



Case Report

Irreversible neurological effects of late diagnosis phenylketonuria: A case presentation

 Khyati Gupta,  Aviral Jain,  Vishal Dnyaneshwar Sawant,  Sushma Save

Department of Paediatrics, Topiwala National Medical College and B.Y.L Nair Charitable Hospital, Mumbai, India

Abstract

Phenylketonuria (PKU) is an autosomal recessive hereditary disorder due to deficiency of enzyme phenylalanine hydroxylase or the cofactor tetrahydrobiopterin. Its late manifestation leads to irreversible neurological changes. The aim of our work is to emphasize the difference in presentation in late diagnosis of the disease versus classical presentation making it difficult to correctly diagnose and also point out the reasons for late diagnosis and missed cases in India. A 9-year-old patient presented with global developmental delay and severe behavioral problems. Hypertonia and spasticity with low intelligence quotient (IQ) were seen. Baseline investigations such as renal function, thyroid function, electrolytes, uric acid, folate, and blood adrenocorticotropic hormone level were within range; hence, magnetic resonance imaging (MRI) was advised which revealed areas of bilateral demyelination suggesting metabolic leukodystrophy. PKU was thereafter confirmed with metabolic profile and clinical exome study. Early routine screening of all newborns for common inherited and metabolic disorders should be mandatory to later prevent irreversible damage. Cases of delayed diagnosis deviate considerably from classical clinical and radiological findings of the disease making correct and prompt diagnosis difficult. Education of parents and prenatal counseling should be encouraged.

Keywords: Irreversible neurological changes, metabolic leukodystrophy, new-born screening, phenylalanine, Phenylketonuria, restricted diet

How to cite this article: Gupta K, Jain A, Sawant VD, Save S. Irreversible neurological effects of late diagnosis phenylketonuria: A case presentation. Int J Med Biochem 2023; 6(2):133-136.

Phenylketonuria (PKU) is an inborn error in metabolism of amino acid phenylalanine, inherited in an autosomal recessive pattern. It is because of either deficiency of enzyme phenylalanine hydroxylase accountable for catalyzing the conversion phenylalanine to tyrosine or deficiency of enzyme dihydrobiopterin reductase needed to make active cofactor tetrahydrobiopterin needed in this reaction. This makes tyrosine an essential amino acid for the body. The circulating phenylalanine concentrations in classical PKU case are generally 10-fold higher (more than 1200 mmol/L) than that of an unaffected person. The severity of the clinical phenotype directly correlates with blood phenylalanine levels that reflect the degree of enzymatic deficiency. Prevalence of the disease varies across the globe due to disparity concern-

ing early screening in infants but it is highly curable. In the United States, PKU occurs in 1 in 10,000–15,000 new-borns. Prevalence in India is 0.6% [1]. Accumulated phenylalanine is diverted towards alternative pathways to generate phenylacetate (gives classic musty odor to urine), phenyl-lactate, and phenylpyruvate. In untreated patients, these biochemical metabolites get accumulated in the central nervous system and are hypothesized to cause neurological deficits and impaired transport of other aromatic amino acids like tryptophan. This disease shows the phenomenon of pleiotropy meaning one gene contributes to multiple phenotypic effects such as light skin, musty body odor, seizures, and intellectual disability. Strict adherence to diet restricted of phenylalanine is fortuitously deterrent against foreseen neurological complications.

Address for correspondence: Khyati Gupta, MD. Department of Paediatrics, Topiwala National Medical College and B.Y.L Nair Charitable Hospital, Mumbai, India

Phone: +9172655044 **E-mail:** khyatigupta9909@gmail.com **ORCID:** 0000-0003-0440-7986

Submitted: December 28, 2022 **Accepted:** February 01, 2023 **Available Online:** March 09, 2023

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



Supplementation with large number of neutral amino acids (includes tyrosine, tryptophan, threonine, methionine, valine, isoleucine, leucine, and histidine) is now a standard practice.

In this case report, we present the history of a 9-year-old child originally not a case of any known metabolic disorder who presented with global developmental delay, hyperactivity, aggressiveness, and irritability. He was incidentally suspected of a metabolic disorder on the basis of radiological findings which was later confirmed to be PKU.

Case Report

A 9-year-old child presented with complaints of hyperactivity, irritability, repetitive temper outbursts out of proportion to situation, head banging, stereotypical, vindictive, argumentative, and defiant behavior without any known triggering event. He was socially and academically lagging behind. Parents attested he eats by self but had decreased appetite and was unable go to the toilet and undress himself. He had to be kept reception in fear of him wandering off. He had no complaints of fever, seizures, visual symptoms, or untoward infections.

The child was born out of non-consanguineous marriage by lower segment caesarean section and antenatal history was uneventful. The child has signs of developmental delay noted on all four domains, that is, gross motor, fine motor, language, and social. On clinical evaluation, severe global developmental delay with a developmental quotient of 25 (Normal >75) was noted. Head circumference is 48 cm, height is 106 cm, weight is 21.2 kg and skin examination normal.

Neonatal history is as follows: The child started sitting with support at 2 years, stand without support at 4 and a half years, and walking without support at 5 years of age. He could climb up and down the stairs at 6 years of age. At present, he is only able to speak bisyllabic words. Fine motor could not be assessed.

On questioning, history of hypopigmented skin, spasticity, and below average intelligence quotient (IQ) was present in child's paternal uncle (father's brother).

On examination, the child was oriented to time, place and person, conscious, and cooperative with no cranial nerve deficits. CNS examination revealed hypertonia and spasticity in all four extremities, power >3/5 which is active movement of limbs against gravity and reflexes 3+(brisk). Systemic examination was unremarkable.

With history of developmental delay, positive family history of suspected metabolic disorder, spasticity, behavioral issues, and poor intellectual functioning child was subjected to thyroid function tests which were normal, as were other routine investigations such as renal function, electrolyte, uric acid, folate, and blood adrenocorticotrophic hormone level. His IQ testing showed IQ of 70 that is below average (70–84) and radiological evaluation was advised.

Figure 1 shows multiplanar magnetic resonance imaging (MRI) of the brain which revealed hyperintense signal intensity in bi-

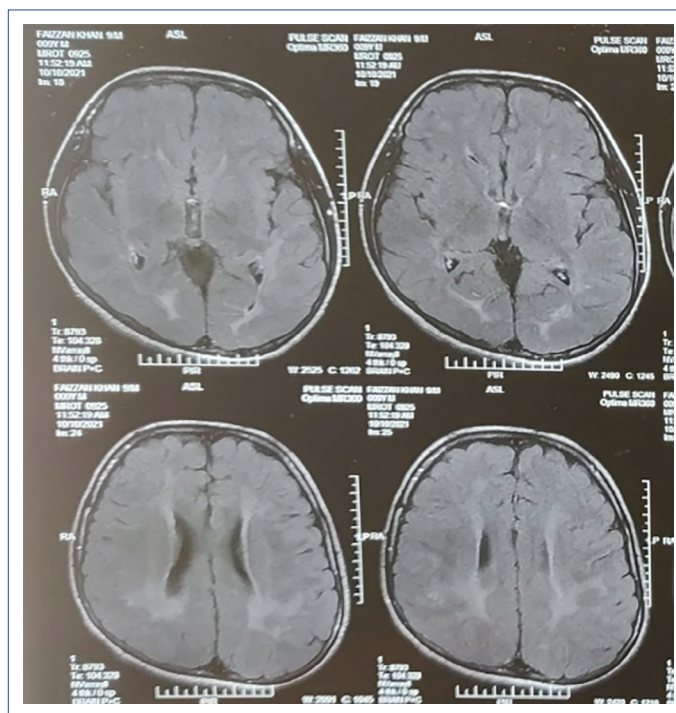


Figure 1. Symmetrical T2 and FLAIR hyperintense signal involving the bilateral fronto-parietal and occipital white matter showing areas of restricted diffusion without post-contrast enhancement.

lateral frontal and parieto-occipital white matter representing dysmyelination/delayed myelination in a T2-weighted image suggestive of metabolic leukodystrophy.

Metabolic profile was sent which confirmed elevated phenylalanine levels of 1125 $\mu\text{mol/L}$. Clinical exome study done there after demonstrated pathogenic variant causative of the reported phenotype- PAH (-) variant c.712A>C (p.Thr238Pro) homozygosity at exon 7 pointing toward PKU and/or non-PKU mild hyperphenylalaninemia.

With the golden therapeutic window of opportunity being lost in our patient to abate irreversible neurological changes along with financial barriers, educating, and counseling, the parents proved to be arduous. Since then, our patient is on a phenylalanine-restricted diet and after 1 month of following the diet blood phenylalanine levels dropped to 290 $\mu\text{mol/L}$ on average. Behavioral complaints have partially amended with risperidone therapy (2 mg OD). Spasticity has resolved with baclofen and regular physiotherapy. However, on 6-month follow-up, the developmental deficits persist and repeat brain MRI shows no changes.

Discussion

The gene encoding PAH is located on chromosome 12 consisting of 13 exons, 12 introns, covering a total of 100 Kb of genetic data and currently, more than 1000 mutations are known in this gene, majority of them being missense. The incidence of PKU varies from 1:10,000 to 1:16,000 throughout the world. It differs from most other causes of intellectual disability by

the possibility of complete cure. However, lack of new-born screening protocols in India and unreliable false-negative results can result in missed diagnoses and rare cases of late diagnosed PKU [2]. The timing of specimen collection in infants is an issue up for discussion. Collecting specimen too early and failure to conduct repeat screenings can lead to missed cases [3, 4]. Hence, formulation of a follow-up policy of infants with incomplete test or positive results should be emphasized [4].

The most striking part about our case is that such a preventable cause of developmental delay was allowed to manifest because of failure to conduct a routine screening test. In the USA, new-borns mandatorily undergo heel-prick test for screening and a phenylalanine value over 1200 $\mu\text{M/L}$ (with a Phe/Tyr ratio >2) is diagnostic. At present, there is no national new-born screening program in India.

Another reason of substantial delay in diagnosis in our case was that the child presented with atypical behavioral symptoms which were not classic of metabolic disorders. Typically, new-borns presenting with PKU have classical features of musty body odor, hypopigmented skin, fair hair, eczema, and seizures. Failure of early diagnosis leads to irreversible neurological deficits and more behavioral complaints such as aggressiveness, temper tantrums, and stereotypical behavior along with global developmental delay like in our case deviating from the classical signs and symptoms. Many of his presenting complaints were actually suggestive of attention deficit hyperactive disorder (ADHD), a common diagnosis in children before 12 years of age, had it not been for his delayed milestones and cognitive disabilities. Interestingly, the literature suggests there is a hypodopaminergic state created in both these disorders causing individuals with PKU to have a greater chance of developing ADHD; however, no definite relation has been identified yet. Furthermore, intellectual disability is present in both early treated as well as untreated patients and IQ scores are related to patient's age at the time of treatment initiation as suggested by various studies [5]. Most of the patients benefit hugely from the introduction of the restricted diet; improvement of motor function and more responsiveness are usually the main positive outcome changes [6]. However, in late diagnosed cases of PKU, non-response to dietary therapy is more common and guidelines suggest to consider possible relaxation or discontinuation of dietary management after a 6-month period of no clinical or behavioral improvement [6–8].

Of note in our patient is the bilateral frontal and occipitoparietal areas of demyelination on brain MRI which led to the diagnosis of PKU. These changes correspond with the pathologic process and progression of the disease and indirectly show the current phenylalanine levels in the patient to tell us how the anomalous changes can be visualized with neuroimaging studies. The exact mechanism by which neurologic impairment occurs is still debated. While some studies suggest direct toxic effect of accumulated phenylalanine on oligodendrocytes causing demyelination, others argue that it is the damage to axonal maturation that

is reflected as secondary demyelination [9, 10]. A comprehensive meta-analysis correlating MRI and CT changes in PKU patients can prove to be helpful in uncovering some of these mysteries in the future.

With dietary obedience of circumventing food containing phenylalanine and also artificial sweeteners like aspartame which are known to contain phenylalanine, improvement in the MRI findings is seen in some cases [10]. Other treatment modalities are BH4, large neutral amino acids, casein glycomacropeptide, phenylalanine ammonia lyase, and gene therapy [11]. In late diagnosis cases, there is a heightened need for individualized treatment.

Conclusion

Early screening for common genetic disorders among new-borns is a necessity to get ahead of the disease and curb its imminent complications to ensure a far better quality of life. Cases of delayed diagnosis deviate considerably from classical clinical and radiological findings of the disease making correct and prompt diagnosis difficult. Inborn error of metabolism disorders should be considered in any child displaying signs of developmental delay and neuropsychiatric symptoms. Metabolic screening tests should be promptly done in children with mental retardation and behavioral problems of unknown origin in countries where new-born screening is not available. Educating parents and prenatal counseling along with treatment standardization are a must. Potentially curable treatment options such as enzyme replacement therapy and gene therapy should be made available to all people.

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – V.D.S., A.J., K.G.; Design – K.G., V.D.S.; Supervision – S.S.; Materials – K.G., A.J.; Data collection &/or processing – K.G., A.J.; Analysis and/or interpretation – K.G., V.D.S., A.J., S.S.; Literature search – V.D.S., K.G.; Writing – K.G., A.J.; Critical review – S.S.

References

1. Krupanidhi I, Punekar BD. A study of the incidence of phenylketonuria in India. *Indian J Med Res* 1963;51:696–702
2. Loukas YL, Soumelas GS, Dotsikas Y, Georgiou V, Molou E, Thodi G, et al. Expanded newborn screening in Greece: 30 months of experience. *J Inher Metab Dis* 2010;33(Suppl 3):S341–8.
3. Holtzman C, Slazyk WE, Cordero JF, Hannon WH. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. *Pediatrics* 1986;78(4):553–8. [CrossRef]

4. Webster D. Quality performance of newborn screening systems: strategies for improvement. *J Inherit Metab Dis* 2007;30(4):576–84. [\[CrossRef\]](#)
5. Mazlum B, Anlar B, Kalkanoğlu-Sivri HS, Karlı-Oğuz K, Özusta Ş, Ünal F. A late-diagnosed phenylketonuria case presenting with autism spectrum disorder in early childhood. *Turk J Pediatr* 2016;58(3):318–22. [\[CrossRef\]](#)
6. Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier DM, et al; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med* 2014;16(2):188–200. [\[CrossRef\]](#)
7. Singh RH, Cunningham AC, Mofidi S, Douglas TD, Frazier DM, Hook DG, et al. Updated, web-based nutrition management guideline for PKU: An evidence and consensus based approach. *Mol Genet Metab* 2016;118(2):72–83. [\[CrossRef\]](#)
8. Abadie V, Berthelot J, Feillet F, Maurin N, Mercier A, de Baulny HO, et al. Consensus national sur la prise en charge des enfants dépistés avec une hyperphénylalaninémie Management of phenylketonuria and hyperphenylalaninemia: the French guidelines. *Arch Pediatr* 2005;12(5):594–601. [\[CrossRef\]](#)
9. Dyer CA, Kendler A, Philibotte T, Gardiner P, Cruz J, Levy HL. Evidence for central nervous system glial cell plasticity in phenylketonuria. *J Neuropathol Exp Neurol* 1996;55(7):795–814.
10. Reynolds R, Burri R, Herschkowitz N. Retarded development of neurons and oligodendroglia in rat forebrain produced by hyperphenylalaninemia results in permanent deficits in myelin despite long recovery periods. *Exp Neurol* 1993;124(2):357–67.
11. Chen S, Zhu M, Hao Y, Feng J, Zhang Y. Effect of delayed diagnosis of phenylketonuria with imaging findings of bilateral diffuse symmetric white matter lesions: a case report and literature review. *Front Neurol* 2019;10:1040. [\[CrossRef\]](#)