Assessment of Infantile Psychomotor Development Status in 6 and 12-Month-Old IUGR Infants: A Historical Cohort Study

Fatemeh Nayeri[1], Sara Bahadoram[1], Zahra Farahani[2], Mamak Shariat[2]

[1] *Breast Feeding Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Maternal, Fetal, and Neonatal Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Intrauterine growth restriction (IUGR) is responsible for different post-natal adverse outcomes. This study aimed to evaluate the post-natal psychomotor development status in 6 and 12-month-old IUGR infants who received early preventive interventions. A historical cohort study was done at an Iranian Hospital (2019). The case group included one-year-old infants with a history of IUGR at birth. This group was visited every 2 months to evaluate their growth and neurodevelopmental status. Their parents had also received some training to improve their infant's sensory and motor skills. The control group comprised one-year-old healthy infants with a history of appropriate for gestational age (AGA) at birth. Data related to psychomotor developmental indices based on the ASQ questionnaire at 6 and 12-month for both groups was extracted from subjects' records. Infants' psychomotor development status was compared between groups. Forty-one infants with a history of IUGR and 43 healthy control infants were included in this study. There were significant differences between 2 groups associated with abnormalities in all evaluated psychomotor skills, including gross motor (P=0.014), problem-solving ability (P=0.049), communication (P=0.031), fine motor (P=0.016) and personal-social (P=0.016) at 6 months. After one year of family-based interventions for the case group, significant differences between groups were notable in only fine motor (P=0.016) and personal-social skills (P=0.031). At 12 months, the psychomotor disorders related to gross motor, problem-solving ability, and communication were significantly alleviated in the IUGR group. Early preventive family-based interventions can improve the neurodevelopmental outcomes in 12-month-old IUGR infants.

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Introduction

Fetal growth restriction (FGR), also known intrauterine growth restriction (IUGR), is defined as failure to achieve specific fetal biometric measures (below the 10th percentile) by a specific gestational age. This frequent complication with a prevalence rate of 3-10% is responsible for different pre- and post-natal adverse outcomes (1). Some maternal, fetal, or placental causes are involved in the etiology of IUGR. IUGR infants are at higher risks of neurodevelopment complications when they compared with infants whose birth weight is appropriate for their gestational age (AGA) (2-4). It has been shown that neurodevelopmental and cognitive deficitsin newborns with IUGR may relate to a significant reduction in intracranial volume, cerebral cortical gray matter and blood flow of the middle cerebral artery (MCA) (5,6).

Several studies have evaluated the correlations between the history of IUGR and postnatal neurodevelopmental disorders. The results of a systematic review indicated that children aged 6 months to 3 years with a history of IUGR were at risk for poor neurodevelopmental outcomes; Evaluating of 16 included studies, results have shown that motor delay, cognitive delay, and language delay were the most prevalent neurodevelopment complications among the study population (7). Another study has also

Corresponding Author: M. Shariat
Maternal, Fetal, and Neonatal Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9123499281, E-mail address: msharia t@tums.ac.ir

demonstrated that children with a history of IUGR at birth were at higher risk for delayed in somatic growth, neurodevelopmental performance, cognition, and school achievements in comparison with the AGA control group. Difficulties in memory performance, learning abilities, visuomotor functions, and attention span were frequent complications among IUGR children (3). An investigation in 2013 compared neurodevelopmental outcomes at 2 years of infants with the history of IUGR and SGA. Results have demonstrated higher risks for adverse short- and long-term outcomes, including neurodevelopmental impairment and growth delay among IUGR infants in comparison with SGA children (8).

Few studies examined the short/long-term neurodevelopmental risks of infants with IUGR (3,7,8). But there is still a paucity of information regarding which of different psychomotor skills may be affected by IUGR or the effectiveness of some preventive interventions on the postnatal adverse outcomes. This study aimed to evaluate the postnatal psychomotor development status in six and twelve-month-old IUGR infants who attended at the Growth and Development Clinic and received some early preventive interventions. Such investigations may provide a more realistic picture regarding the adverse postnatal outcome related to IUGR as well as benefits associated with sooner diagnosis and planned interventions.

Materials and Methods

A historical cohort study was done at Imam Khomeini Hospital complex affiliated with Tehran University of Medical Sciences (Tehran, Iran; 2019).

The case group included one-year-old infants with a history of IUGR at birth. This group had attended at the Growth and Development Clinic in Imam Khomeini Hospital complex. This group was called every 2 months for regular health check-ups to evaluate their growth and neurodevelopmental status. Furthermore, their parents had received some training to improve their infant's senses, sensory and motor skills. Mothers were asked to stimulate the hearing sense of their infants by whispering, singing, and music. Using some colorful papers, tissue, and toys stimulated the infant's eyesight. Gentle, symmetric skin massage and skin stimulation daily, hydrotherapy (water game) and use of mental targeted games were also trained to mothers during one-year investigator-led study. Mothers also received some training packages composed of books, music and game CDs in each session.

The control group involved one-year-old healthy infants who had a history of AGA at birth. This group had regularly attended Health Centers for evaluating their health, growth and neurodevelopmental status, as well as vaccination.

Maternal and neonatal demographic data including mother's age, gravid, para, abortion, type of delivery, obstetric complications and intake medication, gestational age at birth (based on LMP, and ultrasound examination at 11-13 weeks of pregnancy), sex, birth weight, height, head circumference, the first and 5^{th} minute Apgar scores were gathered from medical records as well as parents via self-administered questionnaire.

Data related to psychomotor developmental indices based on the ASQ questionnaire at 6months and 12months for both groups were extracted from subjects' records. Infants with a history of genetic or major congenital malformations as well as incomplete data due to their absences in the appointed visits were excluded from the study.

With respect to assessing the psychomotor domains and completing the ASQ questionnaire, mothers of all participants had been invited for their infant's follow-up visits when infants were6 and 12months.In each visit, the psychomotor status of the subject was assessed by an expert pediatrician on the basis of Age and Stage Questionnaires® (ASQ-3). ASQ questionnaire consists of 30 items (six questions associated with each domain) to assess psychomotor domains, including communication, personal-social, problem-solving ability, fine and gross motor control (six questions associated with each domain). Scores 10, 5 and 0 were considered for answer options ‘yes’, ‘sometimes’ and ‘not yet’, respectively. Conclusions and scores of the questionnaire were stated as normal or abnormal according to cut-off point for each domain written in the guideline (the cut-off for communication was considered 29, for gross motor19, for fine movement 27.5, for problem-solving 37, and for social domain 27.5). Age-specific norms of <2 SDs were considered as ASQ fail on each domain (9,10). The ASQ questionnaire was translated into Persian. Besides, in order to be administered among Iranian children, it was validated using the Children’s Bureau of the Ministry of Health and Medical Education in Iran. Its sensitivity and specificity were determined by 90% and 81-91%, respectively (11).

The main objective of our study was to compare infants' psychomotor development status among 6 and12-month-aged infants with and without a history of

IUGR at birth. Furthermore, the effectiveness of family-based intervention on case group's neurodevelopmental status was assessed.

Sample size

Based on an investigation by Beckezath *et al*., in 2012 (8), the frequency of abnormal neurodevelopment status in IUGR and healthy controls were 25% and 6%. Using a sample size formula regarding comparing ratios between groups, the proposed sample size was considered 50 subjects in each group. With the proposed sample size, the study had a power of 80% and an alpha error of 0.05.

The parents of all participants gave written consent. They were assured about the confidentiality of their personal information. No extra cost was imposed on subjects, and they also had the right to discontinue the study course whenever they wished. The present study was extracted from a subspecialty thesis in pediatrics (ID; 40898). Ethics approval for the study was obtained from the institutional review board of Tehran University of Medical Sciences according to the Helsinki declaration (IR.TUMS.VCR.REC.1397.541).

Data analysis

The Statistical Package for Social Sciences (SPSS), version 19 was used for statistical analysis. Quantitative and qualitative data were reported via means±standard deviations and frequency, respectively. Based on Kolmogorov-Smirnov analysis, T student and Mann–Whitney tests were used for analyzing quantitative variables with normal and non-normal distributions, respectively. Chi-square tests were also performed to analyze the associations between groups' qualitative variables. Demonstrating the effectiveness of other risk factors like history of asphyxia, preterm birth, maternal complications and medication usage besides IUGR on neurodevelopment problems, Binary Logistic Regression and Bootstrap were used. Determining the differences in the severity of abnormalities in 6 and 12 months, the Kendall test was used.

Results

Forty-one infants with a history of IUGR at birth and 43 healthy control infants entered the study. In the case group, the gestational age was 31.5±3.29 weeks (Min: 25& Max: 37 weeks) weeks. The type of delivery in all of them was cesarean section and 21 subjects were male. The mothers' of IUGR infants had a history of one or more prenatal complications, including diabetes, gestational diabetes mellitus, preeclampsia, and hypertensive disorders, thyroid diseases, fauvism, prenatal consumption of medications, and so on. History of neonatal complications like asphyxia or preterm birth was also observed in 36.6% and 92.6% of the case group.

All participants in the control group were term. No mothers in this group had any history of prenatal complications or medication consumption. Detailed data regarding the case and control groups are shown in Table 1.

Table 1. Demographic characteristic in the case and control groups

Variables	Case group (N=41)	Control group (N=43)
Gestational age (Weeks; Mean±SD)	31.5±3.29	38.37±0.88
Type of delivery (n%)		
Cesarean section	41(100)	20 (47)
Vaginal delivery	0	23 (53)
History of prenatal complications (n%)		
Maternal fauvism	1	
Idiopathic thrombocytopenia &Spleenectomy	1	
Diabetes		
Gestational diabetes	1	
Preeclampsia	1	
Hypertension	20	0
Still birth	4	
Abortion	2	
Fatty liver	3	
Thyroid disorders	1	
Oligohydramnios	4	
History of prenatal medication	5	
Head circumference (Cm; Mean±SD)	21	0
Birth weight (g; Mean±SD)	27.5±2.60	35.16±2.65
Neonatal complications (n%)	3000±438	3200±433
Asphyxia	15 (36.5)	0
Preterm birth	38 (92.5)	

Data regarding psychomotor development at 6 and 12 months

As results are demonstrated in Table 2, there were significant differences between groups associated with abnormalities in all domains at 6 months. Psychomotor impairment in all areas wassignificantly higher in the IUGR group; gross motor skill (*P*=0.014), problem-solving ability (*P*=0.049), communication skills (*P*=0.031), fine motor (*P*=0.016) and personal-social ability (*P*=0.016); however, only significant differences were observed in fine motor (*P*=0.016) and personal-social skills (*P*=0.031) at 12 months. In the IUGR group, unlike the previous period (6 months), the prevalence of psychomotor disorder was significantly reduced after one-year family-based interventions. No significant differences were observed between groups with respect to the abnormalities in communication, problem-solving, and gross motor skills at 12 months (*P*>0.05).

Table 2. Comparison of abnormalities in different psychomotordomains among 6 and 12- month-old between the case and control groups (Binary regression analysis)

Variables	Case group N=41 (%)	Control group N=43 (%)	*P*
Abnormality in communication skill			
6 months	8.1	12.8	0.031
12 months	11.1	8.5	0.085
Abnormality in gross motor skill			
6 months	25.6	6.4	0.016
12 months	19.4	6.4	0.075
Abnormality in fine motor skill			
6 months	23.1	12.8	0.016
12 months	27	10.6	0.016
Abnormality in problem-solving skill			
6 months	27	10.6	0.049
12 months	6.5	6.4	0. 051
Abnormality in personal-social skill			
6 months	21.1	10.6	0.015
12 months	17.1	8.5	0.031

The influences of other risk factors like history of asphyxia, preterm birth, maternal complications and medication usage besides IUGR on neurodevelopment problems at 6 and 12 months were assessed. According to the data analysis by Binary Logistic Regression (with Bootstrapping) IUGR was the only risk factor affecting abnormalities in all neurodevelopmental domains and the other factors had no confounding effect on these skills. Other factors, including maternal drug usage, neonatal asphyxia, or maternal complications, could independently affect the prevalence of abnormality in some skills (Tables 3 and 4).

Table 3. The role of other risk factors on different psychomotor domains at 6 months (Binary regression analysis)

Risk factors/ Domains	Gross motor P	Communication P	Fine motor P	Problem-solving P	Personal-social P
Asphyxia	0.524	0.016	0.188	0.738	0.857
Mother's disease	0.143	0.031	0.219	0.108	0.206
Preterm birth	0.143	0.688	0.141	0.123	0.095
History of medication usage	0.429	0.063	0.438	0.046	0.460

Table 4. The role of other risk factors on different psychomotor domains at 12 months (Binary regression analysis)

Risk factors/ Domains	Gross motor P	Communication P	Fine motor P	Problem-solving P	Personal-social P
Asphyxia	0.851	0.119	0.127	0.017	0.492
Mother's disease	0.388	0.034	0.524	0.305	0.169
Preterm birth	0.119	0.153	0.619	0.305	0.123
History of medication usage	0.448	0.831	0.016	0.017	0.412

Discussion

Infants who experienced IUGR are at increased risk for nervous system damage resulting in impaired neurodevelopment. Moreover, such morbiditiescan seriously affect the quality of life. Early diagnosis and interventions may improve neurodevelopmental outcomes preventing adverse short- and long-term disabilities (7,12). In the present study, we assessed the post-natal psychomotor development status in 6 and12-month-old IUGR infants who attended the Growth and Development Clinic and received some early preventive interventions. The results of such studies may highlight the role of some interventions that may potentially optimize the risks of infantile morbidities.

Based on the results, among different risk factors, including history of IUGR, asphyxia, preterm birth, maternal complications, and medication usage, IUGR as an independent risk factor could influence different psychomotor domains. Our findings were in line with the other studies. A Systematic Review by Levine *et al*., have reported that 6-36 months old children with a history of IUGR were at higher risk for impaired different domains of neurodevelopmental outcomes, including motor, cognitive, language delays, social development, attention, and adaptive behavior when compared with AGA children (7). Hartkopf *et al*., also demonstrated that the MDI scores associated with the developmental state of two years old children (using Developmental Test BSID-II; MDI and PDI), were significantly lower in the IUGR in comparison with the AGA group (13).

Results of the present study have indicated that abnormalities in all domains of psychomotor skills at 6 months were more frequent in the IUGR group compared to the AGA group. Published evidence suggested that IUGR may cause impairment of neural architecture resulting in volume reduction in in frontal lobes, hippocampus, frontal cortex, intracranial volume, grey and white matte. Impairment in these neural architectures may involve cognitive and behavioral deficits, as well as negative effects on learning, memory, attention, executive functions, and motor development (5,14,15). In accordance with our results, Murray *et al.*, demonstrated that the history of IUGR at birth is a risk factor for abnormalities in different neurodevelopmental domains during childhood. They showed that scores related to neurocognitive and motor developmental tests in IUGR infants were significantly lower than control children without IUGR (14). Levine *et al.*, also in a systematic review evaluated the neurodevelopmental outcomes in 6 months to 3-year-old children with IUGR. Of all 16 included studies, poorer neurodevelopmental outcomes in 11, motor delay in 10, cognitive impairment in 8, and language delay in 7 studies were described (7).

According to our results, the significant differences with respect to the frequency of impaired gross motor, communication, and problem-solving abilities between the IUGR and healthy counterpart groups were not observed at the age of 12 months. It seems that our early-onset training program for involving parents had been effective in the improvement of neurodevelopmental status, particularly gross motor and problem-solving abilities after one year. Few studies have assessed the influence of IUGR on neurodevelopmental outcomes. But up to our knowledge, the present study was the only investigation that evaluated the influence of simple preventive interventions on different neurodevelopmental one by one domain among infants with a history of IUGR. Diseases and illnesses may deprive infants of some environmental stimulus exposures and communications while parents' engagement in the treatment process and supportive care could relieve the adverse outcome related to IUGR. Evidence suggests that the involvement of infants in mental practice, exercise and games could enhance neurodevelopmental outcomes (16). It has also been reported that daily massage as a quick, easy, and inexpensive intervention can influence on growth and development of complicated infants (17). Pickler *et al*., reported that complicated infants who involved some care based on their neurobehavioral capabilities showed better motor system organization, improved autonomic regulation, and Bailey motor scores (18). Zhang *et al*., have shown that early familial intervention after NICU discharge (4 days weekly; 30 minutes daily) and follow-up visits in first year of life significantly improved the neurodevelopmental outcome based on scores of physical development index (PDI) (19). The systematic review and meta-analysis by Hughes *et al*., indicated the positive influences of interventions up to 24 months on motor skills for high-risk infants (20). It should be considered that improvement of outcome may also depend on other factors like infant's sex, age at birth, socioeconomic status of family, time of initiation of programs and type of physical activity (21,22).

Based on the results, the frequencies of impaired fine motor and personal-social skills at 12 months in the IUGR group were more notable compared to the healthy

group. We suppose that the improvement of these skills may require further and longer family-based interventions. Although these works up are routinely performed for IUGR subjects until 36 months in our center, we did not follow our cases after 12 months in the present study. In accordance with our finding, another study by Sacchi *et al*., confirmed a lower level of infant responsiveness during mother-child interactions and poorer behavioral responses to social stimuli in the IUGR group at 12 months compared to the control group (23). However, we could not find any studies which evaluated the influences of family-based interventions on neurodevelopmental outcomes in 12-month-old IUGR infants to compare our results.

Our study had several limitations. For instance, the sample size was small and we did not follow our cases after 12 months. It was better that the IUGR and preterm neonates in the case group were compared with the AGA preterm or IUGR term neonates in the control group. But the numbers of IUGR term neonates referring to our clinic was not high enough to enter the study. Moreover, it seems that considering AGA preterm neonates as the controls could provide several confounding factors and bias regarding prematurity. Further studies with larger sample sizes, longer follow up periods, or implemention of more advanced assessing tools like Wisconsin and Wechsler Memory Scale for evaluating the possible effectiveness of family-based interventions on different domains of psychomotor skills until preschool age are suggested.

The results of present study showed a high frequency of some neurodevelopmental abnormalities among IUGR infants. Implementing some early preventive and simple family-based interventions during the first year of the infant's life could significantly enhance the neurodevelopmental outcome.

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