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RESEARCH REPORT

Motor Development Skills of 1- to 4-Year-Old Iranian Children with Early Treated Phenylketonuria

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Abstract ***Objective:*** To gauge the gross and fine motor development of early treated phenylketonuria (ETPKU) in children in the age range of 1–4 years.

Methods: A cross-sectional analytic study was conducted in PKU clinics (reference clinics for PKU follow-up), Tehran, Iran. Seventy children with ETPKU were selected as the case group for the study. ETPKU children were those with early and continuous treatment with a phenylalanine-restricted diet (the mean of blood phenylalanine level during the recent 6 months was 2–6 mg/dL or 120–360 μmol/L). Also, 100 healthy and normal children matched with the ETPKU group for age were randomly selected from 4 kindergartens in four parts of Tehran as a control group. The measurements consisted of a demographic questionnaire, Peabody Developmental Motor Scale-2 (PDMS-2), and pediatrician assessment. Motor quotients were determined by PDMS-2 and then compared in both groups by two independent samples *t*-test.

Results: The mean ages in case and control group were 28.5 (± 11.6) and 29.7 (± 11.3) months, respectively. Comparison of the mean fine, gross, and total developmental motor quotients (DMQs) showed statistically significant differences between the two groups ($p < 0.05$). The fine and total DMQs of ETPKU children were also correlated with age. In addition, there was a negative correlation between the phenylalanine level and fine ($p < 0.001$) and total ($p = 0.001$) DMQs.

Conclusion: It seems that ETPKU Iranian children, regardless of following a phenylalanine-restricted diet or not, have lower motor development. It is recommended to plan programs for early detection and intervention of developmental delays in these children.

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By reading this article, the reader will better understand the motor consequences of early dietary intervention in Iranian PKU children.

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Introduction

PKU is a rare metabolic autosomal recessive disease characterized by a deficiency in the phenylalanine hydroxylase enzyme that is necessary for the metabolism of the amino acid phenylalanine (Phe) (Hoeksma et al. 2009).

The incidence of PKU varies widely in different parts of the world. While the average incidence of PKU in Caucasians is approximately 1 in 10,000, it differs several-fold among different populations. The incidence of PKU in Iran can be estimated to be 1 in 3,627 (Koochmeshgi et al. 2002). This is one of the highest incidence values reported.

Untreated PKU typically results in cognitive impairment (Hoeksma et al. 2009; van Spronsen et al. 2009). With dietary treatment, intelligence is usually in the average

range, although it remains somewhat lower than that of peers and siblings without PKU (Hoeksma et al. 2009). Waisbren et al. noted that untreated PKU was associated with significant delays in developmental milestones (e.g., crawling, walking, talking), and approximately 98 % of individuals with untreated PKU fall in the range of global intellectual disability (Waisbren et al. 2007).

Although early diagnosis and dietary treatment prevent the severe impairments associated with untreated PKU, some studies have shown that individuals with early treated PKU (ETPKU) experience significant neurocognitive impairment (Christ et al. 2010). In relation to neuromotor problems, it is unusual for gross motor problems to occur when PKU is diagnosed and treated early (Yalaz et al. 2006), but impairments in fine motor control have also been reported (Moyle et al. 2007).

Screening of PKU in Iran has been ongoing for all newborns since about 2009, and, in the case of diagnosis of PKU, the newborns are placed on an early intervention with a Phe-restricted diet in the reference clinics for PKU follow-up in Tehran, Iran.

Considering the importance of follow-up, and evaluating the consequences of early intervention on developmental status of these children, we decided to prospectively investigate the development of fine and gross motor skills in ETPKU Iranian children using the Peabody Developmental Motor Scale-2 (PDMS-2).

Material and Methods

This cross-sectional analytic study was carried out between 2011 August and 2012 July in the PKU clinics of three children hospitals, Tehran, Iran. The inclusion criteria were neonatal diagnosis of PKU, early and continuous treatment with a phenylalanine-restricted diet (the mean of blood phenylalanine during the most recent 6 months, in three assessments, was 2–6 mg/dL or 120–360 μmol/L), and 1–4 years of age. The exclusion criteria were any other degenerative, genetic, and metabolic diseases; history of other neuromotor diseases in the family; and neurological, orthopedic, and/or other acquired problems which affect motor development.

Dietary regimens for the children with ETPKU are shown in Table 1.

All children were examined by a pediatrician and if they fulfilled the above criteria were enrolled in the study. A total of 150 children with early and continuously treated PKU had been monitored in reference clinics for PKU follow-up in Tehran, Iran. Seventy children aged 1–4 years were enrolled in the study based on inclusion and exclusion criteria and defined as the case group ($n = 70$). Also, 100 healthy and normal children were matched with this case group for age, randomly selected from four kindergartens in four parts of the Tehran.

Table 1 Daily amounts of phenylalanine, protein, and calories for children with PKU

Child's age	Phenylalanine (mg per day)	Protein (g per day)	Energy (kcal per day)
1–3 years	200–450	30–35	900–1,800
4–7 years	225–625	35–40	1,300–2,300

Informed consent form was obtained and then the questionnaire, which contains medical history and demographic information of infants, was completed. Finally, two occupational therapists blinded to the history of infants conducted PDMS-2 for each infant. Assessments were performed in the occupational therapy clinic and infants were examined individually.

The PDMS-2 is one of the most commonly used assessments for measuring motor skills of infants and toddlers from birth through age 5 years. For children with special needs, the Peabody Development Motor Scale is one of the most reliable testing instruments used by many professionals as a diagnostic tool for assessing gross and fine motor skills. It has been used in a number of follow-up studies investigating motor skills in the PKU population (Arnold et al. 1998)]. With the PDMS-2, most motor skill dysfunction will be identified. This test is composed of six subtests that assess related motor abilities that develop early in life: Reflexes, Stationary (body control and equilibrium), Locomotion, Object Manipulation, Grasping, and Visual-Motor Integration. Results from these subtests are used to generate the three composite scores: gross motor quotient, fine motor quotient, and total motor quotient, which has a mean of 100 and a standard deviation of 15 (Connolly et al. 2012).

Data Analysis

Two independent samples *t*-test was used to compare the mean fine, gross, and total developmental motor quotients. P values less than 0.05 were considered significant. The data were analyzed using the SPSS 16 software.

Results

Study population consisted of case group (ETPKU, $n = 70$) and normal healthy children as a control group ($n = 100$). The mean ages were 28.5 and 29.7 months in PKU and normal children, respectively. Repeated measure analysis was used to assess the stability of the three measures of phenylalanine level. The mean ± SD of first, second, and third phenylalanine levels were 4.1 ± 1.5, 4.2 ± 1.3, and 4.2 ± 1.4, respectively. The analysis showed that there

Table 2 Growth variables in normal and PKU children

	Normal		PKU		
Developmental variables	Mean	SD	Mean	SD	P value
Head circumference (cm)	49	10	46	2.4	0.049
Height (cm)	93	72	90	9.8	0.692
Weight (kg)	17	12	15	3.6	0.162
Birth head circumference (cm)	36	1	36	1.3	0.733
Birth height (cm)	51	2.6	52	3.8	0.128
Birth weight (gr)	3165	358	3173	507	0.909

Table 3 Comparison the mean fine, gross, and total motor quotients in normal and PKU children

Variable	Normal mean (SD)	PKU mean (SD)	P value
Fine DMQ	96 (11)	86 (10)	< 0.001
Gross DMQ	96 (13)	91 (8)	0.010
Total DMQ	96 (11)	88 (9)	< 0.001

Table 4 Comparison of the mean fine, gross, and total motor quotients based on age in PKU children

Age		N	Mean	SD	P value
Fine DMQ	<24 m	26	90	8.7	*0.014*
	≥24 m	44	84	10.3	
Gross DMQ	<24 m	26	94	8.5	*0.064*
	≥24 m	44	90	7.2	
Total DMQ	<24 m	26	91	8.6	*0.019*
	≥24 m	44	86	8.1	

was no significant difference between the mean of phenylalanine level measures at three times ($F = 0.729$, $p = 0.492$).

Table 2 shows the growth variables in PKU and normal children. There were no significant differences in indices of growth at birth between the two groups, with the exception of head circumference ($p = 0.049$).

Table 3 shows that there were significant differences between the two groups in mean fine motor ($p < 0.001$), gross motor ($p = 0.010$), and total motor quotients ($p < 0.001$).

There were significant differences between the mean fine motor quotient and total motor quotient of children less than 24 months of age in the case group in comparison with children equal or older than 24 months of age ($p = 0.014$, $p = 0.019$). Conversely, there were no significant differences between the mean fine motor quotient and gross motor quotient of children less than 24 months of age in the case group in comparison to children equal to or older than 24 months of age ($p = 0.064$) (Table 4). In addition, the correlation between the phenylalanine level and developmental motor quotients showed a negative correlation between fine ($p < 0.001$) and total ($p = 0.001$) DMQs.

Discussion

This study sets out to characterize the motor quotients and compare the fine and gross motor development of ETPKU and normal Iranian children in the age range of 1–4 years.

Recent studies showed that although poor neurological outcomes were reported, such as abnormalities in the white matter of the brain, which may compromise brain function in untreated PKU patients (Alvord et al. 1950; Phillips et al. 2001; Anderson et al. 2004), only limited studies address real neurological issues in early and continuously treated PKU patients (Ludolph et al. 1992). Motor problems observed in ETPKU patients include brisk reflexes and tremor that may develop in poorly treated as well as well-treated PKU patients especially after adolescence (Ludolph et al. 1992). On the other hand, in poorly controlled patients, or in those who discontinued the diet in adolescence or adult life, the risk of neurocognitive, emotional, and behavioral dysfunctions and even neurologic complications such as epilepsy, ataxia, tremor, and spasticity may occur more frequently (Janzen and Nguyen 2010; Arnold et al. 1998).

One of the most consistent findings reported through studies of neurocognitive abilities of ETPKU individuals is impairment in executive function (EF) (Christ et al. 2010). Similarly, nonexecutive impairments including slowed information processing speed, motor skill problems, perception and visual–spatial difficulties, language deficits, and memory and learning impairments are found in ETPKU patients (Janzen and Nguyen 2010).

Previous studies reported that gross motor problems were rarely observed when PKU was diagnosed and treated early (Yalaz et al. 2006). Nonetheless, impairments in fine

motor control have been widely reported (Moyle et al. 2007). Some studies have shown correlations between Phe levels and fine motor scores. Arnold et al. found that children with PKU manifested significantly impaired fine motor scores on the Peabody Developmental Motor Scale (Arnold et al. 1998). Gassio et al. reported that individuals with PKU showed significantly poorer fine motor scores than controls on the Purdue test. In both of these studies, there were negative correlations between Phe levels and fine motor scores (Arnold et al. 1998; Gassio et al. 2005). Brandalize et al. mentioned that fine motor scores have also been associated with the early implementation of dietary Phe restriction in children with PKU (Brandalize and Czeresnia 2004). Weglage et al. reported poorer performance for children with ETPKU than control children on measures of arm–hand–finger precision and speed using a motor performance battery, and these deficits were significantly correlated with blood Phe levels (Weglage et al. 1995).

In our study, although both fine and gross motor development of the ETPKU cohort showed significant differences in comparison to normal children, the mean value of gross and fine DMQs showed that these differences were more prevalent in fine DMQ, with less impact on gross DMQ. Furthermore based on the Guide to interpreting PDMS-2 quotient scores in the Peabody examiner's manual, the mean of all DMQs in the ETPKU group were in the range of 80–89. This suggests that the motor development of the ETPKU group was below the average (16 %). On the other hand, the mean of all DMQs in the normal group were in the range of 90–110 which means that motor development of this group was average (50th centile). Finally, we found that the fine and total DMQs of ETPKU children correlated with age. In children less than 24 months, DMQs were significantly higher than the children older than 24 months. This may relate to poor dietary control and variation in the phenylalanine level. Several previous studies have found a relationship between Phe levels and cognitive and executive function (EF). These studies mentioned that concurrent Phe level, lifetime Phe level, and Phe level variability are the best predictors of variation in the current EF performance (Vera et al. 2008).

In conclusion, the key result of our study suggests that motor developmental delay in ETPKU children occurs regardless of following a phe-restricted diet or not. Our studies suggest that developmental screening and follow-up be conducted on all ETPKU infants, and that early intervention be undertaken in children with developmental delays.

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Compliance with Ethics Guidelines

Details of the Contributions of Individual Authors

Sepideh Nazi: Conducting, data gathering, and reporting the work

Firoozeh Sajedi: Planning and reporting the work

Akbar Biglarian: Planning and data analyzing

Farzaneh Rohani: Case providing

Arya Setoodeh: Case providing

Firoozeh Sajedi serves as guarantor for this article, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Conflict of Interest

Sepideh Nazi, Firoozeh Sajedi, Farzaneh Rohani, Akbar Biglarian, and Arya Setoodeh declare that they have no conflict of interest.

Details of Funding

The author(s) confirm(s) independence from the sponsors; the content of the article has not been influenced by the sponsors.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study and is available upon request.

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