Research Paper

Assessing Phenylalanine Blood Level in Children With Phenylketonuria in Southern Khorasan Province and Determining the Affecting Social and Demographic Factors

Tayebeh Chahkandi[1], Bita Bijari[2], Niloofar Hamidi Laeen[3*], Sayeh Shaban[3], Emad Asgari Jafarabadi[4]

1. Department of Pediatrics, Medical Toxicology & Drug Abuse Research Center, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.
2. Department of Community Medicine, Cardiovascular Diseases Research Center, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.
3. School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.
4. Department of Pediatrics, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.

Use your device to scan and read the article online

Citation Chahkandi T, Bijari B, Hamidi Laeen N, Shaban S, Asgari Jafarabadi E. Assessing Phenylalanine Blood Level in Children Having Phenylketonuria in Southern Khorasan Province and Determining the Affecting Social and Demographic Factors. Journal of Pediatrics Review. 2022; 10(4):349-358. http://dx.doi.org/10.32598/jpr.10.4.1005.1

http://dx.doi.org/10.32598/jpr.10.4.1005.1

Article info:
Received: 23 Aug 2021
First Revision: 24 Nov 2021
Accepted: 02 Jan 2022
Published: 01 Oct 2022

Keywords:
Phenylketonuria, Phenylalanine level, Disease control, Demographic factors, Social factors

ABSTRACT

Background: Phenylketonuria is a metabolic disorder resulting from a defect in phenylalanine metabolism with a global prevalence of 1 in 10000. Delayed initiation of dietary modification leads to brain injury and cognitive and behavioral problems. The main objective of this study was to assess the demographic and social factors affecting the metabolic control of patients having phenylketonuria in Southern Khorasan Province, Iran.

Methods: In this cross-sectional descriptive-analytic study which was performed during the summer of 2019, a total of 32 out of 37 known children and adolescents having phenylketonuria in Southern Khorasan Province were assessed. The age and gender of patients, parents' marital status, parents' occupational status, parents' educational level, the distance between home and phenylketonuria clinic, and the number of affected siblings having phenylketonuria were documented. We were not able to contact five patients having phenylketonuria in Southern Khorasan Province. Data were analyzed by SPSS software, version 16 using the Mann-Whitney U test and the Kruskal-Wallis test. The significance level was considered P<0.05.

Results: Totally, 32 patients with a Mean±SD age of 6.6±4.7 years enrolled in this study among whom 23 were male (71.9%) and 9 patients were female (28.1%). The Mean±SD phenylalanine level in this study group was 8.1±5.2 mg/dL. The disease was optimally controlled in 14 patients (43.3%) and poorly controlled in 18 patients (56.3%). There was not any statistically significant relation between the metabolic control of the disease and any of the assessed social and demographic factors.

Conclusion: The disease was properly controlled in 43.3% of the assessed population, and 56.3% had poor metabolic control. There was not any statistically significant relation between the metabolic control of patients having phenylketonuria in Southern Khorasan Province and the assessed demographic and social variables. As the number of known cases in South Khorasan province is limited, the small sample size could be one of the main limitations of our study.

** Corresponding Author:*
Niloofar Hamidi Laeen, PhD.
Address: *School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.*
Tel: *+98 (915) 7099762*
E-mail: *niloofarhamidi4@yahoo.com*

Introduction

Phenylketonuria is an autosomal recessive genetic di sorder. The estimated worldwide incidence is 1 in 10000 [1]. According to the data obtained from neonatal screening between 2000 and 2005 in the Fars province of Iran, an incidence of 1 in 4698 was reported [2]. An incidence of 1 in 6662 live births was also reported in the Chaharmahalobakhtiari province of Iran between 2012 and 2015 [3]. According to another study performed between 2010 and 2011 in Yazd province on 22131 neonates, an incidence of 1.8 in 10000 births was reported [4]. Consanguinity is thought to be the most important factor regarding the higher incidence of this disease in some parts of the world [2]. Phenylketonuria is the most common disorder of amino acid metabolism [5].

Normally ingested phenylalanine is metabolized to tyrosine through the action of phenylalanine hydroxylase and a cofactor called tetrahydrobiopterin. Deficient phenylalanine hydroxylase cannot metabolize phenylalanine to tyrosine, which leads to phenylalanine accumulation in the body [6]. Phenylalanine accumulation mainly damages the brain. Normally, subsequent metabolic processes convert tyrosine into several metabolites including skin and hair pigments, and final metabolites are excreted from the body [7]. Over 950 genes are associated with phenylalanine hydroxylase deficiency [5]. Measuring phenylalanine blood level is a practical and reliable method to diagnose the disease and monitor the treatment course [4]. In classic phenylketonuria phenylalanine blood level is more than 20 mg/dL. Following strict specific diets in which the consumption of natural proteins is restricted and amino acid formulas are consumed instead; phenylalanine intake is limited and brain damage is prevented. A specific diet must be followed throughout life [6]. Every 1.66 mg/dL increase in phenylalanine blood level is associated with 1.3 up to 3.1 points reduction in intelligence quotient (IQ) [4]. Phenylketonuria is the first metabolic and genetic disorder that has been successfully treated [8]. According to the Iranian national phenylketonuria guideline, the accepted phenylalanine level after starting the treatment is 2-6 mg/dL and 2-10 mg/dL for those under and those over 12 years old, respectively.

Normally a limited amount of phenylalanine is metabolized to phenylketones, including phenylpyruvate, phenylacetate, and phenyllactate; in patients having phenylketonuria, high amounts of phenylketones are produced. High phenylpyruvate level interferes with myelin synthesis in the brain, leading to mental retardation. Another proposed cause of mental retardation in these patients is the deficient synthesis of the neurotransmitter dopamine, which is normally synthesized from tyrosine. Normally, the only source of tyrosine production in the human body is the metabolism of phenylalanine through the action of phenylalanine hydroxylase; as a result, tyrosine is an essential amino acid in patients having phenylketonuria which must be obtained through an appropriate diet.

The early weeks of life is a critical period for the developing brain of the infant, and feeding infants having phenylketonuria with breast milk and normal formulas could cause irreversible neurologic damage, and later treatments and therapeutic diets would not be effective.

Later in life, untreated infants present developmental delay, vomiting, growth retardation, seizure, blond hair, and blue eyes. During early childhood, microcephaly, restlessness, attention deficit, repetitive limb movement, and mental retardation are among other manifestations. The presence of an excessive amount of phenylalanine metabolites is the cause of musty urine odor in untreated patients. Urticarial skin rash is one of the other presentations of untreated patients.

The disease could be screened from day two of life onward using a blood or urine sample; a phenylalanine blood level of 4 mg/dL or more is suggestive of phenylketonuria. As a result of early diagnosis and administration of specific formulas to affected infants, affected children could have normal intelligence and brain function. The goal of treatment is to reduce phenylalanine blood level to a safe amount. During infancy and childhood, patients can consume a variety of foods including vegetables, fruits, starch, fat, rice, bread, and a limited amount of grains. Blood phenylalanine levels should be checked regularly. According to blood phenylalanine level, the diet of each patient must be planned by a dietician. The recommended diet must be followed throughout life [7]. Despite early diagnosis and an appropriate therapeutic diet, patients having phenylketonuria may have problems maintaining attention and poor academic performance [9].

Assessing possible factors that might affect patients' adherence to the therapeutic diet could be an important progress in achieving better care for them. According to a systematic review article by Medford et al., age, sex, the family composition including separated parents

or cohabitant parents, parent's educational level, child knowledge about phenylketonuria, parent employment or occupational status, and the number of siblings with phenylketonuria are factors that have a significant positive correlation with phenylalanine blood level [6]. The authors of this review article state that there is a paucity of studies examining the potential demographic or psychosocial influences on metabolic control of patients having phenylketonuria, which could be due to the rarity of this disease and the small sampling pool [6].

In 2011 in a study performed on 105 children with phenylketonuria at Mofid Hospital, Tehran, the following factors were found to be correlated with the metabolic control of these patients. Metabolic control was better in those under 12 years old. The number of siblings having phenylketonuria, divorced parents and occupational status of parents were among other affecting factors. The authors concluded that the social status of patients affects phenylalanine levels to some degree [10].

In a study performed by Mahmoudi-Gharaei et al., 49 caregivers of children having phenylketonuria who were presented to a psychiatry outpatient clinic were assessed [11]. Based on the results of this study, 57.1% and 50.1% of caregivers had depression and anxiety respectively; and employment status played a meaningful role in their mental health. The authors recommended performing similar studies in other parts of Iran [11].

Considering the lack of similar studies in the eastern part of Iran, this study was conducted to assess the effect of several suggested socioeconomic factors that are presumed to be correlated with phenylalanine blood level.

Methods

This is a cross-sectional descriptive-analytic study that was conducted in the summer of 2019 in South Khorasan Province, Iran. A total of 32 out of 37 known children and adolescents having phenylketonuria in Southern Khorasan Province were assessed.

Inclusion criteria

The main inclusion criteria were living in South Khorasan province and being under 18 years of age.

Exclusion criteria

The main exclusion criteria was dissatisfaction of the patient or legal guardian for participation in the research.

Sample size

There were 37 known cases of phenylketonuria under 18 years old at the time of performing this study in South Khorasan province. A total of 32 patients and their families were thoroughly interviewed and assessed; it was not possible to contact five cases, so the sample size was 32.

Method

Age, sex, family composition factors including separated parents or cohabitant parents, occupational status of parents, living in Birjand city where the phenylketonuria clinic is located or living out of Birjand city, and the number of siblings having phenylketonuria were the socioeconomic factors that were assessed among children and adolescents having phenylketonuria in South Khorasan province, and the relation of these factors with metabolic control of the disease was assessed. It must be noted that Birjand is the capital city of South Khorasan Province.

Data was gathered during regular and periodic visits of patients at the main phenylketonuria clinic of South Khorasan Province, in Valieasr Hospital. To assess the metabolic control of patients, the mean blood phenylalanine of patients was also recorded. According to the Iranian National Phenylketonuria guideline, the acceptable blood phenylalanine level of patients aged below 12 years old, and those above 12 years old are 2-6 mg/dL and 2-10 mg/dL respectively; a mean blood phenylalanine blood level above the mentioned values is indicative of poor metabolic control. Blood phenylalanine level was measured using serum HPLC phenylalanine level in selected reference laboratories in South Khorasan Province.

Data analysis

Data were analyzed using the SPSS software, version 22, using the Kolmogorov-Smirnov test to show the normal distribution of data. As blood phenylalanine level was not normally distributed (P=0.007), the Mann-Whitney U test and the Kruskal Wallis test were used to compare the mean phenylalanine blood level of patients based on their demographic and socioeconomic conditions. A $P<0.05$ was considered statically significant.

Results

Totally, 32 patients with Mean±SD age of 6.6±4.7 years old were enrolled in this study; the lowest recorded age was one year old and the highest was 18 years old. In general, 71.9% of patients were male and 28.1% were

Table 1. Demographic characteristics of patients and families, their number and relative frequencies

Variables		No. (%)
Sex	Male	23(71.9)
	Female	9(28.1)
Age (y)	<6	18(56.3)
	>6	14(43.8)
Parents' educational status	Illiterate	3(9.4)
	High school (undergraduate)	12(37.5)
	Diploma education	11(34.4)
	University education	6(18.8)
Family composition	Cohabitant parents	30(93.8)
	Separated parents	2(6.3)
Father's occupational status	Employed	28(87.5)
	Unemployed	4(12.5)
Place of residence	Inside Birjand city	18(56.3)
	Outside Birjand city	14(43.8)
The number of affected siblings having PKU	1	25(71.8)
	2	7(21.9)

PKU: Phenylketonuria. Journal of Pediatrics Review

The mean blood phenylalanine level was 8.1±5.2 mg/dL. The min and max blood phenylalanine levels were 0.4 mg/dL and 21.4 mg/dL respectively.

female. The demographic characteristics of patients and their families are presented in Table 1.

According to the data presented in Table 2, none of the assessed demographic and social factors were statistically related to blood phenylalanine level. The national phenylketonuria screening program in Iran has been started since late 2012; and our study was performed in 2019. In our study, children who have been screened by the national phenylketonuria screening program were 6 years old or younger; and children older than 6 years old have not been screened. This is why the cut-off of 6 years old has been implemented in the data analysis. Although there are differences between the blood phenylalanine level of patients with different demographic and social characteristics, the differences are not statistically significant. The metabolic control of 14 patients (43.3%) was acceptable, and 18 patients (56.3%) had poorly controlled blood phenylalanine levels.

Table 3 presents the comparison of the metabolic control of patients based on their social and demographic characteristics.

Good metabolic control had no statistically significant relationship with any of the social and demographic characteristics assessed in this study. Metabolic control was not statistically different in those who were screened (aged below 6 years) and those who were not screened (aged above 6 years).

According to the data presented in Table 4, the assessed social and demographic factors were not statistically different between children who have been screened (aged below 6 years) and those who were not screened (aged above 6 years old).

Discussion

To find the cause of better metabolic control in older individuals in our study, the history of the national phenylketonuria screening program in Iran must be

Table 2. Comparison of blood phenylalanine level based on social and demographic characteristics of patient

Demography		Mean±SD	Median (25th and 75th Quartile)	Statistic	P
Gender	Female	8.78±5.38	7.4 (4.6-12.8)	1.17	0.24
	Male	6.34±4.68	6.5 (2-10.1)		
Age (y)	<6	7.12±3.77	6 (4.3-8.3)	0.76	0.44
	>6	9.35±6.58	7.7 (3.2-14.8)		
Parents' educational status	Illiterate	12±4.08	14 (73-14)	2.4	0.48
	High school (undergraduate)	6.30±3.46	6.6 (3.5-8.1)		
	Diploma education	9.43±6.91	6.5 (3.4-17.4)		
	University education	7.31±4.31	6.4 (4.1-9.4)		
Family composition	Cohabitant parents	8.19±5.37	7.3 (4.1-12.4)	0.0.3	0.96
	Separated parents	6.66±1.89	6.6 (5.3-6.6)		
Father's occupational status	Employed	8.42±5.38	6.9 (4.2-12.6)	0.54	0.60
	Unemployed	5.85±3.64	7.5 (2.1-7.9)		
Place of residence	Inside Birjand City	9.11±5.51	7.7 (5.4-12.4)	1.5	0.12
	Outside of Birjand City	6.80±4.68	4.9 (3.2-9.5)		
The number of affected siblings having PKU	1	7.38±4.52	7.3 (4.2-8.7)		
	2	10.67±7.00	14 (3-17.4)		

PKU: Phenylketonuria.

Journal of Pediatrics Review

considered. The national phenylketonuria screening program in Iran has been started since late 2012, and our study was performed in 2019. In our study, children who have been screened by the national phenylketonuria screening program were 6 years old or younger, and children older than 6 years old had not been screened. Delayed diagnosis of phenylketonuria in those over 6 years old is usually associated with negative effects on the cognitive and intellectual abilities of these children, which could account for the lack of good metabolic control among older individuals.

According to the study performed by Hartnett et al. there was not any statistically meaningful relationship between patient age and blood phenylalanine level, which is similar to the result of our study [12]. On the other hand, based on a study performed by Cotugno et al. patient age and the metabolic control of the disease are statistically related, and those over 10 years old have better metabolic control [13]. As a rule, older patients with normal cognitive function are better oriented regarding the importance of an appropriate diet and potential complications of poor metabolic control.

In a study performed by Cotugno et al. and Freehauf et al. [13, 14] there was no statistically meaningful relationship between gender and metabolic control of the disease, which is similar to the result of our study. On the other hand, MacDonald et al. stated that gender and phenylalanine blood level are statistically related [15]; their study was performed on a small sample size of patients aged between 6-17 years old. Although few studies with small sample sizes have reported a significant relationship between gender and metabolic control of the disease, systematic review articles do not approve of any relationship between these two factors. Our results are similar to the results of the vast majority of reliable research performed in this field. The lack of difference between the level of metabolic control between male and female patients could be the result of gender equality in Iranian families.

Table 3. Comparison of the metabolic control of patients based on their social and demographic characteristics

Demographic Factors		No. (%)		Statistic	P
		Good Metabolic	Poor Metabolic		
Sex	Male	10(43.5)	13(54.6)	χ^2=0.002 df=1	0.63
	Female	5(55.6)	4(44.4)		
Age	<6	9(50)	9(50)	χ^2=0.65 df=1	0.32
	>6	5(35.7)	9(64.3)		
Place of residence	Inside Birjand city	6(33.3)	12(66.7)	χ^2=0.18 df=1	0.16
	Outside of Birjand city	8(57.1)	6(42.9)		
Parents' educational status	Illiterate	0(0)	3(100)	Fisher exact test=2.4	0.56
	Highschool (undergraduate)	6(50)	6(50)		
	Diploma education	5(45.5)	6(54.5)		
	University education	3(50)	3(50)		
Family composition	Cohabitant parents	13(43.7)	17(56.7)	Fisher exact test	1
	Separated parents	1(50)	1(50)		
Father's occupational status	Employed	13(46.4)	15(53.6)	Fisher exact test	0.61
	Unemployed	1(25)	3(75)		
The number of affected siblings having PKU	1	11(44)	14(56)	Fisher exact test	1
	2	3(42.9)	4(57.1)		

PKU: Phenylketonuria.

Journal of Pediatrics Review

In two studies performed by Reber et al. and Fehrenbach et al. there was no relationship between parents' marital status and metabolic control of patients; regarding marital status, the results of our study were the same [16, 17]. On the other hand, according to studies performed by Alaei et al. [18] and Olsson et al. [19] children with separated or divorced parents were more likely to have higher phenylalanine levels than children with married or cohabitant parents [20, 21]. The lack of difference between family composition and disease control could be due to the low rate of divorce in our community compared to western societies in which divorce is more prevalent [22, 23].

According to recent studies performed by MacDonald et al. [24], Alaei et al. [18], and Olsson et al. [19] there was no statistically significant relationship between parents' educational status and the metabolic control of the disease [21, 22]. These findings are similar to our study results. Meanwhile, Shulman et al. identified that children's phenylalanine level was correlated with maternal and paternal education, with higher education associated with lower blood phenylalanine [25]. The lack of difference between disease control in educated families and families with lower education levels could be the result of equal healthcare delivery in our society; in other words, lower socioeconomic classes of our society receive enough healthcare support which results in the same disease control level compared to higher socioeconomic groups.

In studies performed by Griffiths et al. [26] and Alaei et al. [18], family income and metabolic control of the disease were statistically related. On the other hand, MacDonald et al. reported no relationship between family income and metabolic control of the disease, which was similar to the results of our study [24]. The lack of relationship between these two factors could be an indicator of improvement in the healthcare system and better insurance coverage and equality in our society [27].

Table 4. Comparison of the assessed social and demographic factors between patients aged below 6 years and those aged above 6 years

Age Group		No. (%)		Statistic	P
		Under 6 Years Old	Above 6 Years Old		
Place of residence	Inside Birjand city	8(44.4)	10(71.4)	χ^2=2.33 df=1	0.16
	Outside of Birjand city	10(55.6)	4(28.6)		
Parents` educational status	Illiterate	2(11.1)	1(7.1)	Fisher exact test=2.4	0.95
	Highschool (undergraduate)	6(33.3)	6(42.9)		
	Diploma education	6(33.3)	5(35.7)		
	University education	4(22.2)	2(14.3)		
Family composition	Cohabitant parents	17(94.4)	13(92.9)	Fisher exact test	0.69
	Separated parents	1(5.6)	1(7.1)		
Father`s occupational status	Employed	15(83.3)	13(92.9)	Fisher exact test	0.40
	Unemployed	3(16.7)	1(7.1)		
The number of affected siblings having PKU	1	16(88.9)	9(64.3)	Fisher exact test	0.19
	2	2(11.1)	5(35.7)		

PKU: Phenylketonuria.

Journal of Pediatrics Review

Based on the results of our study, the metabolic control of patients living in Birjand, the capital city of South Khorasan Province, is the same as those living outside of Birjand; the lack of difference between the two groups of patients could be due to expansion of healthcare centers across the province. Pediatricians are providing care for PKU patients across the province according to national guidelines, and dieticians are also present in all major healthcare centers. The collaborative working of specialists and dietitians across the province has resulted in a similar quality of healthcare in Birjabd and those living out of Birjand.

According to the study performed by Alaei et al., the metabolic control of the disease was negatively affected by the number of affected siblings having PKU [18]; on the other hand, based on the results of our study these two factors are not statistically related [18]. Having more than one affected child could be both a financial and psychiatric burden, but, as mentioned above, improved healthcare systems and insurance have probably reduced the effects of these factors.

The assessed social and demographic factors were not statistically different between children who have been screened (aged below 6 years) and those who were not screened (aged above 6 years old), indicating that screening has not had any confounding effect in our study.

Limitations

As the number of known cases in South Khorasan Province is limited, the small sample size could be one of the main limitations of our study. We also believe that there could be other possible socioeconomic and psychiatric factors that might affect blood phenylalanine levels in patients having phenylketonuria.

Conclusion

Demographic and social factors including age, gender, parents' marital status, parents' occupational status, the distance between home and phenylketonuria clinic (living in Birjand city or living outside Birjand city), and the number of affected siblings having phenylketonuria were not statistically related to metabolic control of disease in patients with phenylketonuria in South Khorasan Province.

Ethical Considerations

Compliance with ethical guidelines

This study has been performed following the Declaration of Helsinki. This study has been granted an exemption from requiring ethics approval by the Biomedical Research Ethics Committee of Birjand University of Medical Sciences. Further information and

documentation to support this could be available on request. Parents' or legal guardians' informed consent was obtained before participation in the study. The aim of the present study was also explained to the patient's parents or legal guardians.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no competing interests.

References

1. Scriver CR. The metabolic & molecular bases of inherited disease. New York: McGraw-Hill; 2001. [Link]

2. Senemar SA, Ganjekarimi H, Fathzadeh M, Tarami B, Bazrgar M. Epidemiological and clinical study of Phenylketonuria (PKU) disease in the National Screening Program of Neonates, Fars province, Southern Iran. Iran J Public Health. 2009; 38(2):58-64. [Link]

3. Ganji F, Naseri H, Rostampour N, Sedighi M, Lotfizadeh M. Assessing the phenylketonuria screening program in newborns, Iran 2015-2016. Acta Med Iran. 2018; 56(1):49-55. [Link]

4. Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: A systematic literature review and meta-analysis. Mol Genet Metab. 2007; 92(1-2):63-70. [DOI:10.1016/j.ymgme.2007.05.006] [PMID]

5. Blau N. Genetics of phenylketonuria: Then and now. Hum Mutat. 2016; 37(6):508-15. [DOI:10.1002/humu.22980] [PMID]

6. Medford E, Hare DJ, Wittkowski A. Demographic and psychosocial influences on treatment adherence for children and adolescents with PKU: A systematic review. JIMD Reports. 2017:107-16. [DOI:10.1007/8904_2017_52] [PMID] [PMCID]

7. Rocha JC, Martins MJ. Oxidative stress in phenylketonuria: Future directions. J Inherit Metab Dis. 2012; 35(3):381-98. [DOI:10.1007/s10545-011-9417-2] [PMID]

8. Koch R, Burton B, Hoganson G, Peterson R, Rhead W, Rouse B, et al. Phenylketonuria in adulthood: A collaborative study. J Inherit Metab Dis. 2002; 25(5):333-46. [DOI:10.1023/A:1020158631102] [PMID]

9. Van Spronsen FJ. Phenylketonuria: A 21st century perspective. Nat Rev Endocrinol. 2010; 6(9):509-14. [DOI:10.1038/nrendo.2010.125] [PMID]

10. Brumm VL, Bilder D, Waisbren SE. Psychiatric symptoms and disorders in phenylketonuria. Mol Genet Metab. 2010; 99:S59-63. [DOI:10.1016/j.ymgme.2009.10.182] [PMID]

11. Mahmoudi-Gharaei J, Mostafavi S, Alirezaei N. Quality of life and the associated psychological factors in caregivers of children with PKU. Iran J Psychiatry. 2011; 6(2):66-9. [Link]

12. Hartnett C, Salvarinova-Zivkovic R, Yap-Todos E, Cheng B, Giezen A, Horvath G, et al. Long-term outcomes of blood phenylalanine concentrations in children with classical phenylketonuria. Mol Genet Metab. 2013; 108(4):255-8. [DOI:10.1016/j.ymgme.2013.01.007] [PMID]

13. Cotugno G, Nicolo R, Cappelletti S, Goffredo BM, Dionisi Vici C, Di Ciommo V. Adherence to diet and quality of life in patients with phenylketonuria. Acta Paediatr. 2011; 100(8):1144-9. [DOI:10.1111/j.1651-2227.2011.02227.x] [PMID]

14. Freehauf C, Van Hove JL, Gao D, Bernstein L, Thomas JA. Impact of geographic access to care on compliance and metabolic control in phenylketonuria. Mol Genet Metab. 2013; 108(1):13-7. [DOI:10.1016/j.ymgme.2012.09.026] [PMID]

15. MacDonald A, Nanuwa K, Parkes L, Nathan M, Chauhan D. Retrospective, observational data collection of the treatment of phenylketonuria in the UK, and associated clinical and health outcomes. Curr Med Res Opin. 2011; 27(6):1211-22. [DOI:10.1185/03007995.2011.576237] [PMID]

16. Reber M, Kazak AE, Himmelberg P. Phenylalanine control and family functioning in early-treated phenylketonuria. J Dev Behav Pediatr. 1987; 8(6):311-7. [DOI:10.1097/00004703-198712000-00002]

17. Fehrenbach AM, Peterson L. Parental problem-solving skills, stress, and dietary compliance in phenylketonuria. J Consult Clin Psychol. 1989; 57(2):237. [DOI:10.1037/0022-006X.57.2.237] [PMID]

18. Alaei M, Asadzadeh-Totonchi G, Gachkar L, Farivar S. Family social status and dietary adherence of patients with phenylketonuria. Iran J Pediatr. 2011; 21(3):379. [PMCID] [PMID]

19. Olsson GM, Montgomery SM, Alm J. Family conditions and dietary control in phenylketonuria. J Inherit Metab Dis. 2007; 30(5):708-15. [DOI:10.1007/s10545-007-0493-2] [PMID]

20. Vallian S, Barahimi E, Moeini H. Phenylketonuria in Iranian population: A study in institutions for mentally retarded in Isfahan. Mutat Res-Fund Mol M. 2003; 526(1-2):45-52. [DOI:10.1016/S0027-5107(03)00015-0]

21. Anjema K, van Rijn M, Verkerk PH, Burgerhof JG, Heiner-Fokkema MR, van Spronsen FJ. PKU: High plasma phenylalanine concentrations are associated with increased prevalence of mood swings. Mol Genet Metab. 2011; 104(3):231-4. [DOI:10.1016/j.ymgme.2011.05.017] [PMID]

22. Viau KS, Wengreen HJ, Ernst SL, Cantor NL, Furtado LV, Longo N. Correlation of age-specific phenylalanine levels with intellectual outcome in patients with phenylketonuria. J Inherit Metab Dis. 2011; 34(4):963-71. [DOI:10.1007/s10545-011-9329-1] [PMID]

23. Habib A, Fallahzadeh MH, Kazeroni HR, Ganjkarimi AH. Incidence of phenylketonuria in Southern Iran. Iran J Med Sci. 2010; 35(2):137-9. [DOI:10.30476/IJMS.2010.39771]

24. MacDonald A, Davies P, Daly A, Hopkins V, Hall SK, Asplin D, et al. Does maternal knowledge and parent education affect blood phenylalanine control in phenylketonuria? J Hum Nutr Diet. 2008; 21(4):351-8. [DOI:10.1111/j.1365-277X.2008.00891.x] [PMID]

25. Shulman S, Fisch RO, Zempel CE, Gadish OR, Chang PN. Children with phenylketonuria: The interface of family and child functioning. J Dev Behav Pediatr. 1991; 12(5):315-21. [DOI:10.1097/00004703-199110000-00006]

26. Griffiths PV, Demellweek C, Fay N, Robinson PH, Davidson DC. Wechsler subscale IQ and subtest profile in early treated phenylketonuria. Arch Dis Child. 2000; 82(3):209-15. [DOI:10.1136/adc.82.3.209] [PMID] [PMCID]

27. Nelson DL, Cox M. Lehninger principles of biochemistry: International edition. Macmillan Learning; 2017. [Link]

This Page Intentionally Left Blank