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Original Article

Effect of large neutral amino acids treatment on blood phenylalanine, tyrosine, and tryptophan levels in adolescent and young adult PKU patients

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ABSTRACT

Objective: We aimed to evaluate the change in phenylalanine (Phe), Tyrosine (Tyr), and Tryptophan (Trp) blood levels in classical PKU patients treated with large neutral amino acids (LNAA) supplementation.

Methods: Twenty-nine PKU patients treated with LNAA between 2013-2022 were enrolled in the retrospective observational study. Four cases were excluded from the statistical analysis due to missing data.

Results: The median age (min-max) onset of LNAA was 11.6 (8-38.1) years, and the median duration (min-max) of LNAA use was a median of 42.7 (5-105) months. The mean current age of the patients was 19.70±9.96 years. The final blood levels of Phe, Tyr, and Trp did not change significantly ($p>0.05$) from the baseline. At the last measurement, the Hb value increased significantly ($p<0.05$) compared to the baseline, while the vitamin B12, total protein, albumin, and ferritin values did not change from the baseline ($p>0.05$). It was seen that there was an increase in the employees' productivity at work, the success of the students in the course, and the focus on maintaining attention.

Conclusions: We want to highlight that LNAA could be a treatment option for adolescents or adults who are not adhering to a Phe-restricted diet.

Keywords: large neutral amino acid, phenylalanine, phenylketonuria, tyrosine, tryptophan

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive amino acid metabolism disorder. It is caused by phenylalanine hydroxylase (PAH) enzyme deficiency due to mutations in the *PAH* gene. Although there are different classification approaches in the literature, the approach accepted in Turkey is phenylalanine (Phe) level between 2 and 6 mg/dl is defined as hyperphenylalaninemia, 6-10 mg/dl as mild; 10-20 mg/dl as moderate, and >20 mg/dl as severe PKU.[1-4]

Central nervous system damage (CNS) may occur due to increased Phe. The brain dysfunction exhibited in PKU patients is caused by several different factors, not just Phe concentration. Large amino acid transporter-1 (LAT-1) protein enables the competitive passage of large

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neutral amino acids, including phenylalanine, across the blood-brain barrier in the CNS and intestine. After Phe crosses the blood-brain barrier, it serves as a precursor for dopamine, norepinephrine, and epinephrine. Hence, elevated plasma and brain Phe concentrations affect brain functions, and the patients present neurocognitive and behavioral problems. Patients diagnosed with PKU will likely exhibit behavioral issues such as hyperactivity, stereotypic movements, aggression, anxiety, and social disengagement if they remain undiagnosed or untreated.[5] Although disagreements and debates continue regarding the cut-off Phe level for preventing neuropsychological issues, guidelines and expert opinion reports exist in the literature.[2,6-10] The goal of PKU treatment is to keep blood Phe levels strictly regulated. American guidelines recommend a target range of 2–6 mg/dL for patients of all ages.[11] However, European guidelines suggest a target range of 2–6 mg/dL for patients younger than 12 years and during pregnancy while recommending a target range of 2–10 mg/dL for patients older than 12 years to prevent neurodevelopmental issues and potential impairment of neurocognitive function.[8]

Diagnosis and starting a Phe-restricted diet in the first days of life [2], the main treatment option, are vital for classic PKU patients. For this reason, it has been screened in newborn screening programs for years in many countries, including Turkey.[6] In case of untreated or late and inadequate treatment, behavioral and psychiatric problems and motor skills deterioration could be observed.[3,6]

Large neutral amino acids (LNAA) are histidine (His), isoleucine (Ile), leucine (Leu), methionine (Met), threonine (Thr), Trp, Tyr, valine (Val), and Phe. LNAA supplements containing these amino acids are an option for treating PKU. It is known that LNAA protects from CNS damage by acting on the transfer of Phe to the brain; this is thought to do so using the same transporter system as Phe (LAT-1). Thus, neurophysiological and neuropsychiatric improvement is observed in patients. It is believed that LNAA supplementation reduces the amount of Phe in the brain, gives patients a supplementation rich in Tyr and Thr, and contributes to the production of dopamine and serotonin. Another hypothesis suggests that being rich in essential amino acids contributes to well-being. In contrast, another opinion indicates that since it is a Phe-free supplement, it reduces the level of phenylalanine in the blood, contributing to decreased Phe in the brain. The LNAA treatment also provides dietary liberalization, which is described as increased dietary Phe or natural protein intake. Therefore, LNAA treatment could be an option in adolescents or adults with low adherence to Phe restricted diet.[7-9,12-17]

We aimed to evaluate the change in phenylalanine (Phe), Tyrosine (Tyr), and Tryptophan (Trp) blood levels in classical PKU patients treated with LNAA supplementation.

MATERIALS AND METHODS

We collected retrospective data from the patients' medical records, ensuring that all procedures were carried out with respect to ethical standards and following approval from the ethical committee by the Medical Research Ethics Committee of Ege University Faculty of Medicine (Document Number: 22-11.1T/9). The study used the principles outlined in the Helsinki Declaration (1964). Data were gathered between January 2013 and December 2022. Twenty-nine patients diagnosed with PKU and under LNAA supplements treatment for longer than six months between 2013 and 2022 were included in the study cohort.

Four cases were excluded from the statistical analysis due to missing data. All of the patients were diagnosed with classic PKU and unresponsive to sapropterin. Demographic and laboratory data were obtained from patients' medical records. The specified total protein subscription of 1 g/kg and total LNAA account for approximately 60% of daily protein intake, divided into four doses. Before the LNAA supplement period, the recommended Phe content of the diet was based on age and gender according to national and international consensuses (4, 18). The Phe-free protein substitutes were also added to the protein content of the three-day food diaries. The Phe content in the Phe-restricted diet was adjusted according to the blood Phe levels at each outpatient clinic visit. Individuals with PKU who started LNAA supplementation were those who were not compliant with the phenylalanine-restricted diet treatment. The recommended daily LNAA supplement dose, about 60% of total daily protein, was divided into three doses with meals. Dietary content, Phe, Tyr, Thr, vitamin B12, ferritin, hemoglobin, total protein, and albumin levels were compared to the LNAA supplement before and after.

Observations, including academic performance or attention span from the patients or their caregivers, were based solely on subjective reports from parents, teachers, and social interactions; however, no objective tests were conducted.

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured using the Kolmogorov-Simirnov and Shapiro-Wilk test. Wilcoxon test was used to analyze dependent quantitative data. Spearman correlation analysis was used in the correlation analysis. SPSS 28.0 program was used in the analysis.

RESULTS

Ten (40%) patients were female, and 15 (60%) were male. The median age at diagnosis was 15 months (0.04-32.75 years), the follow-up period was 13.1±3.5 years (7.8-24.5), the median current age was 15.79 years (7.8-41.17), the median age of initiation of LNAA supplement was 11.6 years (8-38.1), and the duration of under LNAA treatment median 42.7 months (min:5-max:105 months). There was

Table 1. Patients' demographic, molecular, daily protein intake, daily LNAA supplement, intellectual state, educational and occupational status.

Patient Number	Gender	Age of diagnosis	Age of LNAA treatment initiation	Current age	PAH gene		Total protein intake (g/d)	Natural protein intake (g/d)	LNAA Supplement (g/d)	Follow-up duration	ID	Educational/ Occupational status
					Allele 1	Allele 2						
1	F	4y	28y	29y	c.842C>T	c.842C>T	98	39.2	58.8	24y	Severe	
2	F	20d	11y	17y	c.441+5G>T	c.1066-11G>A	46	18.4	27.6	16y	N	High School
3	M	3y	11y	19y	c.1066-11G>A	c.1066-11G>A	99	39.6	59.4	16y	N	University
4	M	25y	34y	41y	c.165delT	c.1049C>A	83	33.2	49.8	15y	Severe	
5	M	16y	25y	32y	c.842C>T	c.1066-11G>A	54	21.6	32.4	16y	Severe	
6	M	35d	11y	15y	c.116_118delTCT	c.116_118delTCT	58	23.2	34.8	15y	N	High School
7	F	1y	8y	16y	c.194T>C	c.1066-11G>A	96	38.4	57.6	15y	Severe	
8	F	8y	18y	22y	c.441+5G>T	c.441+5G>T	50	20	30	14y	N	Employed
9	F	24d	12y	14y	c.970-1G>T	c.1066-11G>A	41	16.4	24.6	14y	N	High School
10	F	18d	9y	14y	c.638T>C	c.638T>C	30	12	18	14y	N	High School
11	M	40d	12y	14y	c.168+5G>C	c.168+19T>C	75	30	45	14y	Mild	High School
12	M	50d	8y	13y	c.1199+1G>C	c.1199+1G>C	45	18	27	13y	Mild	High School
13	F	42d	12y	14y	c.143T>C	c.473G>A	49	19.6	29.4	14y	N	High School
14	M	2y	13y	16y	c.638T>C	c.638T>C	42.5	17	25.5	14y	N	High School
15#	M	44d	10y	13y	c.1089delG	c.1238G>C	38	15.2	22.8	12y	Severe	Middle School
16	M	25y	28y	12y	c.1066-11G>A	c.1222C>T	36	14.4	21.6	12y	N	Middle School
17	M	3y	12y	37y	c.1066-11G>A	c.728G>A	82	32.8	49.2	12y	Mild	Employed
18	M	25y	27y	16y	c.143T>C	c.331C>T	83	33.2	49.8	13y	N	High School
19#	F	52d	8y	36y	c.1066-11G>A	c.1066-11G>A	88	35.2	52.8	11y	Severe	
20	M	32d	9y	10y	c.1162G>A	c.1162G>A	28	11.2	16.8	10y	N	Middle School
21	M	9y	15y	10y	c.1066-11G>A	c.842C>G	36.5	14.6	21.9	10y	Mild	Middle School
22	F	40d	11y	14y	c.441+1G>A	c.441+1G>A	78	31.2	46.8	13y	N	High School
23	F	9y	38y	17y	c.473G>A	c.1222C>T	39	15.6	23.4	8y	Severe	High School
24#	F	11y	12y	18y	c.473G>A	c.1222C>T	45	18	27	8y	Mild	High School
25	M	33y	8y	41y	c.1066-11G>A	c.143T>C	72	28.8	43.2	8y	N	Employed
26	M	15y	28y	20y	c.1066-11G>A	c.1066-11G>A	66	26.4	39.6	5y	N	University
27	M	32y	11y	35y	c.168+5G>C	c.1066-11G>A	85	34	51	3y	Severe	
28	M	28d	11y	12y	c.1066-11G>A	c.1066-11G>A	34	13.6	20.4	12y	Mild	Middle School
29#	M	32d	34y	8y	c.441+5G>T	c.1066-11G>A	23	9.2	13.80	8y	Severe	

F: female, M: male, d: day, y: year, g: gram, ID: intellectual disability, LNAA: large neutral amino acid. # Excluded due to missing data.

no additional disease or supplement replacement that would affect the nutritional status of the cases (Table 1).

Before starting the LNAA supplement, the mean levels were Phe 16.74±8.86 mg/dL, Tyr 1.13±0.69 mg/dL, and Trp 1.24±0.54 mg/dL. Under LNAA treatment and diet liberalization, the Phe and Tyr levels in the first, second, and third months and at the last visit did not change from baseline (p>0.05) (Table 2).

Before the LNAA supplement, the mean levels were Hb 13.04±1.34 g/dL, vitamin B12 668.8±244.0 pg/mL, total protein 7.29±0.49 g/dL, albumin 4.71±0.36 g/dL, ferritin 40.64±23.83 ng/mL. At the last measurement, only the Hb value increased significantly (p<0.05) (Table 3).

There was a negative correlation between the difference in dietary protein intake of the cases (rho= -0.452, p<0.05) and the difference in the Phe change between the basal

Table 2. Phenylalanine, tyrosine, and tryptophan differences before and after LNAA supplementation. (n=25)

Plasma amino acid levels		Min-Max	Median	Mean±SD	p†	p‡
Phe (mg/dl)	Basal	1.20-33.40	14.60	16.74±8.86	-	
	1st month	1.70-27.20	15.20	15.74±6.95	0.501 ^{w}	
	2nd month	1.80-26.10	18.00	16.85±6.52	0.481 ^{w}	0.977 ^{w}
	3rd month	1.40-27.60	17.55	16.30±7.02	0.659 ^{w}	0.836 ^{w}
	Last visit	5.30-29.60	17.10	17.25±6.56	0.192 ^{w}	0.224 ^{w}
Tyr (mg/dl)	Basal	0.50-3.10	0.90	1.13±0.69		
	1st month	0.50-2.80	0.85	1.28±0.79	0.598 ^{w}	
	2nd month	0.50-4.40	1.20	1.62±1.22	0.232 ^{w}	0.409 ^{w}
	3rd month	0.40-3.00	1.00	1.16±0.58	0.940 ^{w}	0.887 ^{w}
	Last visit	0.60-3.40	1.10	1.42±0.81	0.036* ^{w}	0.055 ^{w}
Trp (mg/dl)	Basal	0.60-2.80	1.20	1.24±0.54		
	Last visit	0.70-2.90	1.10	1.31±0.54	0.435 ^{w}	
Phe/Tyr	Basal	1.50-56.00	17.10	18.05±12.78		
	1st month	2.80-48.00	14.90	16.77±12.08	0.426 ^{w}	
	2nd month	1.80-43.80	14.90	16.65±13.25	0.355 ^{w}	0.975 ^{w}
	3rd month	1.80-53.80	13.90	16.98±11.64	0.932 ^{w}	0.492 ^{w}
	Last visit	4.80-37.30	12.10	15.16±9.73	0.563 ^{w}	0.773 ^{w}

Max: maximum, Min: minimum, Phe: phenylalanine, Trp: tryptophan, Tyr: tyrosine. ^{w} Wilcoxon test. † The difference between basal and last visit values. ‡ The difference with the previous measurement. * Indicates significance at p <0.05.

Table 3. Hematological and nutritional results baseline and last visit (n=25)

		Min-Max	Median	Mean±SD	P
Hb (g/dL)	Baseline	10.70 - 15.60	13.10	13.04 ± 1.34	0.033* ^{w}
	Last	11.20 - 15.30	13.40	13.50 ± 1.14	
Vitamin B12 (pg/mL)	Baseline	206.0 - 1169.0	705.0	668.8 ± 244.0	0.149 ^{w}
	Last	150.0 - 1072.0	616.5	560.2 ± 246.4	
Total protein (g/dL)	Baseline	5.90 - 8.10	7.30	7.29 ± 0.49	0.676 ^{w}
	Last	6.50 - 8.10	7.41	7.35 ± 0.42	
Albumin (g/dL)	Baseline	3.70 - 5.40	4.70	4.71 ± 0.36	0.562 ^{w}
	Last	4.19 - 5.40	4.70	4.78 ± 0.31	
Ferritin (ng/mL)	Baseline	11.00 - 101.00	40.10	40.64 ± 23.82	0.964 ^{w}
	Last	9.06 - 114.00	33.40	42.91 ± 28.87	

Hb: Hemoglobin, ^{w} Wilcoxon test, * Indicates significance at p <0.05.

Table 4. Spearman correlation analysis results between the difference in dietary protein intake of the cases and the difference between baseline and last levels (n=25)

	Difference in daily dietary protein intake	
	Correlation coefficient (rho)	p
Phe	-0.452	0.023*
Tyr	0.420	0.037*
Trp	0.435	0.030*
Phe/Tyr	-0.561	0.004
Hb	0.229	0.281
Vitamin B12	0.116	0.590
Total protein	-0.170	0.449
Albumin	0.295	0.183
Ferritin	-0.104	0.637

Phe: phenylalanine, Trp: tryptophan, Tyr: tyrosine, Hb: Hemoglobin.
* Indicates significance at p <0.05.

and final measurement, a positive correlation between the Tyr change cases (rho= 0.420, p<0.05), and a positive correlation between the Trp change (rho=0.435, p<0.05) (Table 4).

There was not a significant correlation between dietary protein content and Hb, serum total protein, albumin, and ferritin levels change (p> 0.05) (Table 4).

Among the patients, 17 (68%) were students, and three (12%) were employed. At the beginning of the LNAA supplement, 24% of the participants had a moderate-severe intellectual disability, and 28% had mild intellectual disability. Under the LNAA supplement, improvements were observed in employee productivity, student academic performance, and attention span. We provided the changes patients experienced after using LNAA treatment in Table 5.

DISCUSSION

Our research had a large cohort compared to previous studies, and our initial finding in this study was that the LNAA starting age was younger than that of the previous studies.[1,18]

Our results show that the final measurement Phe, Tyr, and Trp values did not change significantly, similar to the previous reports.[14,17] In another study, nine out of ten patients had considerably higher plasma Tyr levels[19], while five had significantly lower Phe/Tyr ratios. Scala et al. reported that Tyr levels considerably increased with LNAA supplementation in PKU patients.[1] Along with providing patients with supplements Tyr and Trp and helping to produce dopamine and serotonin, it is believed that LNAA lowers the quantity of Phe in the brain.[7-9, 12-17]

Our cohort's B12, Hb, and ferritin values did not change between the baseline and last visit, and we hypothesized this was due to the patients being supplemented with a Phe-free medical formula rich in these micronutrients before LNAA treatment. No large study in the literature compared data on these parameters before LNAA treatment, under a Phe-restricted diet, and after initiating LNAA treatment with diet liberalization.

Burlina et al. reported a significant decrease in the Phe/Tyr ratio, even though there was no notable change in blood

Table 5. Changes in patients' emotions after LNAA supplements as reported by themselves or their caregivers.

Patient Number	Describing Person	Answer
2	Father	"She concentrates on her studies better; her sleep periods are more regular."
8	Sister	"She works as a worker in the factory; she works much more harmoniously and efficiently at work."
9	Parents	"School success is better."
10	Mother	"Her attention is much better than before."
11	Father	"His attention is much better than before."
12	Teacher	"An increase in fine skills and musical talent was observed."
17	Himself	"My nights of sleep periods were regular; I had had severe insomnia problems before. My fatigue has decreased."
18	Himself	"No change"
24	Himself	"I am feeling more active and social individual than before."
25	Himself	"I used to be forgetful before."
26	Father	"He is much more attentive compared to before."

Phe levels.[20] All subjects receiving the LNAA supplement indicated that they felt better. While the quality of life scale showed a significant decrease in aggression, no significant changes were noted in mood assessments.[21] No specific tests were performed to assess the participants' moods in the presented study. Nevertheless, it was noted that two individuals experienced more regular sleep patterns, two became more social and harmonious, and one developed an increased interest in music and began playing instruments. All participants reported a significant improvement in the regularity of their sleep patterns.

Research on mice with PKU revealed that supplementing with Tyr and Trp produced effects comparable to a high-protein diet in those given specific Ile, Leu, and Thr. The group receiving Tyr and Trp supplements exhibited significantly elevated serotonin levels.[21] Another experiment on animals demonstrated that LNAA supplementation increased brain serotonin and norepinephrine levels in mice while dopamine levels remained unchanged.[22] A separate study group showed that LNAA supplementation had beneficial effects on various cognitive and physical functions, including executive functioning, sustained attention, vigilance, distress, well-being, exercise training, motor skills, and mental performance.[1] These findings suggest a potential hypothesis regarding the impact of LNAA treatment on mood and cognition.

The limitations of our study were that the age and clinics of the cases were heterogeneous, the assessment of cognition and mood performances was not standardized, our study did not include measurements related to parents or caregivers, and we did not have data about other amino acids.

The mainstay treatment of sapropterin-unresponsive classical PKU is still a Phe-restricted diet. Diet compliance of patients and caregivers decreases after the first years of life, especially during adolescence. Therefore, new treatment alternatives are important to protect patients from long-term complications.[1,7,11] The caregivers of every case in our study reported that their charges struggled with dieting due to their advanced age at each control. It was noted that the diet consumption lists were incompatible, particularly regarding the controls, and that formulas without phenylalanine did not want to be ingested. It is stated in the literature that similar problems are experienced by the patients and their caregivers.[21-24]

CONCLUSION

Our results demonstrated no significant changes in Phe, Tyr, and Trp levels, but increased Hb levels were observed during LNAA treatment. LNAA seems to be a potential treatment option for older patients and may merit further consideration in clinical settings.

Ethical approval

This study has been approved by the Medical Research Ethics Committee of Ege University Faculty of Medicine (approval date 17.11.2022, number 22-11.1T/9). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: FE, HY, SKU; Data collection: FE, EC, HY, SKU, MÇ; Analysis and interpretation of results: FE, EC, HY, SKU, MÇ; Draft manuscript preparation: FE, HY, SKU. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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