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Long term neuromotor outcome in children born at term with asymmetrical intrauterine growth restriction

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Aim: Intrauterine growth restriction has an important influence on a child's neurological development. The aim of this study was a long-term follow up of a group of children born at term with asymmetrical intrauterine growth restriction until the age of 12 to 14.

Methods: Examinees were children born at term with asymmetrical intrauterine growth restriction matched to the control group according to age, gender, gestational age, and maternal education. Participants were between 12 and 14 years old at the time of examination. Exclusion criteria were central nervous system infections, congenital infections, major malformations, severe asphyxia, chromosomal disorders, and the presence of genetic syndromes. Neurological examination for minor neurological dysfunction according to Hadders-Algra was performed. The results were compared to their first neurological assessment at the age of 5 to 7.

Results: There were 43 participants (22 female and 21 male) in the IUGR group and 42 in the control group (21 female and 21 male). Children with intrauterine growth restriction had significantly lower values for associated movements (p=0.034) and coordination (p=0.001) than the control group. There was a positive correlation between birth weight and associated movements (p=0.015, corellation coefficient).

Conclusion: At pubertal age, examinees born at term with asymmetrical intrauterine growth restriction still show impairments in coordination and associated movements, which is an improvement when compared to the result from preschool age, but indicate that some neurological impairments are irreversible.

Key words: CHILD; FETAL GROWTH RETARDATION; MOTOR SKILLS DISORDERS; NEURODEVELOPMENTAL DISORDERS

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INTRODUCTION

Intrauterine growth restriction (IUGR) is defined by birth weight below the 10th percentile for gestational age, parity, and gender, or below 2nd standard deviation for gestational age (1). IUGR is characterised by fetal limitation for reaching its genetic potential, diagnosed in approximately 6.4 % of newborns (2). IUGR increases the risk of perinatal mortality and perinatal complications but can also have a long-term impact on adult health by causing alterations in gene expression activated during early intra-uterine life, as an answer to adverse intrauterine conditions (3). Fetal adaptation to an adverse prenatal environment is important for survival but could lead to an abnormal long-term outcome (4). Fetal chronic hypoxia is the main pathological mechanism (3). Epigenetic changes of the genome due to antenatal effects like impairment of fetal growth induce the fetal developmental reprogramming that results in a changed metabolic pattern and leads to transgenerational effects of intrauterine malnutrition (5). Depending on the pregnancy period affected by IUGR, two forms of IUGR can be observed: symmetrical and asymmetrical IUGR. IUGR is symmetrical when a disturbing factor impacts the pregnancy before the 26th gestational week, taking place in 30 to 40 % of total IUGR cases. In symmetrical IUGR, anthropometric parameters are symmetrically reduced. It is caused mainly by chromosomopathies, genetic syndromes, congenital anomalies, and viral central nervous system infections (6).

In asymmetrical IUGR, pregnancy is interfered with after the 30th gestational week, mostly due to placental insufficiency or maternal chronic diseases, especially arterial hypertension (6). Head circumference is preserved, but with smaller other anthropometric parameters. Head circumference is protected by a brain-sparing mechanism, in which the brain obtains blood flow but with restricted adaptive capacity (7).

IUGR affects cerebral white and grey matter resulting in a smaller intracranial volume, reduced cerebral grey matter, mostly frontal lobe volume (8, 9). Those changes persist through the childhood. Also, myelination deficits seen in term newborns with IUGR are still present at the ages of 6 years (10, 11). That indicates the impact of the white matter impairments on long term neurological outcome of the IUGR children born at term.

IUGR has an important influence on a child's neurological development and a negative impact on neurocognitive functions. Children born with asymmetrical IUGR are at risk for developing impairments of fine motor skills, balance, and coordination, have a large number of associated movements, body tone disorders, and clumsiness. When it comes to motor deficits, fine motor skills and coordination impairment were noticed already at the preschool age (12,13). Other neurological disorders like cerebral palsy, epilepsy, learning and attention difficulties, or neurobehavioral disabilities can also occur (14 - 17).

Former studies have shown that asymmetrical IUGR in term-born children leads to neuropsychological and cognitive difficulties but without a significant impact on their general intellectual functioning (12, 18, 19).

This study followed up two groups of children: the first one born at term with asymmetrical IUGR and the second group of children born with normal birth weight. Participants were followed up for 7 years, from preschool age. The first part of the neurological outcome study was performed when examinees were between 5 and 7 years of age. At that time, statistically significant differences between two groups of children were found in a few motor variables: fine motor skills, associated movements, posture, coordination, balance, and quantity of movements, with the most discriminative power of fine motor skills (12).

In this article we discuss the neurological outcome of the same two groups of children, now at the age 12 to 14 years. The aim of this long-term follow-up of children with asymmetrical IUGR is to distinguish whether impairments in motor variables are still present in the pubertal age. The study is one of rare studies investigating motor outcome in pubertal age of term born children with asymmetrical IUGR.

METHODS

Examinees were children born at term with asymmetrical IUGR, with birth weight below the 10th percentile for gender, parity, and gestational age, according to the Croatian percentile curves (20).

Table 1. Comparison between IUGR and control group for neurological variables at the age 12 to 14

Group		N	Mean	Std. Deviation	Minimum	Maximum	Percentiles			P
							25th	50th (Median)	75th	
N1: posture	IUGR	43	0.05	0.21	0.00	1.00	0.00	0.00	0.00	0.628
	Control	42	0.07	0.26	0.00	1.00	0.00	0.00	0.00	
N2: reflexes	IUGR	43	0.05	0.30	0.00	2.00	0.00	0.00	0.00	0.545
	Control	42	0.10	0.43	0.00	2.00	0.00	0.00	0.00	
N3: quantity of movements	IUGR	43	0.16	o.53	0.00	2.00	0.00	0.00	0.00	0.181
	Control	42	0.05	0.31	0.00	2.00	0.00	0.00	0.00	
N4: coordination	IUGR	43	2.19	1.68	0.00	6.00	0.00	2.00	4.00	0.001
	Control	42	1.07	1.63	0.00	6.00	0.00	0.00	2.00	
N5: balance	IUGR	43	0.21	0.60	0.00	2.00	0.00	0.00	0.00	0.100
	Control	42	0.05	0.31	0.00	2.00	0.00	0.00	0.00	
N6: fine motor skills	IUGR	43	1.02	1.71	0.00	8.00	0.00	0.00	2.00	0.242
	Control	42	0.69	1.57	0.00	8.00	0.00	0.00	0.25	
N7: associated movements	IUGR	43	7.44	3.42	2.00	16.00	4.00	8.00	10.00	0.034
	Control	42	5.74	3.25	0.00	12.00	2.75	6.00	8.00	
N8: visual function	IUGR	43	0.07	0.26	0.00	1.00	0.00	0.00	0.00	0.666
	Control	42	0.05	0.22	0.00	1.00	0.00	0.00	0.00	
N9: cranial nerves	IUGR	43	0.02	0.15	0.00	1.00	0.00	0.00	0.00	0.297
	Control	42	0.07	0.26	0.00	1.00	0.00	0.00	0.00	
Actual weight (kg)	IUGR	42	47.55	11.50	30.00	72.00	38.75	46.00	53.50	0.234
	Control	41	50.07	10.80	33.00	78.00	41.00	50.00	58.50	
Actual height (cm)	IUGR	42	156.23	8.58	141.00	176.00	151.75	154.00	161.13	0.061
	Control	42	158.79	6.83	145.00	175.50	154.00	158.00	163.00	
Actual head circumference (cm)	IUGR	43	53.61	1.64	50.50	58.00	52.50	53.50	54.50	0.009
	Control	42	54.52	1.58	52.00	58.00	53.38	54.50	55.50	

Estimated gestational age was calculated according to the date of the mother's last menstrual period. Examinees were matched to the control group according to chronological and gestational age, gender, and maternal education.

Participants were aged 5 to 7 years at the first assessment, and were 12 and 14 years old at the second one. Exclusion criteria were central nervous system infections, congenital infections, major malformations, chromosomal disorders, and the presence of genetic syndromes, as well as severe asphyxia.

In the last 7 years, 7 participants in the IUGR group and 8 in the control group dropped out from the initial assessment because they moved to another county or country.

Motor functioning was assessed using a standardised examination of minor neurological dysfunction developed by Touwen and modified by Hadders-Algra (21). This neurological examination for minor neurological dysfunction assesses the following domains: posture, reflexes, involuntary movements, coordination, fine manipulation, associated movements, sensory function, and cranial nerve function.

The assessment was carried out by two independent examiners, the first one was a pediatrician and the second was a child neurologist, without significant intra-examiner differences.

The protocol for this study was approved by the "Ethics Committee of General County Hospital" in Požega, Croatia. The study was conducted in accordance with the Declaration of Helsinki. Full informed consent was given by one of the parents.

STATISTICAL ANALYSIS

For the statistical analysis, descriptive and inferential statistical methods were used. Nonparametric statistical methods were used to compare non-normally distributed variables. The median

was calculated as a measure of central tendency, and the interquartile range as a measure of variability. The Mann-Whitney U test was used to compare the two groups on numerical variables, while the correlation between numerical variables was done using the Spearman test. Multiple testing correction was performed.

To adjust the analysis for the effects of anthropometric parameters, correlation coefficients were calculated. The analysis was conducted using SPSS (SPSS Inc., Chicago, Illinois). $p < 0.05$ was considered statistically significant in all tests used.

RESULTS

There were 43 participants (22 female and 21 male) in the IUGR group, and 42 examinees in the control group (21 female and 21 male). The study compared children with IUGR (median gestational age 277 days; interquartile range 12.0 days 270-282; median head circumference 51.5 cm 49.5-51,6; interquartile range 2.1 cm) and a control group of children born with a normal birth weight (median gestational age 279 days 275-283; interquartile range 8.0 days, median head circumference 52.36 cm; 52.4-54 interquartile range 1.6 cm). All children were born at term.

There were no statistically significant differences between groups with respect to chronological age, gestational age and parity, gender, maternal education and Apgar scores, as well as anthropometric parameters (weight and height). Between group comparisons for anthropometric parameters indicated significant differences in actual head circumference with significantly lower values in head circumference in the IUGR than control group (p=0.009).

Table 2. Comparison between IUGR and control group for neurological variables

	Mann-Whitney U	Z	P
N1: posture	880.500	-0.485	0.628
N2: reflexes	881.000	-0.605	0.545
N3: quantity of movements	841.000	-1.337	0.181
N4: coordination	545.000	-3.319	0.001
N5: balance	820.000	-1.644	0.100
N6: fine motor skills	796.500	-1.169	0.242
N7: associated movements	664.000	-2.124	0.034
N8: visual function	883.000	-0.431	0.666
N9: cranial nerves	859.500	-1.042	0.297
Actual weight (kg)	730.500	-1.190	0.234
Actual height (cm)	672.500	-1.877	0.061
Actual head circumferrence (cm)	608.500	-2.599	0.009

According to neuromotor variables, when examined at the age of 12 to 14 years, children with IUGR had significantly lower values for associated movements (p=0.034) and coordination (p=0.001) than the control group (Tables 1 and 2).

Spearman correlation coefficients between anthropometric parameters indicate that there was a statistically significant positive correlation between birth weight and associated movements (p=0.015, correlation coefficient 0,368).

DISCUSSION

In the first part of the study, preschool children were assessed, and the differences between the two groups were analysed. The first group was born at term after asymmetrical IUGR, and the control grcorrelatinup was matched for all variables except birth weight, which was normal. In the preschool age, there were statistically significant differences between the two groups. The group of children born after IUGR has had lower results on the examination for minor neurological dysfunction, showing deficits in fine motor skills and coordination, a large number associated movements, and body tone disorder (12).

In this particular study, we examined the same two groups of children, but now at the age of 12 to 14 years, to investigate whether the same motoric difficulties were still present. When examined at the age of 12 to 14 years, examinees born with IUGR still show impairments in coordination and associated movements, which improved when compared to the results from preschool age, when they also performed lower results in fine motor skills, and fine motor skills were the most distinguished variable. None of these children were included in physical or work therapy.

The explanation for the neurodevelopmental improvement in children with IUGR could be in findings reported in rats, where severe IUGR exhibit white matter damage that persists to adulthood,

while moderate IUGR cause transient hypomyelination, mild microglial activation and astrogliosis (22, 23). Specific impairments in neurological domains persist due to chronic brain damage caused by IUGR (23, 24).

Former studies assessing neuromotor outcome in children with IUGR have shown that asymmetrical IUGR in term born children leads to neuropsychological and cognitive difficulties (12,13,18). Strauss et al in 2000 analysed adolescents and young adults at the age of 16 to 26 years, and concluded that at term born children with IUGR had relatively lower academic achievement (24).

Leitner et al studied a group of IUGR children at the age of 9 to 10 and showed statistically significant differences in coordination, graphomotor skills, and muscle tone, with lower results in the IUGR group than in the control group (13). Tanis et al 2015 didn't find a difference in motor skills between term-born children with IUGR and with normal birth weight (25). In the LEMON study on twins with IUGR, more neurodevelopmental difficulties have been found in twins with lower birth weight at the age of 11 years (26).

Although children with IUGR mostly have mild motor difficulties, the incidence of cerebral palsy is also higher in this population (18). Being born with IUGR seems to increase the risk of future neuromotor impairments.

The main limitation of the study is the relatively low number of participants, but our findings agree with the scientific literature on neuromotor outcome after IUGR. Nevertheless, we present an extensive long-term follow-up of motor functioning until pubertal age, which is one of the rare studies of children in that age. Also, whereas previous studies primarily reported on the neuromotor development of premature newborns, our assessment was made in children born at term. The information provided by our study allows clinicians to identify children at risk so targeted interventions can be administered to optimise their neuromotor development.

CONCLUSION

Conclusively, at the pubertal age, examinees born at term with asymmetrical IUGR still show impairments in coordination and associated movements, which is an improvement when compared to the result from preschool age, but obviously, some motor impairments caused by IUGR are irreversible. The improvement of long-term neurological outcome of term-born children with asymmetrical IUGR during childhood is not achieved as a result of any treatment. Maybe the reason for improvement is maturation of the brain, but further studies are needed to investigate that possibility. So, neurological difficulties are still present in pubertal age, although in less volume. Even though the impairments in our study population are mainly mild, children's later daily functioning and academic achievement can be impaired.

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SAŽETAK

Dugoročno praćenje neuromotornog razvoja terminske djece rođene s asimetričnim intrauterinim zastojem rasta

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Cilj: Intrauterini zastoj rasta ima važan utjecaj na neurološki razvoj djeteta. Cilj ovog istraživanja bilo je dugoročno praćenje djece rođene u terminu s asimetričnim zastojem u rastu, do dobi 12 do 14 godina.

Metode: Ispitanici su djeca rođena u terminu s asimetričnim zastojem u rastu koja su usklađena s kontrolnom skupinom djece s obzirom na dob, spol, gestacijsku dob i obrazovanje majke. Ispitanici su u vrijeme istraživanja bili dobi 12 do 14 godina starosti. Kriteriji isključivanja bili su infekcije središnjeg živčanog sustava, kongenitalne infekcije, malformacije, teška asfiksija, kromosomske aberacije i prisutnost genetskih sindroma. Svima je učinjen neurološki pregled po Hadders – Algri. Rezultati su uspoređeni s prvom neurološkom procjenom u dobi od 5 do 7 godina.

Rezultati: U istraživanju je sudjelovalo 43 ispitanika (22 djevojčice i 22 dječaka) u skupini djece s intrauterinim zastojem rasta i 42 u kontrolnoj skupini (21 djevojčica I 21 dječak). Djeca s intrauterinim zastojem rasta imala su značajno niže vrijednosti varijable pridruženih pokreta (p=0,034) i koordinacije (p=0,001) nego kontrolna skupina. Uočena je pozitivna korelacije između porođajne mase i pridruženih pokreta (p=0,015, koeficijent korelacije=0,368).

Zaključak: U pubertetskoj dobi, ispitanici rođeni u terminu nakon asimetričnog intrauterinog zastoja u rastu i dalje pokazuju odstupanja u koordinaciji I pridruženim pokretima, što je poboljšanje u usporedbi s rezultatima iz predškolske dobi, ali pokazuje da su neka neurološka odstupanja ireverzibilna.

Ključne riječi: DIJETE; ZAOSTAJANJE U RASTU FETUSA; POREMEĆAJI MOTORIČKIH SPOSOBNOSTI; NEUROLOŠKI RAZVOJNI POREMEĆAJI