Indian Journal of Pediatrics (August 2023) 90(8):839
https://doi.org/10.1007/s12098-023-04654-1

SCIENTIFIC LETTER

A Rare Genetic-Metabolic Cause of Epileptic Spasms: Dihydropyrimidine Dehydrogenase Deficiency

Vykuntaraju K. Gowda[1] · **Varunvenkat M. Srinivasan**[1]

Received: 26 February 2023 / Accepted: 2 May 2023 / Published online: 19 May 2023

To the Editor: Dihydropyrimidine dehydrogenase deficiency (DPD) is an autosomal recessive disorder due to *DPYD* gene mutations [1, 2]. Phenotypes can range from asymptomatic to severe neurological disorders with no genotype-phenotype correlation [3].

A 4-y-old male born to non-consanguineous marriage presented with seizures from the newborn period. Despite treatment with multiple antiseizure medications (ASMs), he had seizure episodes once in 20-30 d. He developed epileptic spasms in the 5th month with incomplete response to steroids and vigabatrin. At 20 mo he developed tonic seizures and was diagnosed with Lennox Gastaut syndrome (LGS) based on clinical and electrophysiology evidence and was treated with ASMs with partial response. There was only mild improvement in his development: he attained sitting and recognizing his parents. On examination, the child has microcephaly (<3 Z score), normal weight, and length, and hypotonia with brisk deep tendon reflexes.

Investigations revealed normal liver and renal function tests, arterial lactate, ammonia, arterial blood gases, and tandem mass spectrometry. MRI brain showed mild cerebral atrophy. EEG showed modified hypsarrhythmia. Urinary GCMS showed a 25.74-fold elevation of Uracil-2 with 180.19% (reference: 0.00-7.00%) and Thymine at 117.12% (Peak at 13.17 minu). Whole exome sequencing showed two pathogenic heterozygous variants c.1905+1G>A and c.851-1G>C in the *DPYD* gene and upon Sanger sequencing showed segregation with the disorder in the family. The child still has frequent seizures despite multiple ASMs. The differential diagnosis considered was developmental epileptic encephalopathies and other metabolic disorders. There are no Indian reports on the disorder but the *DPYD* gene variants are reported in the context of 5-fluorouracil toxicity in cancer patients [4].

There is no definitive therapy but one should avoid 5-fluorouracil. To conclude, DPD deficiency should be suspected in cases with urinary excretion of Uracil and Thymine on the background of refractory seizures including West syndrome and LGS.

Declarations

Conflict of Interest None.

References

1. Canellakis ES. Pyrimidine metabolism. I. Enzymatic pathways of uracil and thymine degradation. J Biol Chem. 1956;221:315–22.
2. Daher GC, Harris BE, Diasio RB. Metabolism of pyrimidine analogues and their nucleosides. Pharmacol Ther. 1990;48:189–222.
3. Van Kuilenburg AB, Vreken P, Abeling NG, et al. Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. Hum Genet. 1999;104:1–9.
4. Saif MW, Mattison L, Carollo T, Ezzeldin H, Diasio RB. Dihydropyrimidine dehydrogenase deficiency in an Indian population. Cancer Chemother Pharmacol. 2006;58:396–401.

✉ Vykuntaraju K. Gowda
drknvraju08@gmail.com

[1] Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Near NIMHANS, Bengaluru, Karnataka 560029, India