Original Article

Total Head Growth in Patients with Phenylketonuria Diagnosed by Newborn Screening Test

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Abstract

Background: Phenylketonuria is an inborn error of phenylalanine metabolism caused by phenylalanine hydroxylase enzyme deficiency. It is a relatively common disorder that is inherited as an autosomal recessive disease. Phenylketonuria can be diagnosed by newborn screening tests. The diagnosis is established when a plasma phenylalanine concentration persistently above 120 µmol/ phenylketonuria can cause microcephaly, intellectual disability, attention deficit hyperactive disorder, epilepsy, and eczema due to the accumulated toxic effect of phenylalanine in the blood. **Objective:** The aim of this study was to determine whether phenylalanine control can improve head growth in early-diagnosed and treated children. **Materials and Methods:** The head circumference records of 28 early detected patients with phenylketonuria at diagnosis and at 3-month intervals till the age of 3 years were studied. These measurements were compared between two groups those with phenylalanine median readings below 360 µmol/L but never above 600 µmol/L as the accepted control group and those with readings higher than 600 µmol/L as the poor control group. **Results:** The total number of children included in this study was 28 children. The patient's age ranges from 3 years to 8 years. Males represented 57.14% of them. The median age at diagnosis and starting treatment was 18.5 days and 58 days, respectively. In this study, higher occipitofrontal circumference *z*-score readings were noticed among children with relatively lower phenylalanine levels at diagnosis (38.89% of them had *z*-score greater than zero) compared to those with higher Phenylalanine level (only 20% of them had *z*-score greater than zero) with a statistically significant difference. The same finding was observed at 3 years of age (head circumference *z*-score more than zero in 27.28% of accepted phenylalanine level control vs. 10% of poor phenylalanine level; however, the difference exceeded the acceptable level of significance ($P = 0.057$)). **Conclusion:** In patients with phenylketonuria diagnosed by newborn screening test, the higher the phenylalanine level at diagnosis, the smaller the head size compared with those with lower phenylalanine levels. At 3 years of age, the head growth of those with stricter phenylalanine control does not vary greatly from those with less strict control.

Keywords: Head circumference, head growth, microcephaly, phenylalanine hydroxylase, phenylketonuria

Introduction

Phenylketonuria, often referred to as (PKU), is an inborn error of phenylalanine (Phe) metabolism caused by a lack of the phenylalanine hydroxylase (PAH) enzyme, which is responsible for converting phenylalanine to L-Tyrosine. Its deficiency causes toxic byproducts to build up in the blood and brain, causing irreversible neurological damage.[1] Phenylketonuria is a relatively common disease that is inherited in an autosomal recessive manner through the hPAH gene on chromosome 12q22-12q24. The majority of patients are compound heterozygotes. The incidence of PKU varies by ethnicity; in the United States, one out of 13,500-19,000 neonates have PKU, whereas Japan has the lowest incidence (one in every 108,823 people). PKU is most common among the Turkish population (1 in 2,600 newborns).[2,3] There is no single study revising the incidence of PKU in Iraqi children; however, in 2015 a study in Sulaimani City revealed that the annual incidence of PKU was 12.11 per 100,000 neonates,[4]

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another study in Baghdad/Al-karkh Health Directorate in 2014, found that 7.46 per 100,000 neonates was diagnosed with PKU.[5]

Intellectual disability, mental retardation, delayed speech, behavioral disorders, attention deficit hyperactive disorder (ADHD)-inattentive type, microcephaly, epilepsy, spasticity, and fair texture are some of the numerous PKU symptoms. Notably, brain imaging of patients with PKU reveals posterior periventricular white matter changes extend anteriorly in severe cases.[6-9]

PKU is typically diagnosed soon after birth using a blood spot obtained from a heel prick (Guthrie test, enzymatic techniques, tandem mass spectrometry (MS/MS) or high-performance liquid chromatography [HPLC]). When the plasma Phe concentration is consistently above 120 µmol/L, PKU is confirmed, while some laboratories additionally use a phenylalanine/tyrosine (Phe/Tyr) ratio > three[3] for diagnosis. Genetic screening for pathogenic mutations in PAH is also useful.[10] Phenylketonuria is classified into three groups based on Phe levels in the blood as follows: classic PKU (Phe > 1200 µmol/L), moderate PKU (Phe = 600–1200 µmol/L), and mild hyperphenylalanimea, in which blood Phe concentration is raised but less than 600 µmol/L.[11] Another manner of classification consists of classical PKU >1200 µmol/L, moderate PKU (900-1200 µmol/L), mild PKU (600-900 µmol/L), and mild hyperphenylalanimea (360–600 µmol/L).[12,13]

Treatment aims to achieve normal cognitive and neuropsychological development by keeping Phe concentrations within a given target range for a selected age.[14] For children less than twelve years of age, a Phe level of 360µmol/l should be considered the highest level.[1] This balance is usually achieved through a phe-restricted diet. The levels of targets varied among countries and even between medical centers within the same country. However, most centers begin therapy at one of the three phenylalanine level thresholds: higher than 360 µmol/L), higher than 400 µmol/L) or greater than 600 µmol/L).[15] Notably complying with the recommended diet (avoiding eggs, meat, fish, nuts, and dairy, besides certain fruits and vegetables) can be challenging due to limited food choices and strong and unpleasant taste and odor of the available synthetic Phe-free medical foods and supplemental formula providing tyrosine and other nutrients, in addition to economic burden on families leading to non-compliance.[16,17]

Aim of study

The aim of this study was to determine whether there is a relationship between phenylalanine levels and head circumference, and if phenylketonuria control can improve head growth in these children diagnosed by newborn screening test.

Materials and Methods

A retrospective study was conducted from June 2022 to June 2023, using the medical records of children diagnosed with phenylketonuria by newborn screening test exclusively in the metabolic clinic of Central Child Teaching Hospital, Baghdad, Iraq. The data were documented at scheduled monthly check-up visits as part of the follow-up protocol used in the clinic. The duration of 3 years was selected specifically because the first three years of life are crucial for brain growth and development as mentioned in previous published studies.[18]

Exclusion criteria:

(1) Infants whose Phe levels were between 120 µmol/L and 360 µmol/L with continuous neurological deterioration despite a low-Phe diet due to suspicion of Biopterin metabolism disorders. (2) Those whose follow-up duration was less than 3 years.

Detailed information including date of birth, age of diagnosis, initial Phe concentrations, Phenylalanine/tyrosine ratio, age of starting treatment, family history and consanguinity, compliance to diet, serum Phe readings monthly, head circumference measurement at diagnosis and each visit till the age of 3 years; the phase during which rapid growth of both brain and body occur.[19] The data at diagnosis and at 3-month intervals were considered in the study.

Head circumference measurement was taken by pediatrician seniors exclusively, the tape was wrapped above the eyebrows anteriorly and over the most prominent part of the occiput posteriorly, and the highest of three readings was taken.[20] The OFC number is plotted on the Centers for Disease Control and Prevention (CDC) growth charts (for either girls or boys) to obtain a percentile ranking and *z*-score calculated by anthropometric PediTools electronic calculator depending on CDC charts.[21,22] The studied population was divided into two groups, those with Phe readings mean were less than 360 µmol/L) but their reading never exceeds 600 µmol/L (labeled as an accepted control group) due to the difficulty of keeping Phe reading below 360 µmol/L all the times during the 3-year follow-up duration and those with readings higher than 600 µmol/L labeled as the poor control group).

Statistical analysis

All statistical analyses were performed using SPSS software version 25.0 (SPSS, Chicago, Illinois). Continuous data were subjected to a normality test (Shapiro–Wilk test) and were found to be non-normally distributed; accordingly, they were presented as median and range, and analyzed with a non-parametric Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages and analyzed with a chi-square test. Pearson's and Spearman's correlation were used as

required to explore the possible correlation of differences in OFC and *z*-score with demographic characteristics. A value of $P < 0.05$ was considered to indicate a statistically significant difference.

Ethical approval:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol, the subject information, and the consent form were reviewed and approved by a local ethics committee according to the document number (4/2022 in 17/04/2022).

Questionnaire

Name:			
Gender:			
Date of birth:			
Date of diagnosis			
Age at diagnosis			
Age of starting treatment:			
Duration of treatment:			
Compliance with treatment; Any gap in treatment and duration of this gap			
Level of Phe on diagnosis			
Phe/TYR RATIO at diagnosis			
Regular visit			
Consanguinity			
AGE	**Phe LEVEL**	**OFC**	**Z- SCORE**
At diagnosis			
3 month			
6 month			
9 month			
12 month			
15 month			
18 month			
21 month			
24 month			
27 month			
30 month			
33 month			
36 month			

Results

Demographic characteristics of PKU patients

Total number of children included in this study was 28 children. The patient's age ranges from 3 years to 8 years. Males represented 57.14% of them. The median age at diagnosis and starting treatment was 18.5 days and 58 days, respectively. Consanguineous marriage was reported in 82.14% of the parents. More than two-thirds of the children (71.43%) had regular clinic visits (monthly). The median Phe concentration was 1044µmol/L, while the median Phe/Tyr ratio was 18.95 as shown in Table 1.

Table 1: Demographic characteristics of the neonates (n = 28)

Variables	Values
Gender	
Male	16(57.14%)
Female	12(42.86%)
Age at diagnosis, days	
Mean ± SD	34.96 ± 24.39
Median	18.5
Range	14-130
Age at treatment, days	
Mean ± SD	64.96 ± 44.38
Median	58
Range	20-195
Consanguinity	
No	5(17.86%)
Yes	23(82.14%)
Clinic visit/3 years	
Regular	20(71.43%)
Irregular	8(28.57%)
Phenylalanine, µmol/L	
Mean ± SD	1069.8 ± 756.6
Median	1044
Range	204-2556
Phenylalanine/tyrosine ratio	
Mean ± SD	19.13 ± 13.24
Median	18.95
Range	1.2-37.8

Association of demographic characteristics with Phe level control

Out of 28 included patients, 18 patients (64.29%) had accepted Phe level control, while 10 patients (35.71%) had poor controls. The median age at diagnosis among patients in the accepted control group was 23.5 days which was significantly lower than that of children with poor control group (33 days). The vast majority (88.89%) of the accepted control group had regular clinic visits compared with 60% of those with poor controls who had such visits, with a significant difference. The median concentration of Phe and Phe/Tyr ratio in patients with accepted control was 471 µmol/L and 8.9, respectively compared with 1635 µmol/L and 31, respectively in children with poor control group with significant differences [Table 2].

Association of *z*-score of head circumference with Phe control

Z-score was categorized into 4 categories (<–2, –2 to –1, –1 to zero and more than zero) at diagnosis and at 3 years old.

Larger head circumferences (*z*-score greater than zero) was more common among children with relatively lower Phe levels at diagnosis (38.89% of children with accepted control

level had *z*-score more than zero) than those with higher Phe levels (only 20% of them had head *z*-score greater than zero) with a significant difference. The same finding was also observed at 3 years of age (27.28% of accepted Phe level control had a head *z*-score more than zero vs. 10% of poor Phe level control; however, the difference exceeded the acceptable level of significance [Table 3].

Association of differences in OFC and *z*-score with gender, consanguinity and regular visits

Children with regular clinic visits had a higher median OFC *z*-score of a difference than those with irregular visits (0.4 vs. 0.11) with a significant difference. Although females showed a higher median OFC *z*-score difference than males (0.37 vs. 0.11), the difference was not significant [Table 4].

Table 2: Association of demographic characteristics with Phe control

Variables	Accepted Phe controls (n = 18)	Poor Phe controls (n = 10)	*P*-value
Gender			0.434
Male	9(50%)	7(70%)	
Female	9(50%)	3(30%)	
Age at diagnosis, days			0.04
Median	23.5	33	
Range	14-60	20-130	
Age at treatment, days			0.869
Median	63.5	46.5	
Range	25-195	20-165	
Consanguinity			0.315
No	2(11.11%)	3(30%)	
Yes	16(88.89%)	7(70%)	
Clinic visit			0.011
Regular	16(88.89%)	6(60%)	
Irregular	2(11.11%)	4(40%)	
Phenylalanine, µmol/L			0.002
Median	471	1635	
Range	204-2238	510-2556	
Phenylalanine/ tyrosine ratio			0.013
Median	8.9	31	
Range	1.2-37.5	15-37.8	

Discussion

To the best of our knowledge, there are no previous studies comparing occipitofrontal circumference and head growth with the Phe levels. On the other hand, there are many studies comparing growth parameters between PKU patients and normal children.

In this study, larger head circumference z-scores were more common among children with relatively lower Phe levels at diagnosis than those with higher Phe levels (of whom 50% had their OFC *z*-score below 2 standard deviations from normal). This this also observed at 3 years although statistically not significant.

In Iran, Shakiba *et al.*[23] study found that the OFC in children with PKU tended to be smaller compared to the normal population, particularly in their first three years of life. However, the largest difference at any age was less than 0.5 cm. This disparity was even more noteworthy in patients over two years old, there was a negative correlation found between OFC and plasma Phe levels (r = –0.445, P = 0.01) before treatment. These findings agreed with the current study the higher Phe levels the smaller the head circumferences.

In the Netherlands, van der Schot *et al.*'s[24] study found that mean OFC z-scores were statistically normal at the first month and 2 years of age. However, head circumference at I month tended to stay below the averages. At 1 year of age mean z-scores for head circumference were significantly below the norm. There was no significant correlation between the phenylalanine parameters on one hand, and the growth parameters on the other, at any of the three time intervals.

In the USA, Mcburnie *et al.*'s[25] study did not find any relationship between the serum phenylalanine level and either height or head circumference. The differences between children with PKU and unaffected children were mainly seen in weight, with higher serum phenylalanine levels associated with higher weight levels, especially in girls. So, the serum phenylalanine level appeared to be

Table 3: Association of *z*-score of head circumference with Phe Control

Z-score	At diagnosis		At 3 years	
	Poor Phe level control (n = 10)	Accepted Phe level control (n = 18)	Poor Phe level control (n = 10)	Accepted Phe level control (n = 18)
<-2	5(50%)	0(0%)	2(20%)	0(0%)
–2 to –1	2(20%)	6(33.33%)	4(40%)	3(16.67%)
–1 to zero	1(10%)	5(27.28%)	3(30%)	7(38.89%)
Greater than zero	2(20%)	7(38.89%)	1(10%)	5(27.28%)
P-Value	0.011		0.057	

Table 4 Association of differences in OFC and *z*-score with gender, consanguinity, and regular visits

Variables	Mean OFC difference	Median *z*-score difference
Gender		
Male	14.9 ± 1.14	0.11
Female	14.77 ± 1.0	0.37
P-value	0.77	0.167
Consanguinity		
No	15.2 ± 1.03	0.15
Yes	14.76 ± 1.08	0.32
p-value	0.42	0.721
Visits		
Regular	15.13 ± 1.19	0.4
Irregular	14.72 ± 1.01	0.11
P-value	0.385	0.042

related to weight but not to height or head circumference in this study.

Furthermore, Enns *et al.*[26] mentioned that children and adolescents who adhere to a phenylalanine-restricted diet in their early years of life tend to display cases of growth retardation. This constraint affects both their overall height and head circumference. The main reasons speculated behind these trends could be either the low protein content in the therapeutic diet or poor adherence to the diet.

Dokoupil *et al.*[27] reviewed the influence of phenylketonuria and its dietary restriction on growth but found limited evidence. Its data suggested that more than half the studies report abnormal growth indices in patients with PKU compared to normal populations. Abnormalities often include decreased head circumference and/or height, or increased body weight. However, many studies were small or outdated, lacking recent and extensive data that accounts for changes in dietary practices.

On the contrary, Acosta *et al.*[28] found that neither plasma phenylalanine nor tyrosine concentration was correlated with growth in infants with Phenylketonuria.

Hoeksma *et al.*'s[29] study in Dutch infants with phenylketonuria suggested that there was a significant relationship between the total protein and natural protein intake with head growth, but not with height growth during the first three years of life. Interestingly, the study also found that the head circumference growth was impacted by the natural protein intake.

Evans *et al.*[30] showed that growth issues observed in young children with PKU include impaired linear growth, and moderate growth retardation in the first 2 years of life. However, it's also noted that there can be a catch-up in growth later on. Based on this study, patients with PKU exhibited advanced linear growth compared to the control. There is also some risk of obesity during later adulthood life. The paper did not provide clear information on head growth issues specifically in young children with PKU. Nevertheless, it mentioned that natural protein intake rather than total protein intake was an important factor in head circumference growth in PKU.

Zaffanello *et al.*[31] stated that phenylketonuric and hyperphenylalaninaemic (HPA) newborns revealed statistically significant reductions in certain growth parameters compared to healthy neonates. More specifically, a significantly higher proportion of PKU and HPA patients exhibited decreased body length and head circumference ($P < 0.05$ for both parameters). When looking at comparisons using *z*-scores, which standardize the measurements, PKU newborns showed a significant reduction in all three growth parameters (weight, length, cranial circumference). The study suggested that body length and cranial circumference were more crucial than birthweight in assessing the growth of PKU babies a result goes with the current study findings.

Thiele *et al.*[32] primarily focused on the overall height and growth rate, noting that patients maintained on this diet display reduced height from birth, leading to a reduced final height it didn't explicitly discuss the impact of a phenylalanine-restricted diet on head growth in patients with Phenylketonuria.

The inconsistencies in growth parameter indices observed in different studies are primarily explained by several factors including different diet protocols which can have varying impacts on growth parameters, also the availability of specific dietary products and food supplements in different geographical and socio-economic states may affect their growth. In addition, the availability of micronutrient substitutes can vary between different studies, affecting growth parameters.

Another important cause is the techniques of diet therapy: Some studies have described normal growth in PKU patients, while others have reported PKU patients being smaller than the normal population. This could be due to different approaches in diet therapy applied in the studies.[33]

Finally, the timing of diagnosis and treatment: Patients diagnosed and treated early (before developing clinical manifestations) may show different growth patterns compared to those diagnosed later.

Conclusion

In patients with phenylketonuria diagnosed by newborn screen test; the higher the phenylalanine level at diagnosis, the smaller the head size compared with those with lower phenylalanine levels. While at 3 years of age, the head growth of those with stricter phenylalanine control did not vary greatly from patients with less strict control.

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Conflicts of interest
There are no conflicts of interest.

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