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Original Research

Developmental and Cognitive Outcomes in 342 Patients With Different Types of Hyperphenylalaninemia

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Abstract

Objectives: The aim of this study is to evaluate neurodevelopmental and cognitive outcomes in patients diagnosed with different types of hyperphenylalaninemia (HPA), identify the factors influencing these outcomes, and contribute to the debate regarding the thresold for initiating dietary treatment based on plasma phenylalanine (Phe) levels.

Methods: Patients with hyperphenylalaninemia (HPA) who were followed up and had developmental and/or cognitive evaluations at the Division of Pediatric Metabolism and Nutrition, Department of Pediatrics, between 1984 and 2018, were retrospectively assessed. The study included patients with mild (Phe:360-600 µmol/L), moderate (Phe:600-1200 µmol/L), or classic Phenylketonuria (PKU) (Phe ≥1200 µmol/L) treated with diet and/or tetrahydrobiopterin (BH4), along with untreated HPA patients (Phe:240-360 µmol/L). This classification was based on plasma Phe levels measured at the time of diagnosis. Denver Developmental Screening Test (DDST), Stanford-Binet test, and Wechsler Intelligence Scale for Children (WISC-R) adapted for Turkish children were applied for developmental and cognitive evaluation. Intellectual disability or developmental delay (ID/DD) was defined as a full-scale intelligence quotient (IQ) <70 on the Stanford-Binet or WISC-R, or as delay in two or more developmental domains on the DDST, with children meeting any of these criteria classified as having ID/DD. The relationships between ID/DD, age at diagnosis, diagnostic methods, plasma Phe levels, and brain MRI findings were analyzed.

Results: A total of 342 patients were included in the study, comprising 182 (53.2%) females and 160 (46.8%) males. Of these, 53 (15.5%) had mild PKU, 97 (28.4%) had moderate PKU, 102 (29.8%) had classic PKU, and 90 (26.3%) were diagnosed with HPA. A significant association was found between ID/DD and both the age at diagnosis and diagnostic method in patients treated with diet and/or BH4 ($p < 0.001$ and $p < 0.01$, respectively). In patients with ID/DD, the median plasma Phe levels at the first, third, and last years of follow-up were significantly higher compared to patients without ID/DD ($p < 0.024$). White matter abnormalities observed on brain MRI were significantly associated with PKU severity, the presence of ID/DD, and the median plasma Phe levels in the last year of follow-up ($p = 0.01$, $p < 0.001$, and $p < 0.001$, respectively). Notably, 9 (10%) of untreated HPA patients exhibited ID/DD, despite regular follow-up and the absence of known risk factors.

Conclusion: In addition to early diagnosis and treatment, lifelong adherence and regular follow-up are essential for achieving normal neurodevelopmental and cognitive outcomes in individuals with PKU. However, clinical management remains heterogeneous across centers. The presence of developmental delay in 10% of untreated HPA patients underscores the need to urgently re-evaluate current plasma Phe thresholds for treatment initiation and follow-up.

Keywords: Developmental delay, diet, early diagnosis, hyperphenylalaninemia, intellectual disability, phenylketonuria

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Phenylketonuria (PKU) is a rare autosomal recessive inherited disorder of phenylalanine (Phe) metabolism caused by mutations in the PAH gene (12.q22-24.1), which encodes the enzyme phenylalanine hydroxylase (PAH).[1] The PAH enzyme converts Phe to tyrosine using BH4 as a cofactor, along with molecular oxygen, and iron.[2] Deficiency of either the PAH enzyme or BH4 results in the accumulation of Phe in the blood and brain.

Untreated PKU is associated with irreversible intellectual disability, microcephaly, motor dysfunction, eczema like rash, seizures, developmental delay, abnormal behavioral patterns, autism spectrum features, and psychiatric symptoms.[3] Although the precise mechanisms through which elevated Phe causes neurotoxicity remain unclear, several potential mechanism have been proposed.[4] These include reduced glutamatergic synaptic activity and decreased function of enzymes such as pyruvate kinase and HMG-CoA reductase, contributing to myelin disruption and white matter abnormalities. Elevated Phe levels also inhibit tyrosine hydroxylase and tryptophan hydroxylase key enzymes involved in neurotransmitter synthesis. In addition, competitive inhibition of the large neutral amino acid transporter reduces the availability of neurotransmitter precursors in the brain, impairing neurotransmission.[4-6]

The prevalence of PKU varies globally, with higher incidence in countries such as Ireland (1:2,700) and Turkey (1:4,500), compared to much lower rates in Finland and Japan (<1:100,000).[7, 8] Since 2006, Turkey's national newborn screening program has achieved >95% coverage.[9] Despite early detection, long term neurocognitive outcomes largely depend on consistent lifelong adherence to treatment. Current guidelines recommend treatment initiation at plasma Phe levels >360 µmol/L, while levels between 120-360 µmol/L are considered safe.[4, 10] Nevertheless, the threshold for initiating treatment remains controversial. Some studies have indicated that patients with Phe levels between 240 and 360 µmol/L may still experience cognitive and attention-related difficulties. Maintaining Phe levels at or below 240 µmol/L has been associated with better neuropsychological outcomes, including improved cognitive flexibility and inhibitory control.[11, 12] At our center, treatment is initiated when plasma Phe levels exceed 360 µmol/L.

This study aims to evaluate patients with different types of HPA from a neurodevelopmental and cognitive perspective, identify factors influencing these outcomes, and contribute to the literature regarding the plasma Phe threshold for initiating phenylalanine restricted dietary treatment.

Methods

This study was approved by the Çukurova University Ethics Boards and Commisions (Approval date: December 2, 2016; Meeting number: 59; Decision number: 13) and conducted in accordance with the Declaration of Helsinki.

Study Population

This study evaluated 342 patients with HPA who were followed up at the Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, between 1984 and 2018 and had formal neurocognitive and developmental assessments. Data were retrospectively collected from hospital records. The cohort included patients diagnosed with mild (Phe: 360-600 µmol/L), moderate (Phe: 600-1200 µmol/L), classic PKU (Phe ≥1200 µmol/L) who were managed with a phenylalanine restricted diet and/or BH4 therapy, along with untreated HPA patients with Phe levels between 240-360 µmol/L. Patients were classified into mild, moderate, classic PKU, or untreated HPA groups based on their plasma Phe concentrations measured at the time of diagnosis.

Neurocognitive and Laboratory Evaluation

Neurodevelopmental and cognitive outcomes were assessed using age appropriate standardized tests. The Denver Developmental Screening Test (DDST) was applied for children aged ≤2 years, the Stanford-Binet Intelligence Scale for those aged 2-6 years, and the Wechsler Intelligence Scale for Children-Revised (WISC-R) for children aged ≥7 years. Intellectual disability was defined as a full-scale intelligence quotient (IQ) score <70 on either the Stanford-Binet or WISC-R. For children assessed with the DDST, a delay in two or more developmental domains (gross motor, fine motor-adaptive, language, and personal-social) was considered indicative of developmental delay. Clinical judgment including caregiver reports, observed functional abilities, and overall clinical evaluations was used to support test findings. Based on these criteria, children were classified as having intellectual disability or developmental delay (ID/DD).[13] Since age at diagnosis and initiation of treatment are directly related to neurodevelopmental outcomes, treated patients were categorized into seven groups according to age at diagnosis (in days): group I (3-14), group II (15-29), group III (30-59), group IV (60-89), group V (90-179), group VI (180-360), and group VII (>360). In the treated group, the relationship between age at diagnosis and the outcomes of the DDST, Stanford-Binet, and WISC-R tests was analyzed. Neurodevelopmental and cognitive test results were compared between patients diagnosed through the newborn screening program and those diagnosed outside the newborn screening program. In addititon, the relationship between age of diagnosis, diagnostic method, PKU type, median plasma Phe levels during the first, second, third, and last years of follow-up, brain MRI findings, and the presence of ID/DD was investigated.

Plasma Phe levels were measured using high performance liquid chromatography (HPLC) in the Pediatric Metabolism Laboratory of the Department of Pediatric Metabolism and Nutrition. Blood samples were collected in EDTA tubes, centrifuged to separate plasma, and stored under appropriate conditions until analysis. Phe concentrations were determined by comparing the sample values with internal calibrators and validated quality control standards.

Statistical Analysis

All statistical analyses were conducted using SPSS software, version 23 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as medians with minimum and maximum values (median; min-max). Associations between categorical variables were analyzed using the Pearson chi-square test. Differences in plasma Phe levels, presence of ID/DD, and brain MRI findings were evaluated using the Mann-Whitney U test.

Results

Demographics

A total of 342 patients were included in the study, comprising 182 (53.2%) females and 160 (46.8%) males. Among these, 53 (15.5%) patients had mild PKU, 97 (28.4%) had moderate PKU, 102 (29.8%) had classic PKU, and 90 (26.3%) were diagnosed with HPA. Demographic and clinical characteristics including PKU subtype, gender distribution, consanguinity, family history, age and method of diagnosis, need for special education, duration of follow-up, and age and clinical status at the last follow-up are summarized in Table 1.

Table 1. Demographic characteristics and comorbidities of patients with Phenylketonuria and Hyperphenylalaninemia

Hyperphenylalaninemia (HPA) classification	Phenylketonuria (PKU)			Hyperphenylalaninemia (240 < Phe < 360 µmol/L)
	Mild PKU	Moderate PKU	Classic PKU	
Number of patients, n (%)	53 (15.5)	97 (28.4)	102 (29.8)	90 (26.3)
Sex (F), n (%)	31 (58.5)	50 (51.5)	57 (55.9)	44 (48.9)
Consangunity	16 (30.2)	65 (67)	75 (73.5)	44 (48.9)
Family History, n (%)	15 (28.3)	27 (27.8)	31 (30.4)	16 (17.8)
Age at diagnosis*	0.66 (0.17-13.2)	0.66 (0.13-268.5)	1.01 (0.17-93.3)	1 (0.33-74.1)
Diagnosis methods, n (%)				
Newborn screening	46 (86.8)	79 (81.4)	78 (76.5)	85 (94.4)
Outside newborn screening	7 (13.2)	18 (18.6)	24 (23.5)	5 (5.6)
Reason for admission (diagnosis outside of newborn screening), n (%)				
Psychomotor retardation	1 (14.2)	8 (44.4)	17 (70.8)	1 (20)
Family history	6 (85.7)	10 (55.5)	6 (25)	4 (80)
Epilepsy	0	0	1 (4.1)	0
Treatment, n (%)				
Phenylalanine restricted formula	10 (18.9)	79 (81.4)	101 (99)	No treatment
Sapropterin dihydrochloride + phenylalanine restricted formula	5 (9.4)	8 (8.2)	1 (1)	
Sapropterin dihydrochloride + unrestricted diet	38 (71.7)	10 (10.3)	0	
Comorbidities, n (%)				
Psychomotor retardation	1 (1.8)	14 (14.4)	25 (25.4)	2 (2.2)
Epilepsy	2 (3.7)	4 (4.1)	10 (9.8)	0
Malnutrition	0	12 (12.3)	7 (6.8)	1 (1.1)
Osteoporosis	0	2 (2)	3 (2.9)	0
Obesity	0	0	4 (3.9)	0
Follow-up duration*	38 (1-181)	75 (9-342)	110 (3-403)	16 (1-227)
Age at last follow-up*	39 (1-188)	76 (13-356)	112 (3-414)	17.5 (2-241)
Requires special education/Unable to attend school n (%)	2 (4.5)	10 (22.7)	30 (68.1)	2 (4.5)
Median plasma Phe levels last year of follow-up, n (%)				
Normal (<120 µmol/L)	1 (1.9)	3 (3.1)	2 (2.0)	3 (3.3)
Follow-up (120-360 µmol/L)	30 (56.6)	28 (28.9)	22 (21.6)	83 (92.2)
Poor control (>360 µmol/L)	22 (41.5)	66 (68)	78 (76.5)	4 (4.4)
Patient follow-up status, n (%)				
Actively followed	52 (98.1)	95 (97.9)	100 (98)	88 (97.8)
Lost to follow-up	1 (1.9)	2 (2.1)	2 (2)	2 (2.2)

*Months, median (min-max); Sapropterin dihydrochloride (synthetic tetrahydrobiopterin, BH4).

Developmental/Cognitive Evaluation

Neurodevelopmental and cognitive outcomes were assessed using age appropriate standardized tests: 106 (30.9%) patients were evaluated with the WISC-R, 165 (48.2%) with the Stanford-Binet test, and 71 (20.9%) with the DDST. Among the 252 patients receiving a phenylalanine restricted diet and/or BH4 therapy, a significant association was observed between age at diagnosis and the presence of ID/DD (p<0.001). Notably, ID/DD was identified in 62.5% of patients diagnosed after 90 days of age (Fig. 1). Of these 252 patients, 203 (80.6%) were diagnosed through the newborn screening program, while 49 (19.4%) were diagnosed outside the newborn screening program. In patients diagnosed through newborn screening, 23 (11.3%) had ID/DD, whereas 23 (46.9%) of those diagnosed out of the screening program had ID/DD, and this relationship was statistically significant (p<0.001) (Table 2).

A significant relationship was found between the type of HPA and the presence of ID/DD (p<0.001) (Table 2). As the phenotype progressed from HPA to classic PKU, the incidence of ID/DD increased. Among patients with ID/DD, plasma Phe levels at the first, third, and last year of follow-up were significantly higher compared to those without ID/DD (p=0.007, p=0.035, and p<0.001, respectively) (Table 3).

In the present study, the most important result was the presence of ID/DD in 9 (10%) of untreated HPA patients with plasma Phe levels between 240 µmol/L and 360 µmol/L, despite regular follow-up and the absence of other risk factors such as prematurity, hypoxic-ischemic encephalopathy, hypothyroidism, vitamin deficiencies, and epilepsy.

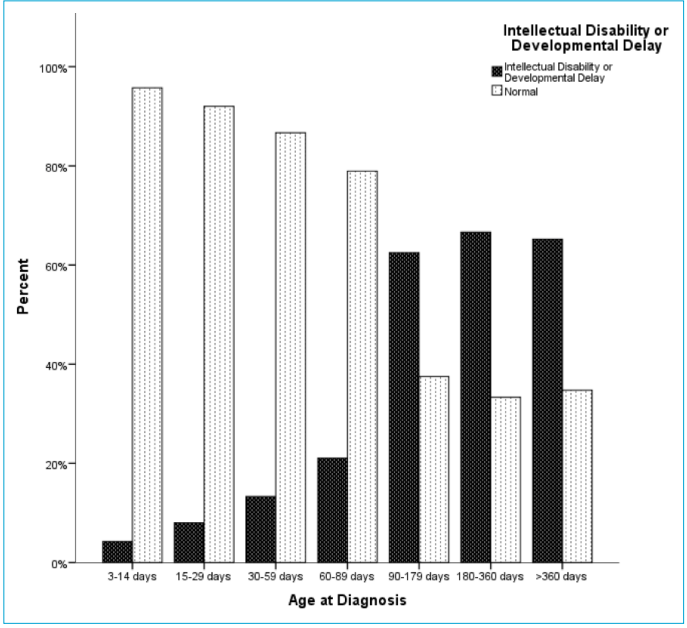

Figure 1. Intellectual disability or developmental delay results based on age of diagnosis in patients followed with treatment (p <0.001).

Brain MRI was performed in 116 patients as part of the neurological evaluation, revealing white matter involvement in 74 (63.8%) cases, including 2 (1.7%) with HPA, 2 (1.7%) with mild PKU, 23 (19.8%) with moderate PKU, and 47 (40.5%) with classic PKU. MRI findings from selected patients in our cohort are shown in Figure 2, which illustrates mild gliotic changes in the bilateral periventricular peritrigonal regions in a patient with moderate PKU, and in Figure 3, which depicts more extensive bilateral periventricular white matter hyperintensities and ventricular enlargement due to cerebral atrophy in a patient with classic PKU. A significant relationship was found between white matter abnormalities and both PKU type and the presence of ID/DD (p=0.01, p<0.001, respectively). In addition, plasma Phe levels during the last year of follow-up were significantly higher in patients with white matter involvement (p<0.001). Of the 44 patients who required special education, 34 (77.2%) had white matter abnormalities on brain MRI. Among these 44 patients, 19 (43.2%) were diagnosed through the newborn screening program.

Table 2. Intellectual disability and developmental delay according to PKU subtypes and diagnostic method

	Intellectual disability/ developmental delay		p
	Yes, n (%)	No, n (%)	
Hyperphenylalaninemia classification			
Hyperphenylalaninemia	9 (10)	81 (90)	<0.001
Mild PKU	3 (5.6)	50 (94.3)	
Moderate PKU	14 (14.4)	83 (85.5)	
Classic PKU	29 (28.4)	73 (71.5)	
Diagnostic methods			
Newborn screening	23 (11.3)	180 (88.7)	<0.001
Outside of newborn screening	23 (46.9)	26 (53.1)	

Table 3. Comparison of median plasma phenylalanine levels by presence of Intellectual disabilityand developmental delay

Post diagnosis follow-up period	Intellectual disability/ developmental delay		p
	Yes	No	
1st year *	318 (162-600)	264 (78-858)	0.007
2nd year *	300 (90-612)	294 (84-942)	0.290
3rd year *	372 (66-816)	306 (78-1200)	0.035
Last year at follow-up*	690 (168-1860)	330 (66-1410)	<0.001

* Values are expressed as median (min–max), in µmol/L.

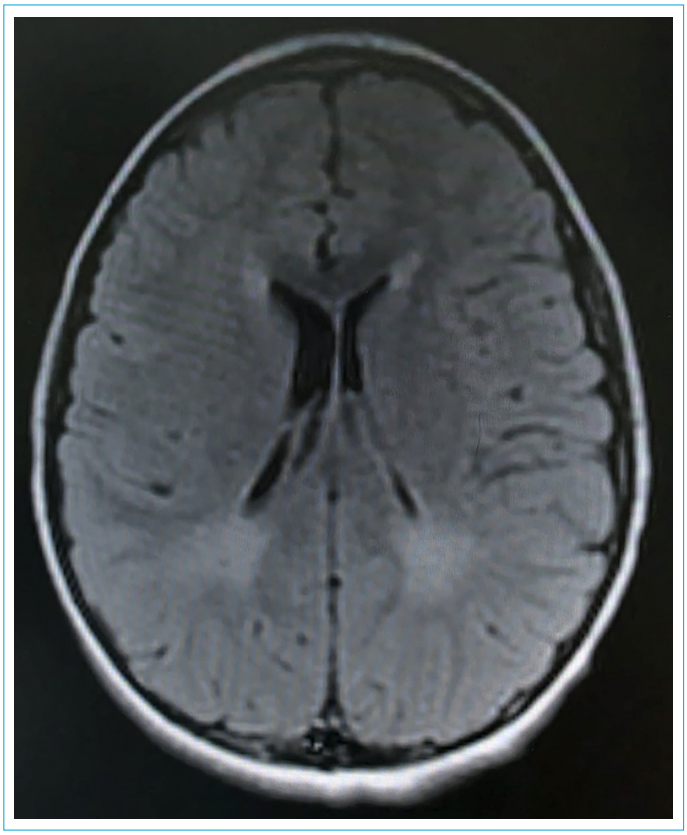

Figure 2. Axial T2-FLAIR brain MRI of a patient with moderate PKU, showing mild gliotic white matter changes in the bilateral periventricular peritrigonal regions, more prominent posteriorly.

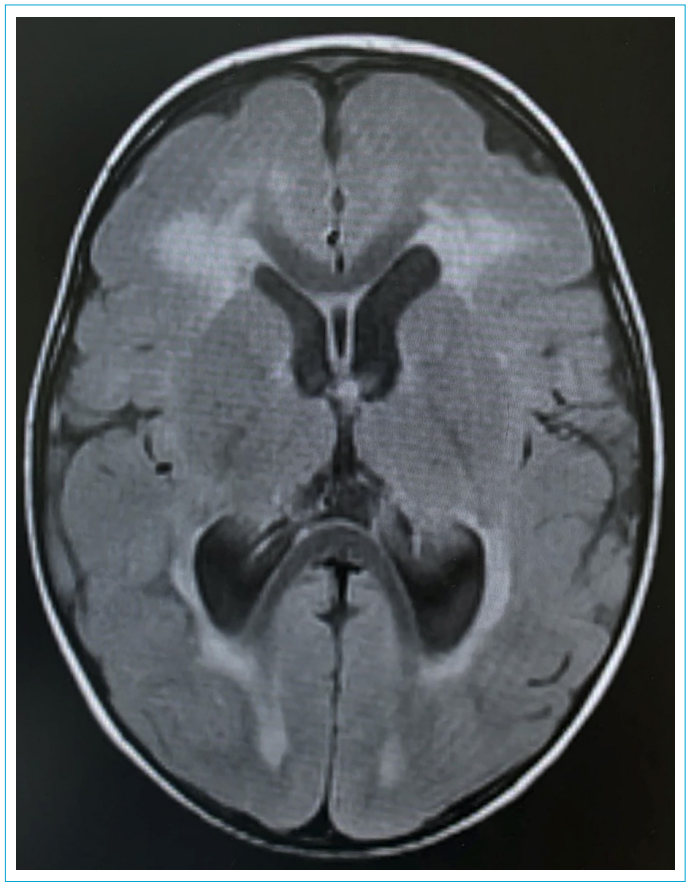

Figure 3. Axial T2-FLAIR brain MRI of a patient with classic PKU, demonstrating bilateral symmetric hyperintensities in the periventricular white matter, consistent with gliotic changes. The lateral ventricles appear enlarged, secondary to atrophy.

Discussion

Phenylketonuria is an inherited metabolic disorder in which normal cognitive and neuromotor development can be achieved through early diagnosis via newborn screening and timely initiation and maintenance of appropriate treatment.[4] In our study, normal neurocognitive outcomes were more frequently observed in individuals diagnosed via newborn screening. Among 203 PKU patients diagnosed by newborn screening programme and followed up with treatment, ID/DD was identified in 4.3% (n=2) of mild, 7.6% (n=6) of moderate, and 19.2% (n=15) of classic PKU cases. These results highlight the importance of early diagnosis and timely intervention in achieving favorable neurodevelopmental outcomes in PKU. The timing of diagnosis and initiation of treatment plays a pivotal role in neurological development, as several studies have demonstrated an inverse correlation between the timing of treatment initiation and cognitive performance, particularly IQ, in treated patients.[14, 15] One study reported that patients who began treatment within three weeks had significantly higher IQ scores compared to those who started between three and six weeks.[15] Smith et al.; found that each four week delay in initiating a phenylalanine restricted diet was associated with a 4-point decrease in IQ.[16] In our study, a significant relationship was observed between age at diagnosis and developmental/cognitive outcomes among 252 treated patients. Intellectual disability and/or developmental delay was found in 62.5% of patients diagnosed after 90 days of age, and the frequency of ID/DD increased with later diagnosis.

In the study by Yalaz et al.,[17] mental retardation was reported in 67% of patients who received early treatment and in 100% of those who remained untreated, among a cohort of 146 individuals with PKU.

The authors noted that none of the patients who initiated treatment after 12 months of age achieved normal neurodevelopmental outcomes, and a statistically significant difference in IQ scores was observed between those who began treatment within the first two months of life and those who started later. Similarly, a study evaluating neurological outcomes in 38 late diagnosed patients with classical PKU found intellectual disability in 37 cases.[18] Although early diagnosis and dietary treatment significantly reduce the risk of severe neurocognitive impairment, executive function deficits, particularly in planning and organizational skills, have been reported

even among patients treated early.[19, 20] Furthermore, within the phenotypic spectrum of PKU, cases of neurocognitive impairment have also been described in patients maintaining blood Phe levels consistently below 6 mg/dL (360 µmol/L) during follow-up.[21-23] Parra et al.[24] reported that children with mild HPA (Phe 2-6 mg/dL), diagnosed early, demonstrated average range cognitive performance, significantly higher than peers with PKU (Phe >6 mg/dL) who were also diagnosed and treated early. However, both groups showed similar difficulties in working memory and attention. In the present study, neurodevelopmental and cognitive evaluations were performed in 90 untreated patients with plasma Phe levels between 240–360 µmol/L. Notably, 9(10%) of these patients were identified as having ID/DD.

Evinc et al.[23] evaluated cognitive and behavioral profiles in 41 untreated children with HPA aged 6-16 years, with lifetime median plasma Phe levels between 240–600 µmol/L. Both the 240–360 µmol/L and 360–600 µmol/L subgroups demonstrated significantly lower full-scale IQ and verbal comprehension scores compared to healthy controls. Moreover, children in the higher Phe range exhibited more pronounced attention deficits and difficulties in inhibitory control. Based on these findings, the authors concluded that even plasma Phe levels between 240–360 µmol/L may pose a risk for neurocognitive impairment and recommended re-evaluating the current treatment initiation threshold.

We analyzed the relationship between median plasma Phe levels at the first, second, and third years following diagnosis, as well as during the last year of follow-up, and developmental or cognitive assessment outcomes. Consistent with previous studies, our findings revealed a negative association between higher plasma Phe levels and the presence of ID/DD.[12, 25] In patients with ID/DD, plasma Phe levels at the first, third, and last years of follow-up were significantly higher than in those without ID/DD. According to the study by Parra et al., patients diagnosed through newborn screening with initial Phe levels exceeding 15 mg/dL who maintained median Phe concentrations below 240 µmol/L during the first year of life demonstrated significantly higher IQ scores compared to those with levels between 240–360 µmol/L and above 360 µmol/L. The authors concluded that maintaining Phe levels above 360 µmol/L during the first year is consistently associated with impaired cognitive development.[26]

In our study, brain MRI was performed in 116 patients, and white matter abnormalities were identified in 74 (63.8%) cases, most frequently among children with classic PKU. White matter involvement has generally been associated with elevated plasma Phe levels and patient age in the literature.[27, 28] We observed a significant association between plasma Phe levels during the last year of follow-up and the presence of white matter abnormalities on MRI. Moreover, patients with white matter involvement had a significantly higher rate of ID/DD compared to those with normal MRI results. One study found no association between white matter abnormalities and neurocognitive impairment,[29] while another reported a significant relationship between brain MRI abnormalities and plasma Phe levels during the last five years of follow-up, though no significant correlation was observed with IQ scores.[30]

As demonstrated in our study, the neurocognitive and developmental outcomes observed in HPA patients, whether diagnosed through newborn screening or following symptomatic presentation, may represent only the tip of the iceberg, underscoring the need for further research to optimize long term neurological outcomes.

This study has several limitations, primarily its retrospective design. Developmental and cognitive assessments were not conducted uniformly at diagnosis or at standardized intervals but instead occurred at various points during routine follow-up. Despite these limitations, the study has notable strengths: it includes a large cohort representing all subtypes of HPA and provides formal neurodevelopmental evaluations for all participants. Importantly, it contributes to the ongoing debate regarding treatment thresholds by identifying that 10% of patients with plasma Phe levels between 240–360 µmol/L had intellectual disability or developmental delay.

Conclusion

As shown in our study although early diagnosis with newborn screening program is essential for normal mental and motor development and cognitive functions in PKU patients, but also ensuring the lifelong treatment compliance and follow-up are the other important determinants playing role for satisfactory outcomes. The most striking finding of our study is the 10% rate of ID/DD among patients with plasma Phe levels between 240-360 µmol/L. This concerning result underscores the unmet need for clearer guidance on the appropriate threshold for initiating treatment.

This manuscript is based on the pediatric residency graduation thesis of Dr. Sibel Öz.

Disclosures

Ethics Committee Approval: The study was approved by Çukurova University Ethics Boards and Commissions (Approval date: December 2, 2016, and meeting number: 59, decision number: 13).

Informed Consent: Informed consent was obtained.

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