ePO20

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.

https://doi.org/10.1016/j.gim.2022.01.058

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.

Case presentation: Patient 1
The proband is an 11-year-old girl, second child of healthy non-consanguineous parents of Mexican-Mestizo origin (Northern Mexico). She has a family history of a younger brother similarly affected. She was born at 39 weeks of gestation following a normal pregnancy; birth weight was 3,710 g (>90th centile), and height of 57 cm (>90th centile). She began crawling at 12 months, walking at 24 months and said her first word at 5 years. Bilateral moderate hearing loss was diagnosed at 9 years old following a history of recurrent otitis in infancy. The physical examination showed height of 138 cm (5th centile), weight of 3,680 g (25th centile), and head circumference of 50.5 cm (<3th centile), language delay, coarse flat facies, broad forehead with prominent metopic suture, thick eyebrows, oblique upward palpebral fissures, telecanthus, and blue nevus on sclerae, anteverted nostrils, dental anomalies, hypertrichosis, lubar blue spots, prominent abdomen, hepatomegaly and skeletal anomalies.
Patient 2
This is a 6-year-old boy, brother of patient 1, who was born at 35 weeks of gestation following an uncomplicated pregnancy. At birth he presented respiratory distress, the weight was 2,800 g (50th centile) and length was 52 cm (>90th centile). He began walking at 25 months and at present days he is not able to talk. He has history of bilateral inguinal hernia, recurrent otitis, hypoacusia and tonsillectomy. The physical examination showed somatometry in normal percentiles, language delay, coarse facies, dolichocephaly, broad forehead with frontal protuberances, blue nevus on sclerae, flat nasal tip, telecanthus, mid-facial retrution, hypertrichosis, blue dorso-lumbar spots, prominent abdomen, hepatomegaly and skeletal anomalies.
According to the clinical features, AM type 2 was suspected; therefore, an enzymatic determination of leukocyte alpha-mannosidase (E.C. 3.2.1.24) was performed in the patient and his sister. The residual enzyme activity was found to be decreased (6%: 3.57 nMol/mg prot/h; ref: 56.53 - 200.42 nMol/mg prot/h). *MAN2B1* gene was analyzed using the massive sequencing technique based on amplicon sequencing. The amplicons cover both the coding region and the highly conserved exon-intron junctions. The minimum coverage for each amplicon is >20x. The reference sequence is: MAN2B1: NM_000528.3.
A homozygous duplication of a cytosine at position 89 (c.89dup, p.Pro31Thrfs*43) was identified in both patients, which causes a change in the reading frame from codon 31 and a termination codon 42 positions forward.
Conclusion: The worldwide prevalence of AM is estimated in 1/500,000–1/1,000,000 live births. Most of the patients have been reported in Germany, United States, United Kingdom, Turkey and Poland. This disease is widely underdiagnosed, particularly in Latin American countries. The prevalence of AM in Mexico is unknown. The present familial case is the first reported in our country.
Alpha-mannosidose deficiency was confirmed in this case by gold standard study and by molecular study. The *MAN2B1*: c.89dupC variant does not have a clinical designation in public databases, however, based on established guidelines it can be classified as a probably pathogenic as it is a loss-of-function variant that has not been reported in any population.
The differential diagnosis includes other lysosomal storage diseases such as mucopolysaccharidoses (MPS) and Gaucher's disease; it is therefore advisable to include a α-mannosidase testing for all patients suspicious to MPS but with a negative MPS test result.
AM although rare, should be considered in the approach to a child with hearing loss, dysmorphism, ID, skeletal deformities, and visceromegaly.
The early detection of the disease, allows, besides accurate genetic counselling, better therapeutic management, since it is currently treatable with enzyme replacement therapy (velmanase alfa). Access to early treatment brings great benefits to patients relieving some severe manifestations, improving the quality of life.

https://doi.org/10.1016/j.gim.2022.01.059

eP022

Action myoclonus-renal failure syndrome: An atypical storage disorder with a treatment dilemma

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Background: Action myoclonus-renal failure syndrome (AMRF) is a rare, autosomal recessive form of progressive myoclonic epilepsy associated with renal dysfunction, ranging from proteinuria to nephrotic syndrome and end stage renal disease, peripheral demyelinating polyneuropathy, and sensorineural hearing loss. *SCARB2*, the causative gene, encodes lysosomal-membrane type 2 protein (LIMP-2), a transmembrane protein responsible for trafficking of beta-glucocerebrosidase (GCase) to the lysosomes. LIMP-2 is particularly essential to GCase trafficking in neuronal cells, and in brains of LIMP-2 deficient mice, the significant reduction in GCase activity led to lipid storage, disturbed lysosomal function, and alpha-synuclein accumulation leading to neurotoxicity. although its necessity is somewhat tissue-dependent. Thus, *SCARB2* pathogenic variants result in a shortage of GCase in lysosomes, similar to the pathology underlying Gaucher disease (GD), and yet affected patients have a vastly different phenotype to GD.
AMRF typically starts presenting in the late teens to early twenties, and is rapidly progressive, with most patients surviving only 7 to 15 years after symptoms first develop and succumbing to complications of aspiration pneumonia and renal failure. Typically, patients with AMRF are managed symptomatically with antiepileptics for myoclonus and seizure prevention, physical therapy, and dialysis or kidney transplantation for renal insufficiency, however these do not improve neurologic disease.
We report a case of AMRF in a young adult male and discuss the theoretical basis for treatment with substrate reduction therapy classically used in GD.
Case presentation: Our patient, a male of Gambian descent, initially presented at 24 years old with imbalance, falls, and jerking movements in his arms, legs, and jaw. Over time, the intensity and frequency of these symptoms increased. He was admitted to an outside hospital for a seizure-like episode which started during sleep, and video EEG was suggestive of myoclonic epilepsy. Head CT and MRI were normal. EMG showed evidence of conduction blocks, with some motor and sensory axon loss, and he was diagnosed with demyelinating polyneuropathy. An epilepsy gene panel was obtained by his neurologist, which revealed *SCARB2* homozygous pathogenic variants (NM_005506.4(SCARB2):c.956del (p.Leu319fs). The patient denied any family history of AMRF or other hereditary disorders. He was started on valproic acid and levetiracetam and had no further seizures.
The patient was referred to our clinic for evaluation and discussion of possible treatment for a lysosomal storage disorder. On our exam, he had tongue fasciculations, jerking movements of the face and jaw while speaking, and dysarthria. He had a resting tremor of the upper extremities and feet, and he had cerebellar signs with dysmetria and poor coordination with rapid alternating movements. His gait was stable, but he was unable to do heel-to-toe walk without losing balance. He reported difficulty chewing and progressive proximal muscle weakness. He was hypertensive and endorsed foamy-appearing urine.
He was found to have an elevated serum creatinine, microscopic hematuria, and moderate albuminuria, and we referred him to nephrology for further evaluation. A subsequent kidney biopsy showed diffuse podocytopathy without deposits in the glomeruli. A renal ultrasound showed mildly echogenic kidneys, consistent with nonspecific parenchymal disease. An audiology exam was normal. On follow-up several months later, the patient's dysarthria had worsened,