Case Study: Pyridox(am)ine-5’-phosphate oxidase deficiency

Clinical Overview:
A 4-month-old male presents to clinic with a history of intractable neonatal seizures and status epilepticus. His parents reported no family history of similar symptoms. The GeneDx infantile epilepsy panel, which includes sequencing and deletion/duplication analysis of 38 genes, was ordered. A homozygous PNPO missense mutation was identified, consistent with a diagnosis of pyridox(am)ine-5’-phosphate oxidase (PNPO) deficiency. This finding not only establishes the correct diagnosis but also allows effective treatment for the patient, as seizures caused by PNPO deficiency resolve with administration of pyridoxal-5’-phosphate (PLP).1,2

Patient Information:
Age: 4 months Specimen: Blood
Referral diagnosis: Neonatal seizures, status epilepticus
Family history: No known family history of similar symptoms

Diagnostic Summary:
POSITIVE. Homozygous Arg225Cys mutation in the PNPO gene.

Infantile Epilepsy Panel: Sequence analysis and deletion/duplication analysis of 38 genes revealed the homozygous Arg225Cys mutation in the PNPO gene. This mutation has not been identified in approximately 5,000 individuals of European or African American ethnicity, indicating that it is not a common benign variant in these populations.3 Additionally, it alters an amino acid residue that is critical for normal enzyme function.4 Mutations in the PNPO gene cause autosomal recessive pyridox(am)ine-5’-phosphate oxidase (PNPO) deficiency.1 Individuals with PNPO deficiency have decreased cerebrospinal fluid (CSF) levels of pyridoxal-5’-phosphate (PLP) and may also exhibit abnormal CSF, urine, and/or plasma levels of specific neurotransmitters and amino acids due to secondary dysfunction of enzymes that require PLP as a cofactor.5,6 The clinical presentation is characterized by early-onset, severe epileptic encephalopathy with onset typically in the first few days of life.1 PNPO deficiency is believed to be a very rare cause of neonatal seizures, and only a small number of cases have been reported in the published literature. Importantly, receiving this molecular diagnosis immediately impacts treatment, which can improve the outcome of the patient.1,2

Diagnostic Implications:
There are many different causes of epilepsy, including genetic disorders, metabolic diseases, and structural brain abnormalities. Knowing the genetic cause of an individual’s seizures can clarify the prognosis, assist in treatment and management of the patient, and predict the risk of a disease in family members. In the case of PNPO deficiency, seizures do not respond to treatment with anticonvulsants or pyridoxine but resolve with administration of PLP.1,2 This patient was started on PLP shortly after receiving the GeneDx test results and was responding to therapy within 4 days. He has now started cooing, looking around and making eye contact, and moving his limbs. His seizures dramatically improved and his EEG normalized, though he is still having occasional clusters of spasms. Additionally, knowing the genetic cause provides the family with a more accurate estimate of the risk of having another child with the same disease.

References: