Our Experience with Long Neutral Amino acid supplementation in Paediatric PKU patients in India

Kudalkar KV[1], Madhavi Korti[2], Pranathi Gutta[2], Jalan AB[1]
1. Division of Biochemical Genetics, Navi Mumbai Institute of Research in Mental and Neurological Handicap, India-400705
2. The Butterflies Clinic, Hyderabad, India

Introduction: Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism caused by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH), which results in severe intellectual disability if untreated. The mainstay of treatment in pediatric patients with classical PKU and pterin metabolism disorders presenting with hyperphenylalaninemia is lifelong Phe-restricted diet, however this is difficult to adhere to due to compliance issues and hence alternative therapies have been introduced, including use of Long Neutrals Amino acids (LNAA)[1,2].We herewith present our experience with using LNAAs in 1 patient with classical PKU and one with PTPS deficiency and 2 suspected PAH Def (Normal Pterins and DHPR Enzyme).

Objective: To study effect of LNAA therapy in pediatric patients with PKU.

Methods: This is a retrospective study analyzing the biochemical and clinical parameters in patients with hyperphenylalaninemia on LNAA therapy. 3 patients with classical PKU and one patient with PTPS deficiency gathered information about LNAA therapy from internet and asked for a trial of LNAA due to non-compliance to standard dietary restrictions. All 4 patients were diagnosed symptomatically. We monitored the clinical and biochemical parameters. Data of these patients is summarized below:

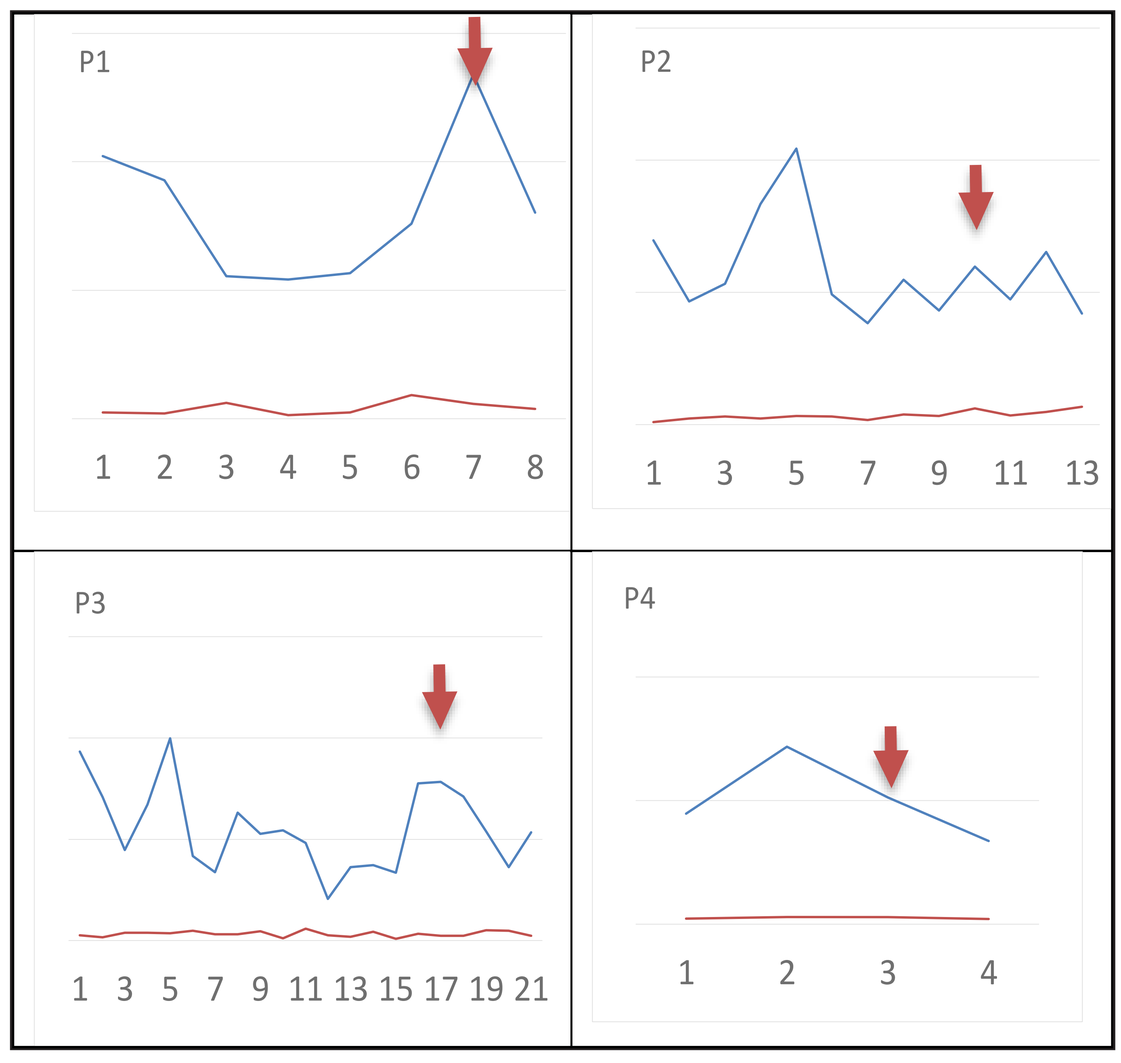
Patient	Gene defect	Clinical presentation
1 EB	Pending, (Normal Pterins and normal DHPR)	GDD, myoclonic jerks, hypopigmentation
2 AM	Pending, (Normal Pterins and normal DHPR)	Seizures, GDD, hypopigmentation
3 MA	PAH: c.472C>T / p.Arg158Trp	Irritability, GDD, hypopigmentation
4 P	PTS: .98A>G/p.Asp33Gly(het) c.201del / p.Gly7Alaf*25 (het)	Dystonia, delayed milestones, hypopigmentation

Plasma amino acids, urine organic acids, Vitamins B12 and D3 and clinical features were monitored at regular intervals as a part of their treatment process. All 4 patients were given LNAAs to provide approximately 30% of total protein intake (along with 40% from natural sources, 30% from PKU formula). Each sachet of LNAA powder (5g) contained 2.5g amino acids which included no phenylalanine (Manufactured by a local Company – Pristine Organics). Levels of Phe and Tyr before and after introduction of LNAA therapy were used for monitoring.

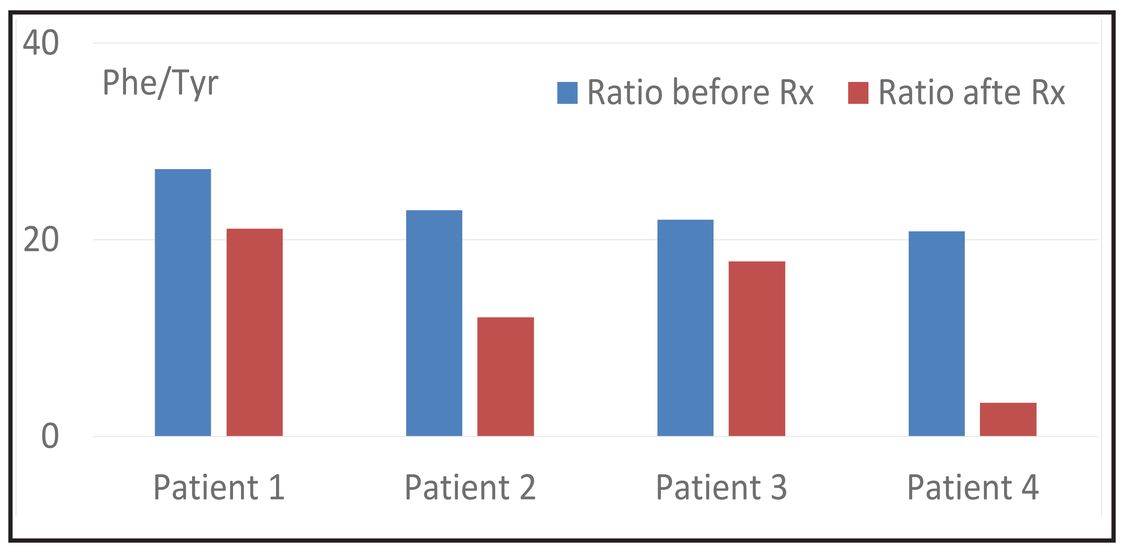
Results: LNAA were introduced to these 4 patients due to their non- compliance to the standard dietary therapy. LNAA was tolerated and accepted well by all. No side effects have been noted so far in any of these patients. Compliance was good. Clinical improvement was seen in all 4 patients in the form of reduced aggressiveness, reduced hyperactivity, reduced frequency of seizures, increased attention span and improved behavior (as reported by care- givers in each case). In patient 1 significant reduction in seizure frequency was observed within a week of LNAA therapy. Number of anti-convulsants was reduced to 2 from 4 in this patient. Patient with PTPS deficiency also showed reduced aggressiveness and improved behavior.

The levels of Phe in each of these patients before and after treatment with LNAA are summarized in the table and graphs below:

Patient	Age at diagnosis	Phe at diagnosis (µmol/L)	Age at start of LNAA	Phe before LNAA (µmol/L)	Phe after LNAA
P-1	7 months	1022	3 yrs	1340	802
P-2	1 yr	1393	6 yrs	2088	1194
P-3	2 yrs	1864	6 yr 3 mo	1996	1424
P-4	54 mo	1436	7 yr 7 mo	1026	673



There was reduction in levels of phenylalanine seen in all 4 patients after LNAA therapy. A longer follow up of these levels is necessary to ascertain the biochemical and clinical effect of this therapy. Levels of tyrosine did not differ much before and after the therapy. However, the ratio of Phe/Tyr was seen to be consistently reduced post LNAA therapy.



Ratio of Phe/Tyr decreased in all 4 patients on LNAA therapy

Conclusion: In 4 of our patients with PKU, LNAA was used in combination with low phe diet. Clinical improvement was seen in all 4 paediatric patients. Overall adherence to the therapy was excellent. Biochemically, significant improvement was observed in Phe/ Tyr ratios in each patient rather than individual levels (as these may also be influenced by total amino acids/ protein levels). In our experience LNAA therapy had good compliance and showed biochemical and clinical improvements in all 4 patients receiving the therapy.

Conflict of Interest: None

References:

1. van Spronsen FJ, de Groot MJ, Hoeksma M, Reijngoud DJ, van Rijn M. Large neutral amino acids in the treatment of PKU: from theory to practice. J Inherit Metab Dis 2010; 33:671-676
2. Matalon R, Michals-Matalon K, Bhatia G et al. Double blind placebo control trial of large neutral amino acids in treatment of PKU: effect on blood phenylalanine. J Inherit Metab Dis 2007; 30:153-58

Poster submitted to SSIEM, 2023, Jerusalem. Available on: www.metabolicerrors.com