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Expanding the clinical spectrum of asparagine synthetase deficiency

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Background: Asparagine and glutamate are synthesized from aspartate and glutamine using the enzyme asparagine synthetase. A deficiency of this enzyme leads to asparagine synthetase deficiency (ASNSD). ASNSD is an autosomal recessive progressive neurological disorder classically characterized by congenital microcephaly, early onset epileptic encephalopathy, and developmental delay or regression. Seizures are typically present at birth but have been reported to start as late as 9 months of age. Asparagine levels may be low or normal in the serum but have been reported to be low or absent in the CSF. The diagnosis is made through molecular testing. Brain imaging may reveal cerebral atrophy, small pons, delayed myelination and simplified gyri. No treatment is available, and it is thought that most therapies would not be effective as deficiency of asparagine synthetase affects neuronal development during both the embryonic and postembryonic periods. Asparagine supplementation has been trialed, but with negative consequences in some patients. It is reported that seizures may respond well to valproate therapy due to a decrease in aspartate release at excitatory nerve terminals. Drugs that target NMDA or AMPA receptors may also be considered in the management of refractory seizures in ASNSD.

Case presentation: We present a 3-year-old male diagnosed with asparagine synthetase deficiency due to biallelic variants in *ASNS* with associated microcephaly, developmental delay, recurrent seizure episodes in the setting of illness, and oral texture aversion. Perinatal history was unremarkable with the exception of nuchal thickening noted on antenatal ultrasound. Of note, microcephaly was not reported prenatally. His newborn screen was normal.

He initially presented at the age of 9 months with gross motor delays. His first seizure episode was at the age of 11 months in the context of a febrile illness due to adenovirus. His first seizure was focal with unilateral weakness, but this was followed by subsequent generalized seizures in the setting of febrile illnesses. His seizures are now controlled on Keppra. His initial routine electroencephalogram (EEG) was normal, but a subsequent 36-hour video EEG was abnormal with diffuse slowing, intermittent rhythmic slow waves and sharp waves. EEG patterns may vary in patients with ASNSD, but disorganization and intermittent sharp waves have been reported consistently. HIs brain MRI revealed parenchymal volume loss with otherwise normal anatomy. Mild regression of motor skills was noted following seizure episodes, but these skills were regained, and he continued to have developmental progression. He was also noted to have expressive and receptive speech delays and is only able to babble at the age of 3 years. Family history was noncontributory. His weight gain and linear growth were stable. The physical exam findings of hypotonia, hyperreflexia, and microcephaly were consistent with ASNSD. At birth, his head circumference was –0.9 SD, and has now progressed to –2.8 SD on the CDC growth curves. The patient also has mild bilateral myopic astigmatism and pseudo strabismus. Attempts at audiology evaluation have been unsuccessful, and evaluation under sedation is being avoided at this time due to potential risk of neurological decline.

The diagnosis was made on the basis of a paternally inherited pathogenic (c.1192dupT) variant and a maternally inherited likely pathogenic (c.614A>C) variant in *ASNS* (NM_133436.3) detected on an epilepsy panel at a commercial lab. Both variants have not been previously reported in other affected individuals. The pathogenic frameshift variant is predicted to result in protein truncation or nonsense mediated decay. The likely pathogenic missense variant is predicted to be deleterious in computer models. Plasma amino acids were normal with normal glutamate and asparagine levels. CSF amino acids were not obtained.

Conclusion: We present a patient with a mild phenotype of asparagine synthetase deficiency. Our patient did not have onset of seizure-like activity until the age of 11 months which is the latest onset of seizures in this disease reported to our knowledge. His seizures have also been controlled on Keppra. Our patient was identified via an expanded seizure panel, suggesting that the addition of ASNS to seizure panels may lead to the diagnosis of more patients with a mild form of ASNSD. Most patients previously reported were diagnosed via exome sequencing, which may not be pursued for patients with mild phenotypes. These patients may be more amenable to therapy with common antiepileptics, but there continues to be a lack of therapy available for the underlying disorder. Severe phenotypes are expected to be associated with compromised protein function or protein truncation, so we hypothesize that the maternally inherited likely pathogenic variant may have some residual function leading to the milder phenotype. At this time, we are avoiding procedures requiring sedation, but if there is medical necessity for sedation in the future, we will consider obtaining an MR Spectroscopy and/or CSF amino acids at that time.

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ePO21

Case report of a Mexican family with alpha mannosidosis and a novel probably pathogenic variant in the *MAN2B1* gene

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Background: Alpha-mannosidosis (AM: OMIM #248500) is an ultra rare autosomal recessive lysosomal storage disorder characterized by a low enzymatic activity of α-Mannosidase.

The disorder is characterized by a range of progressive clinical phenotypes, mainly, intellectual disability (ID), psychiatric symptoms, hearing impairment, coarse facial features, skeletal changes, recurrent otolaryngological and pulmonary infections (immunodeficiency), and asthma. AM has been classified in 3 types in order to describe its clinical presentation. Type 1 is the mildest form, with onset after age 10 years, without skeletal abnormalities and very slow progression. Type 2 is a moderate form, with onset before age 10 years, presence of skeletal abnormalities and slow progression with development of ataxia by age 20 to 30 years. Type 3 is the severe form, with onset in early infancy, skeletal abnormalities, and obvious progression leading to early death from primary central nervous system involvement or myopathy. Most patients correspond to clinical type 2. Despite the clinical heterogeneity of the disorder, there are no apparent genotype/phenotype correlations.

The *MAN2B1* gene is located to chromosome 19p13.13, spans 21.5 kbp, and consists of 24 exons. 130 pathogenic or probably pathogenic *MAN2B1* variants spread along the gene have been identified in AM patients; the variants include insertions, deletions, duplications, and nonsense, splice site and missense variants. Most of these variants are private, just one missense variant (c.2248C>T, p.Arg750Trp) has been found in 18 patients from eight different countries. Our aim is to describe a familial case of AM from a clinical, biochemical and molecular point of view in a Mexican family with two affected cases.