Palloto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. Clin Obst Gynecol. 2006;49:257-69.
7. Wu YM, Match WM, Crown LA, Grether J, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. Pediatrics. 2004;114:612-9.
8. Froen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pederson B. Restrictid fetal growth in sudden intrauterine unexplained death. Acta Obstet Gyn Scan. 2004;83:801-7.
9. Amarilyo G, Oren A, Minouni FB, Ochshorn Y, Deutsch V, Mandel D. Increased cord serum inflammatory markers in small-for-gestational-age neonates. J Perinatol. 2011;31:30-2.
10. Neta GI, von Ehrenstein OS, Goldman LR, et al. Umbilical cord serum cytokine levels and risks of small-for-gestational-age and preterm birth. Am J Epidemiol. 2010;171:859-67.
11. Yanney M, Marlow N. Paediatric consequences of fetal growth restriction. Semin Fetal Neonatal Med. 2004;9:411-8.
12. Klarić AŠ, Galić S, Kolundžić Z, Bošnjak Mejaški V. Neuropsychological development in preschool children born after asymmetrical intrauterine growth restriction and impact of postnatal head growth. J Child Neurol. 2012;Aug 21. [Epub ahead of print]
13. Gluckman PD, Cutfield W, Hofman P, Hanson MA. The fetal, neonatal, and infant environments-the long-term consequences for disease risk. Early Hum Dev. 2005;81:51-9.
14. Mwaniki MK, Atieno M, Lawn JL, Newton CRJC. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379:445-52.
15. Dražančić A. i sur. Porodništvo. 1. izd. Zagreb: Školska knjiga; 1994:125.
16. Touwen BCL. Examination of the child with minor neurological dysfunction. 2nd ed. London, Philadelphia: Spastics International Medical Publications; 1979.
17. R Development Core Team. A language and environment for statistical computing, reference index version 2.2.1. R Foundation for Statistical Computing. Vienna, Austria. http://www.R-project.org.
18. Šimić Klarić A, Kolundžić Z, Galić S, Mejaški Bošnjak V. Language development in preschool children born after asymmetrical intrauterine growth retardation. Eur J Paediatr Neurol. 2012;16:132-7.
19. Geva R, Eshel R, Leitner Y, Fattal-Valevski A, Harrel S. Neuropsychological outcome of children with intrauterine growth restriction: A 9-year prospective study. Pediatrics. 2006;118:91-100.
20. Martin L, Ley D, Marsal K, Hellstrom A. Visual function in young adults following intrauterine growth retardation. J Pediatr Ophtalmol Strabismus. 2004;41:212-8.

SAŽETAK

Utjecaj novorođenačkih komplikacija za motorički ishod djece rođene nakon asimetričnog intrauterinog zastoja u rastu

Andrea Šimić Klarić, Zdravko Kolundžić, Slavka Galić, Marijana Tomić Rajić, Damir Matoković, Ljerka Banožić

Cilj istraživanja je procjena utjecaja novorođenačkih komplikacija na motorički ishod djece rođene nakon asimetričnog intrauterinog zastoja u rastu. Ispitanici su rođeni na termin s porođajnom masom manjom od 10. centile za gestacijsku dob, paritet i spol, srednje dobi šest godina i četiri mjeseca. Ispitanici su podijeljeni u dvije skupine. Prva je imala pridružene komplikacije u novorođenačkom razdoblju (30-ero djece), dok ih druga skupina nije imala (20-ero djece). Treća je bila kontrolna skupina djece rođene s urednom porođajnom masom, ujednačena s obzirom na kronološku i gestacijsku dob, spol i stupanj majčina obrazovanja (50-ero djece). Isključujući kriteriji bile su infekcije središnjeg živčanog sustava, kromosomopatije, kongenitalne infekcije, malformacije, teška asfiksija i prisutnost prepoznatljivog genetičkog sindroma. Za procjenu neurokognitivnog razvoja primijenjen je neurološki pregled prema Touwenu. Djeca s intrauterinim zastojem u rastu s novorođenačkim komplikacijama imala su lošiju koordinaciju i vidnu funkciju u odnosu na skupinu djece s intrauterinim zastojem u rastu bez novorođenačkih komplikacija. Postoji sugestivna statistički značajna razlika za stav tijela i finu motoriku. Intrauterini zastoj u rastu negativno utječe na neurorazvojni ishod uz sinergističko djelovanje novorođenačkih komplikacija. Novorođenačke komplikacije su povezane s lošijim razvojem motorike. Neurorazvojne poteškoće mogu negativno utjecati na školski uspjeh djece s intrauterinim zastojem u rastu, pa je važno pratiti njihov razvoj, kako bi se moglo navrijeme poduzeti mjere rane intervencije.

Ključne riječi: intrauterini zastoj rasta; dijete