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Impact of Selected Physical Therapy Program on Fine and Gross Motor Development on Early and Late Diagnosed PKU Children

Abstract

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) causing progressive motor developmental delay in children.

Objective: To gauge the gross and fine motor development of early and late treated phenylketonuria in children after selected physical therapy program.

Methods: Thirty children with PKU were selected as the case group from 1 to 4 years old for the study. They were assigned into two study groups (early and late treated PKU children) with equal numbers, 15 children in each group. All PKU children received diet and medication in addition to a selected physical therapy program to facilitate fine and growth development. All children selected with the mean of blood phenylalanine level during the recent 6 months were 2–6 mg/dL or 120–360 µmol/L. 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 group (A&B) were 2.26± 0.68 & 2.34±0.71 years respectively. Comparison of the mean fine and gross developmental motor quotients (DMQs) showed statistically significant differences between the two groups. The results of the study groups A and B revealed statistically significant improvement in measuring variables of the both groups when comparing its pre and post study results and when comparing the post study results of both groups there is statistically significant differences in measuring variables ($P<0.05$).

Conclusion: PKU children, regardless of time of diagnosis and treatment have lower motor development but group (B) more affected than group (A). The selected physical therapy program were effective in improving fine and gross motor development in both groups but the results is better in group (A).

Keywords: Phenylketonuria; Motor development; Gross motor; Fine motor development; (PDMS-2)

Research Article

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Introduction

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH) [1-5]. It results in the accumulation of phenylalanine (Phe), an essential amino acid mainly metabolized in the liver by the Phe hydroxylase (PAH) system [1]. This enzyme hydroxylates Phe to tyrosine, requiring tetrahydrobiopterin (BH4) as a co-factor [1]. Defects in either PAH or the production or recycling of BH4 may result in hyperphenilalaninemia which can cause intellectual disability if untreated [1,6,7].

The severity of the clinical phenotype directly correlates with blood phenylalanine levels that reflect the degree of enzymatic deficiency. Neonatal screening by measuring Phe levels in blood spots on filter paper can be identify affected infants at birth. Early treated PKU patients have normal intellectual quotients (I.Q.) [1], but can have an I.Q. gap when compared to their non-PKU siblings [1,7-9]. In addition, patients with PKU frequently have lower scores for certain neuropsychological functions, with executive function being the most affected area [1,8-10]. The prevalence of PKU varies by country ranging from one in 10,000 and one in 20,000 births in U.S.A. [1] and Europe [11]. Depending on the genotype and severity of the enzyme defect, various forms of PKU with different clinical outcomes have been described [1,12]. These can be classified on the basis of blood Phe levels at diagnosis and dietary Phe tolerance [1,7,13]. Until recently, a strict low-Phe diet was the only therapy available [1]. PKU diet consists of a restriction of natural proteins in the diet and supplementation with special medical formulas that supply vitamins, minerals, and all essential amino acids except Phe [1,7,9]. Dietary treatment has been very effective in the prevention of impaired cognitive development, but still has its short comings [1]. Growth delay and specific deficiencies of calcium, zinc, selenium, iron, and vitamin B12 were

reported with the early formulas [1,7,9,14]. When phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone) which cause progressive impairment of cerebral function leading to progressive motor developmental delay [2-4,15]. Untreated PKU typically results in cognitive impairment [3,16]. With dietary treatment, intelligence is usually in the average range, although it remains somewhat lower than that of peers and siblings without PKU [16]. Waisbren et al. [4] 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 [4].

The child with PKU may have motor developmental delay in sitting, crawling, standing, walking, poor postural control, poor transitional movements, poor motor coordination, and other delays and malfunctions [5]. Gross motor delay is the most important symptom of this illness which can be prevented with adequate treatment [15,17]. Some studies have shown that individuals with early treated PKU (ETPKU) experience significant neurocognitive impairment [10]. Motor problems observed in early treated PKU patients include risk reflexes and tremor that may develop in poorly treated as well-treated PKU patients especially after adolescence [8,18].

Early starting a phenylalanine-restricted diet and medical treatment cause the delay in gross motor skills in these children become better, able to enhance with physical therapy program and keep the intelligence usually in the average range, although it remains somewhat lower than that of peers and siblings without PKU [10,19].

Considering the importance of follow-up, and evaluating the consequences of early intervention and role of physical therapy on developmental status of these children, we decided to prospectively investigate the development of fine and gross motor skills in PKU children using the Peabody Developmental Motor Scale-2 (PDMS-2) before and after selected physical therapy program.

Material and Methods

This study was conducted during the period from January 2014 to July 2014, thirty children with classic Phenylketonuria of both sexes were participated in the study. 30 children were selected from the Genetics Clinic- Pediatric Hospital- Faculty of Medicine- Ain Shams University.

Subjects

The inclusion criteria were: 15 children with neonatal diagnosis of PKU, early and continuous treatment with a phenylalanine-restricted diet represent group (A), and 15 children who diagnosed and treated late after one year represent group (B), all of them with the mean of blood phenylalanine during the most recent 6 months, in three assessments was(2–6 mg/dL or 120–360 μmol/L)) according to enzyme-linked immunosorbent assay (ELISA) [8,19-21] and repeated every 2 weeks during the period of study, and 1–4 years of age. The exclusion criteria were any other degenerative, genetic, and metabolic diseases [8]; history of other neuromotor diseases in the family [8]; and neurological, orthopedic, and/or other acquired problems which affect motor development.

Procedures

For evaluation

All children were examined by a pediatrician and if they fulfilled the above criteria were enrolled in the study. Informed consent form was obtained and then the questionnaire, which contains medical history and demographic information of infants, was completed. Finally, two physical therapists blinded to the history of children conducted PDMS-2 for each child before and after 4 month of selected physical therapy program for one and half hour, three times per week.

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 [16]. 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 [16]. It has been used in a number of follow-up studies investigating motor skills in the PKU population [22]. 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 [23,24]. Results from these subtests are used to generate; gross motor quotient & fine motor quotient, which has a mean of 100 and a standard deviation of 15 [25].

For treatment

The therapeutic exercise program for facilitation of gross motor development was including the following:

a) Facilitation of equilibrium reaction from different positions, facilitation of hooping reactions

b) Facilitation of rising reaction from different positions

c) Facilitation of standing

d) Facilitation of walking

The therapeutic exercise to facilitate fine motor development consisted of

Squeezing a ball by one hand, Squeezing 2 balls by 2 hands, Making circular movements by one hand, Making circular movements by both hands together at the same time, moving a cube by each hand foreword and moving 2 cubes by both hands foreword, mold and roll Play-Doh into balls-using the palms of the hands facing each other and with fingers curled slightly towards the palm, roll Play-Doh into tiny balls (peas) using only the fingertips, use pegs or toothpicks to make designs in Play-Doh, cut Play-Doh with a plastic knife or with a pizza or tracing wheel by holding the implement in a diagonal grasp ,tear newspaper into strips and then crumple them into balls, use the balls of paper as stuffing for scarecrows, puppets, or other art projects [10,11,14].

Statistical analysis

The age, weight, and height were expressed as mean ± standard deviation. T test was conducted for comparing the pre and post treatment mean values of all measuring variables between both groups. Paired T test was conducted for comparing pre and post treatment mean values in each group. The level of significance for

all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through SPSS (statistical package for social sciences, version 19).

Results

Subject characteristics

Table 1, showed the mean ± SD age, weight, height, and head circumference of group A and B. There was no significant difference between both groups in the mean age, weight, height, and head circumference ($p > 0.05$).

Comparison between pre and post treatment

The fine and growth DMQ of group A increased post treatment by 5.69 and 5.17 respectively. There was a significant increase in fine and gross DMQ post treatment compared with pre treatment in group A ($p > 0.0001$) (Table 2 & Figure 1).

The fine and gross DMQ of group B increased post treatment by 7.44 and 9.59 respectively. There was a significant increase in fine and gross DMQ post treatment compared with pre treatment in group B ($p > 0.001$) (Table 3 & Figure 1).

Table 1: Comparison of age, weight, height, and head circumference between group A and B.

	Group A	Group B		
	$\bar{X}$ ±SD	$\bar{X}$ ±SD	t- value	p- value
Age (years)	2.26± 0.68	2.34±0.71	-0.31	0.75*
Weight (kg)	13.63 ± 3.11	12.83±2.3	0.79	0.43*
Height (cm)	81.26 ± 8.63	78.26 ±8.7	0.94	0.35*
Head circumference (cm)	46.86 ±2.92	45.66 ±3.26	1.06	0.29*

x̄: Mean; SD: Standard Deviation; p value: Probability Value; * Non significant

Table 2: Comparison between pre and post treatment of fine and gross DMQ in group A & B.

		Pre	Post				
		$\bar{X}$ ±SD	$\bar{X}$ ±SD	MD	% of change	t- value	p- value
Group A	Fine DMQ	84.33± 3.06	89.13± 3.52	-4.8	5.69	-12.61	0.0001**
	Gross DMQ	87.66± 3.57	92.2± 3.46	-4.54	5.17	-10.16	0.0001**
Group B	Fine DMQ	77.86± 2.44	83.66± 2.94	-5.8	7.44	-10.01	0.0001**
	Gross DMQ	79.8± 2.78	87.46± 3.24	-7.66	9.59	-10	0.001**

x̄: Mean; SD: Standard Deviation; p value: Probability Value; **Significant

Table 3: Comparison post treatment of fine and gross DMQ between group A & B.

		Group A	Group B		
		$\bar{X}$ ±SD	$\bar{X}$ ±SD	t- value	p- value
Pre	Fine DMQ	84.33± 3.06	77.86± 2.44	6.39	0.0001**
	Gross DMQ	87.66± 3.57	79.8± 2.78	6.72	0.0001**
Post	Fine DMQ	89.13± 3.52	83.66± 2.94	4.61	0.0001**
	Gross DMQ	92.2± 3.46	87.46± 3.24	3.85	0.001**

x̄: Mean; SD: Standard Deviation; p value: Probability Value; **Significant

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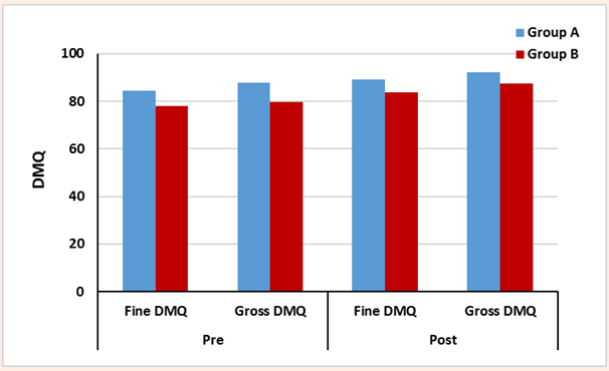

Figure 1: Fine and gross DMQ pre and post treatment of group A and B.

Discussion

This study sets out to characterize the motor quotients and compare the fine and gross motor development of PKU children who diagnosed before and after 1 year 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 [18,26,27], only limited studies address real neurological issues in early and continuously treated PKU patients [28]. 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 [28]. 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 [8,22,29].

One of the most consistent findings reported through studies of neurocognitive abilities of ETPKU individuals is impairment in executive function (EF) [8,10]. 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 [20,29].

Previous studies reported that gross motor problems were rarely observed when PKU was diagnosed and treated early [19]. Nonetheless, impairments in fine motor control have been widely reported [26]. 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 [22]. Gassio et al. [30] reported that individuals with PKU showed significantly poorer fine motor scores than controls on the Purdue test [8]. In both of these studies, there were negative correlations between Phe levels and fine motor scores [22,30]. Brandalize et al. [13] mentioned that fine motor scores have also been associated with the early implementation of dietary Phe restriction in children with PKU [8,13]. Weglage et al. [31] 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 [8,20,31].

In our study, both fine and gross motor development of the PKU children showed significant differences in both groups (early diagnosed and late diagnosed), the mean value of gross and fine DMQs showed that these differences were more prevalent in fine DMQ, with less impact on gross DMQ particularly in the late diagnosed PKU children. 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 & LTPKU were in the range of 77–87 before physical therapy program. This suggests that the motor development of the ETPKU group was below the average . On the other hand, the mean of all DMQs in the both groups were in the range of 83-92 after 4 months of physical therapy program, which means that motor development of this group was improved. Finally, we found that motor improvement was in ETPKU better than in LTPKU children specially gross motor development .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 [32].

In this study the PKU children were selected with ages from one to four years old as motor development impairment is more noted at this age as Cederbaum mention that PKU children appear normal at birth. By the age one year, children are motor developmentally delayed and their skin has less pigmentation than someone without the condition [21,27]. Also Janzen and Nguyen reported that PKU children who are diagnosed and starting diet older than 4 years old had a risk of neurocognitive, emotional, and behavioral dysfunctions and even neurologic complications such as epilepsy, ataxia, tremor, and spasticity may occur more frequently [29].

Pre study mean values of group A&B showed significant difference in gross and fine DMQ, this comes in agreement with Christ et al. who stated that PKU children who followed a program of diet and medical treatment had good improvement of gross motor delay and their intelligence is usually in the average range [10], also Maillot et al. [33] reported that children with untreated classical PKU usually suffer from excessive amino acid phenylalanine in the blood present risks of progressive motor delay according to the time of the diagnosis, the beginning of adequate diet and medical treatment [33].

Phenylalanine levels of all PKU children involved in the study were kept within the accepted range for PKU patients (120-360μmol/l) by measuring it every two weeks with Enzyme-linked immune-sorbent assay (ELISA), this comes in agreement with Gassio et al. [30] who reported that when the levels of phenylalanine increased above the accepted range for PKU children in treated PKU children, motor delay increased, the skin become less pigmented and a smell of musty odor in the urine appeared [30].

The results after four successive months of application selected physical therapy program showed significant improvement in fine and gross motor development in both groups which can be explained by Agarwal et al. who stated that physical therapy program commonly concentrating on improving a child's ability to meet developmental milestones involving sensory, gross and fine motor skills, postural control and flexibility and promote a healthier functioning level [23], goals of physical therapy program in the PKU children was to develop the independence in daily activities and self-care, abilities to play, recreational activities and locomotion with emphasis on the daily functional activities which are priorities of the child with disabilities and his/her family [24,30].

The improvement in gross DMQ in PKU children of both groups could be attributed to facilitate postural reactions from various positions which improve the children's ability to maintain stability of the body when changing position as Shumway-Cook and Wollacott, suggested that balance reactions are necessary precursors to the acquisition of associated development milestones of children with motor delay such as phenylketonuric children [34].

The results of the post study come in agreement with Brandalize and Czeresnia, who reported that the combination of a phenylalanine-restricted diet and medical treatment with physical therapy in PKU children produced improving overall results [13,26]. These findings high light the need for physical therapy program, early diagnosed, starting a phenylalanine-restricted diet and medical treatment for the children with Phenylketonuria to enhance their gross motor development particularly standing and walking milestones as it is considered an interesting and useful approach for the child with PKU.

Previous studies reported that PKU Iranian children who diagnosed and started diet and medication less than 24 months old show improvement more than PKU Iranian children who diagnosed and started diet and medication older than 24 months old in body control, equilibrium and locomotion [35,36]. The combination of a phenylalanine-restricted diet and medical treatment with physical therapy in PKU children give better results than receiving a phenylalanine-restricted diet and medical treatment [13].

In conclusion, the key result of our study suggests that motor developmental delay in PKU children occurs regardless of following a phe-restricted diet and medical treatment or not. Our studies suggested that developmental screening and follow-up be conducted on all PKU infants, early intervention be undertaken in children with developmental delays, and adding physical therapy program to course of management of PKU children.

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