Original Article

Problem-Solving Skills in Children with Early Treated Phenylketonuria

Firoozeh Sajedi, MD.
Pediatric Neurorehabilitation Research Center
University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Sepideh Nazi[1]; Farzaneh Rohani
Iran University of Medical Sciences

Akbar Biglarian, PhD., Guita Movallali, PhD.
University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Objectives: This study aimed to investigate the level of problem-solving skills in 1-4 year-old children with early treated phenylketonuria (ETPKU).

Method: This analytic, cross-sectional study was conducted on 70 1-4 year-old children referred to phenylketonuria (PKU) clinics that had been diagnosed on screening at birth and had been treated. The measurements were a demographic questionnaire, Ages & Stages Questionnaire (ASQ) and clinical assessment by a pediatrician. One hundred children were also selected randomly from Tehran's kindergartens as the control group, who also completed the above questionnaires. Data were analyzed by SPSS 19.0 software.

Results: The mean age of the children was 29.71 months in the control group and 28.51 months in the case group. There were no significant differences between the two groups regarding the type of delivery and the current and birth heights, weights and head circumferences. There was a significant difference between the two groups regarding problem-solving developmental skills (P <0.000). The level of problem-solving developmental skills in the children with ETPKU was lower than normal children.

Conclusion: It seems that Iranian children with ETPKU, regardless of being on a diet, have lower problem-solving skills. It is recommended to revise their diet and treatment and also to plan programs for early detection, and to carry out interventions for developmental delays in these children.

Keywords: Early treated Phenylketonuria (ETPKU), problem-solving skills, children

Submitted: 12 July 2013
Accepted: 11 September 2013

Introduction

Phenylketonuria is the most prevalent metabolic disorder that is inherited as an autosomal recessive condition. The prevalence of this disorder is about 1 /10000 to 1/15000 in newborns across the world (1). The incidence of consanguinity between parents has a major impact on the incidence of PKU in Iran. The incidence of PKU in Iran can be estimated at 1 in 3627. Approximately 50% of these cases can be ascribed to consanguinity (2). In this disorder, the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine is not produced. This results in high blood phenylalanine levels and causes problems in the body's metabolism and also brain damage (1).

Children with PKU are apparently healthy at birth. However, if untreated, they will grow gradually with developmental delays. So at the end of the first year, they have a lower IQ. Half of untreated children have an IQ below 50, and only 1% of them will have normal intelligence without treatment. Other common problems in these children include hyperactivity, autism, seizures and defects in the pigmentation of hair and skin. High phenylalanine blood concentrations also cause delays in cognitive, personal-social and movement development (1). These days, patients are diagnosed by PKU screening in the first few days of birth, and are treated with a phenylalanine limited diet. Thus low levels of phenylalanine and its metabolites in body fluids prevent brain damage (1). The diet of children with early and continuously treated PKU shows that although general intellectual functioning is within

1- All correspondences to Sepideh Nazi, Email: <sepideh.nazi@gmail.com>

normal range, but the level is lower than the general population and their siblings (3, 4). Some studies have shown that despite early treatment, nervous disorders and problems in executive function and performance still persist in PKU patients (5). Despite having average intellectual abilities in ETPKU, academic difficulties are relatively common in children and adolescents with PKU. These academic difficulties may be attention deficit hyperactivity disorder (ADHD), executive functioning deficits, and processing speed deficits, all of which are known to affect academic performance (6). Moreover, a lower than average IQ and nervous problems in ETPKU children and adolescents may lead to lower psychological and academic achievement (7-9).

In our country (Iran, screening was implemented for all newborns 5 years ago and in case of PKU diagnosis, the newborns were placed on an early intervention with a Phe-restricted diet in the reference clinics for PKU follow-up in Tehran. The aim of this study was to determine the level of problem-solving developmental skills in 1-4 year-old children with ETPKU, and if need be, to recommend early intervention and rehabilitation for these children.

Methods

This analytic, cross-sectional study was carried out between August 2011 and July 2012 in the 3 referral PKU clinics in pediatric hospitals; Ali Asghar, Children's Medical Center and Mofid hospitals, in Tehran city. The inclusion criteria were: neonatal diagnosis of PKU, early and continuous treatment with a phenylalanine-restricted diet (The mean blood Phe level during the recent 6 months was 2-6 mg/dl or 120-360 mmol/l), and 1 to 4 years of age. The exclusion criteria were: any other degenerative, genetic, neurologic and metabolic diseases and a history of neuromotor disease in the family. All children were examined by a pediatrician and if they fulfilled the above criteria were enrolled in the study.

From a total of 180 early and continuously treated classic PKU children monitored in the above referral clinics, 70 children aged 1 to 4 years were selected (based on the inclusion and exclusion criteria) as the case group . Also, 100 healthy and normal children matched with the ETPKU group for age were randomly selected from kindergartens in 4 different parts of Tehran as the control group. After, the informed consent form was given to the parents and they were also asked to complete the questionnaire inquiring children's medical history and demographic information.

The main measurements for data collection in this study were the demographic questionnaire, the 'Ages and Stages Questionnaires' (ASQ), and the Pediatrician's clinical assessment. The demographic questionnaire included familial and medical histories, including age, sex, height, weight and head circumference at birth and present, consanguinity of the parents and recorded phenylalanine levels. Next, children's problem-solving developmental skills were assessed using the ASQ, which was completed by the parents. The completed questionnaires were evaluated and scored by the Pediatrician. She compared the scores with the normalized cut-off points of normal Iranian children. The ASQ has been normalized in Iran in 2002-2007 (specificity = 75/0, sensitivity = 86/0, and test-retest reliability=94/0), and the cut-off points have been established for Iranian children (10-12). Then, children with scores matched or below the cut-off points were referred to rehabilitation centers at the University of Social Welfare and Rehabilitation Sciences (USWRS) for specific evaluations and early intervention.

The above assessments were performed for the control group as well, and the results of the two groups were compared. After entering the data into the SPSS software package with the help of descriptive attributes such as mean, standard deviation, and frequency, percentages and inferential tests were used for statistical analysis.

Results

In this study, 70 children with ETPKU (case group) and 100 normal children (control group) participated. The mean ages were 28.51 and 29.71 months in PKU and normal children respectively. Demographic characteristics of these children reported in Table (1).

Table 1. Demographic characteristics of the two groups

Variables		Control		Case	
		Number	%	Number	%
Gender	female	49	49	24	34.3
	male	51	51	45	64.3
Number of children	1	81	81	38	54.3

Variables		Control		Case	
		Number	%	Number	%
in the family	2	18	18	27	38.6
	3	0	0	2	2.9
	4	0	0	2	2.9
	5	0	0	1	1.4
Type of Delivery	cesarean	47	47	42	34.3
	normal	33	33	24	60
The child's birth order	1	88	88	40	57.1
	2	12	12	24	34.3
	3	0	0	3	4.3
	4	0	0	2	2.9
	5	0	0	1	1.4
Consanguinity of parents	yes	10	10	37	52.9
	no	90	90	33	47.1
History of disease in the family	yes	96	96	13	18.6
	no	4	4	56	80
Problems during pregnancy	yes	0	0	9	12.9
	no	92	92	61	87.1

Table (2). Shows growth variables in Phenylketonuria and normal children. There were no significant differences in growth indices at birth and present (Height, weight and head circumference) between the two groups.

Table 2. Descriptive statistics of growth variables in the two groups

Growth Variables	Control		Case		P. Value
	Mean	Std. Deviation	Mean	Std. Deviation	
Head circumference (cm)	48.83	10.23	46.36	2.36	0.049
Height (cm)	93.29	71.54	89.87	9.76	0.692
Weight (kg)	16.68	12.45	14.53	3.64	0.162
Birth head circumference (cm)	35.91	1.13	35.85	1.29	0.733
Birth height (cm)	50.94	2.58	51.69	3.76	0.128
Birth weight (gr)	3165.35	357.85	3173	506.51	0.909

Table (3). shows the mean scores for problem-solving developmental skills compared between the two groups. The mean score of developmental problem solving skills in normal and PKU children were 51.95 and 43.50 respectively, which is higher in normal children. T-test showed that there was a significant difference in the level of problem–solving developmental skills between the two groups ($p<0.000$).

Table 3. Comparison of developmental problem-solving skills between the two groups

Group	Mean	Std. Deviation	df	T. test	P. Value
Control	51.95	5.21	168	6.34	0.000
Case	43.50	11.77			

Discussion

This study showed that the level of developmental problem-solving skills in ETPKU is lower than in normal children. One of the most studied cognitive abilities in PKU is known as executive function (EF). EF is a complex concept. EF have been defined as the higher-order cognitive ability. It facilitates the modification of thoughts and behaviors in response to environment. So, high EF is the ability of deliberate, conscious control over thoughts, actions and emotions (13).

A review article on EF in people with PKU has been published recently . It showed that there are different results from studies on EF in treated PKU by diet. Some studies found EF deficits and some did not in patients; and only some studies not all found a relationship between blood phenylalanine (Phe) levels and EF deficits. The domains of EF that most

commonly involved in diet-treated PKU were working memory and inhibitory control. The study concluded that it was hard to compare different findings of studies because they used different data collecting measures. Another problem was that it was not known how EF scores relate daily functioning (i.e., classroom, home, social and work environments) (14, 15).

Some studies using different tests and parameters have found that treated-PKU patients tend to have slower information processing than control. One meta-analysis study looking at the results from multiple PKU studies, examined many different outcomes including information processing speed. The authors concluded that in different cognitive difficulties found in people with PKU, slow information processing was the most common impairments (4, 16).

Another study tried to determine the relationship between slow information processing speed observed in PKU and the blood phenylalanine (Phe) levels. They carried out their own meta-analysis on studies that reported processing speed and blood Phe levels and age of the PKU- patients. The authors suggested that information processing speed is related to blood Phe levels negatively, and is also depended on age of the PKU- patients. (17) Another study looked at the studies on the academic performance and learning disability in early treated PKU. It showed that there were math difficulties in PKU because math skills require a high degree of abstract reasoning and problem-solving ability. These cognitive abilities affect executive functions (EF), and in some individuals with controlled PKU may be compromised. (6)

Smith et al. showed that children with ETPKU have specific cognitive deficits in executive function skills in school age. These skills were examined in 2 groups (19 children with PKU and 19 age-, sex-, and IQ-matched controls). Five tasks were given to children; three for measuring executive, or frontal-lobe functions (problem-solving, working memory, and verbal fluency) and two as control measures (verbal memory and spatial perception). Children with PKU performed more poorly on two tasks (the problem-solving and verbal memory tasks). The results suggested that cognitive impairments associated with PKU persist into the school-age years. In addition, cognitive performance in children with PKU was corrected to the phenylalanine (phe) levels negatively at the time of testing; the high-phe group performed consistently more poorly than low-phe group on four of the six measures of the problem-solving task and on the verbal memory task (18). Other evidence also suggested that short-term elevations in blood Phe levels caused by diet holidays, in well-controlled PKU patients can result impairment of mental function (as measured by IQ). Therefore, the concept of the lower the Phe levels the better should change to the concept of stable and low blood Phe levels for a lifetime (19).

Conclusion

The result of this study indicates the importance of laying emphasis on early detection and continuous dietary control in ETPKU individuals with a focus on stabilizing the phe level. Also, it is recommended that developmental follow-up be conducted on all ETPKU infants and if needed, early developmental interventions be done. We hope that this study's findings will set off further studies in the field of developmental assessment and early intervention of ETPKU patients in Iran.

Acknowledgements

We would like to thank all the PKU children and their parents who participated in this study, as well as everyone else who helped conduct this study.

References

1. Umphred DA, Roller ML, Burton GU, Lazaro RT. Umphred's Neurological Rehabilitation. 5th ed. Mosby Incorporated; 2007, pp: 1257.
2. Koochmeshgi J, Bagheri A, Hosseini Mazinani SM. Incidence of phenylketonuria in Iran estimated from consanguineous marriages. J Inherit Metab Dis. 2002;25(1):80–1.
3. Gassio R, Artuch R, Vilaseca MA, Fuste E, Boix C, Sans A, et al. Cognitive functions in classic phenylketonuria and mild hyperphenylalaninaemia: experience in a paediatric population. Dev Med Child Neurol. 2005;47(7):443–8.
4. Moyle JJ, Fox AM, Arthur M, Bynevelt M, Burnett JR. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. Neuropsychol Rev. 2007;17(2):91–101.
5. Enns GM, Koch R, Brumm V, Blakely E, Suter R, Jurecki E. Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence. Mol Genet Metab. 2010;101(2-3):99–109.
6. Antshel KM. ADHD, learning, and academic performance in phenylketonuria. Mol Genet Metab. 2010;99(1):S52–58.
7. Araujo GC, Christ SE, Steiner RD, Grange DK, Nardos B, McKinstry RC, et al. Response monitoring in children with phenylketonuria. Neuropsychology. 2009;23(1):130–4.
8. Christ SE, Steiner RD, Grange DK, Abrams RA, White DA. Inhibitory control in children with phenylketonuria. Dev Neuropsychol. 2006;30(3):845–64.
9. Stemerdink BA, Kalverboer AF, van der Meere JJ, van der Molen MW, Huisman J, de Jong LW, et al. Behaviour and school achievement in patients with early and continuously treated phenylketonuria. J Inherit Metab Dis. 2000;23(6):548–62.

10. Sajedi F,Vameghi R, Kraskian Mojembari A, Habibollahi A, Lornejad H, Delavar B. [Standardization and validation of the ASQ developmental disorders screening tool in children of Tehran city (Persian)]. Tehran University Medical Journal. 2012;70(7):436-46.
11. Vameghi R, et al. Early detection diagnosis and an introduction to early intervention in childhood developmental problems(Persian)].University Of Social welfare and Rehabilitation Science.Tehran; 2005.
12. Sajedi F, Vameghi R, Kraskian Mujembari A. Prevalence of undetected developmental delays in Iranian children. Child Care Health Dev. 2013.
13. AboutKidsHealth. Executive Function. Available from: www.aboutkidshealth.ca/ En/News/Series/ Executive Function/ Pages/default.aspx
14. Brumm VL, Grant ML. The role of intelligence in phenylketonuria: a review of research and management. Mol Genet Metab. 2010;99(1):S18–21.
15. Christ SE, Huijbregts SCJ, De Sonneville LMJ, White DA. Executive function in early-treated phenylketonuria: profile and underlying mechanisms. Mol Genet Metab. 2010;99 Suppl 1:S22–32.
16. Janzen D, Nguyen M. Beyond executive function: non-executive cognitive abilities in individuals with PKU. Mol Genet Metab. 2010;99(1):S47–51.
17. Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neurosci Biobehav Rev. 2009;33(3):414–21.
18. Smith ML, Klim P, Hanley WB. Executive function in school-aged children with phenylketonuria. J Dev Phys Disabil. 2000;12(4):317–32.
19. Anastasoaie V, Kurzius L, Forbes P, Waisbren S. Stability of blood phenylalanine levels and IQ in children with phenylketonuria. Mol Genet Metab. 2008;95(1-2):17–20.