NeoReviews™

NeoQuest January 2022: Hypotonic Infant with Seizures

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Article type: Resources

A male infant is delivered by cesarean section at 37 weeks' gestation for decreased fetal movement. Physical exam is notable for small for gestational age size, lethargy, global hypotonia, weak cry, liver edge palpated 2 cm below right costal margin, and facial dysmorphisms (Figure 1A). Biochemical analysis reveals no electrolyte derangements, a normal serum ammonia level, and an elevated direct bilirubin level. The head ultrasound demonstrates pseudocysts of the germinal matrix (Figure 1B; white arrows) and ventriculomegaly (Figure 1C; black arrows).

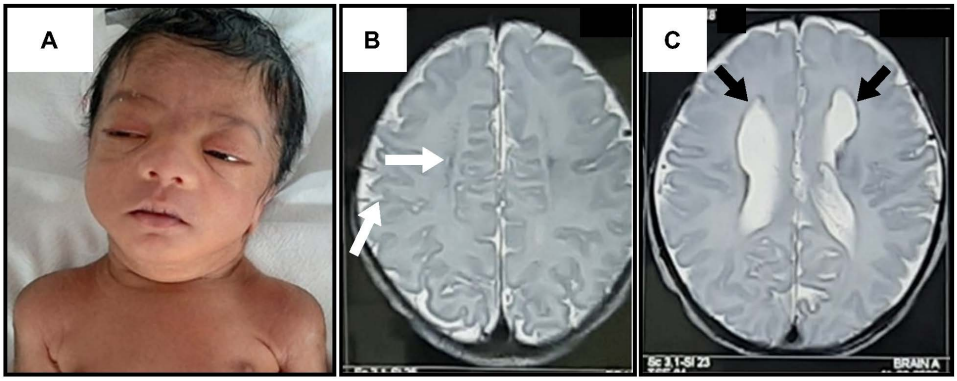

Figure 1. Phenotypic and clinical features of the described infant. A) Facial dysmorphisms include low-set ears, hypertelorism, periorbital edema, flattened nasal bridge, and nuchal redundancy. Head ultrasound findings include B) germinal matrix pseudocysts (white arrows) and C) bilateral ventriculomegaly (black arrows). Adapted from: A Floppy Infant with Facial Dysmorphism. Kumar P, Nerakh G, Katam P, Oleti TP, Pawar S. *Neoreviews*. 2022;23(1):e45–e48. [1]

At one month of age, he develops seizure activity. This condition would most likely be considered a disorder of:

A. Branch-chain amino acid breakdown
B. Lysine degradation
C. Peroxisome biogenesis
D. Phosphomannomutase 2 activity
E. Plasma citrulline accumulation

Answer: C. Peroxisome biogenesis

Explanation:

The infant in this case presents with features of a peroxisome biogenesis disorder (PBD) **(Option C)**. PBDs are rare autosomal recessive disorders characterized by mutations in *PEX* genes, which encode peroxin

proteins involved in the biosynthesis, assembly, and biochemical function of peroxisomes.[2] The neonate described in the vignette has a diagnosis most consistent with Zellweger spectrum disorder (ZSD), a PBD with a range of symptoms in the neonatal period, including craniofacial dysmorphisms, seizures, hepatomegaly, cataracts, sensorineural hearing loss, failure to thrive, and skeletal anomalies **(Figure 2)**.[2–4] The initial diagnosis of PBDs, such as ZSD, includes the detection of elevated very long-chain fatty acids (VLCFA). Elevations of C26:0 and C26:1 fatty acids are most consistent with a peroxisomal fatty acid β-oxidation defect.[2,5] Additional studies to identify defects in peroxisome enzyme pathways include measurement of methyl-branched fatty acids phytanic and pristanic acids, erythrocyte plasmalogens, pipecolic acid in plasma or urine, and bile acid intermediates dihydroxycholestanoic acid and trihydroxycholestanoic acid in plasma or urine.[2,5]

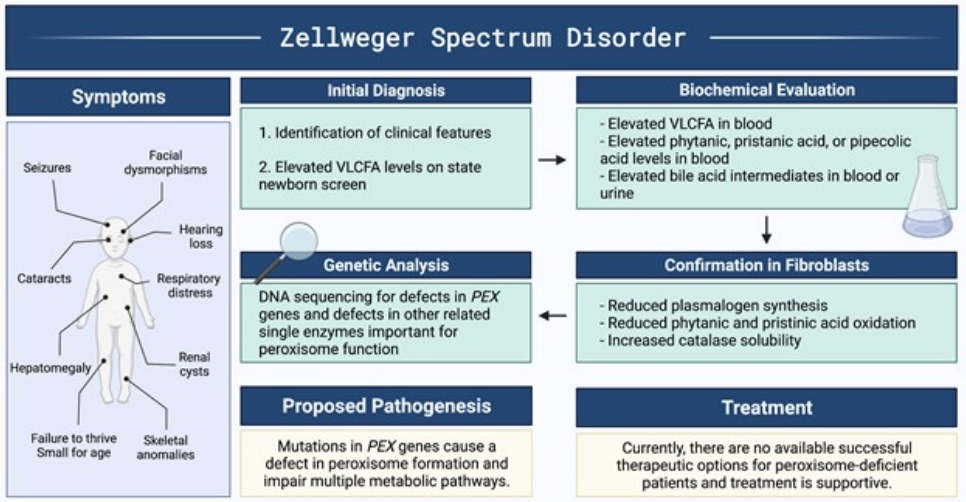

Figure 2. Symptoms, diagnosis, evaluation, pathogenesis, and treatment of Zellweger Spectrum Disorder. Figure created with Biorender.com.[2,5]

Biochemical analysis of patient-derived fibroblasts obtained by skin biopsy and genetic testing is also recommended for the diagnosis of ZSD, as *PEX* mutations can be associated with mild or no elevation in VLCFA.[2] Further, elevated VLCFA have been implemented in blood spot samples in newborn screens as an approach to diagnose X-linked adrenoleukodystrophy (X-ALD), a related PBD.[2] Therefore, newborn screening for X-ALD (performed in select states: https://aldconnect.org/newborn-resources) may also detect ZSD cases with increased blood VLCFA levels. Currently, there are no available successful therapeutic options for peroxisome-deficient patients, and treatment is largely supportive.[2,5]

Seizure activity, encephalopathy, and systemic symptoms can also be seen in neonates with inborn errors of metabolism involving the defective breakdown of branch-chain amino acids, such as maple syrup urine disease (MSUD) **(Option A)**.[6,7] However, infants with organic acidemias such as MSUD typically also present with signs of metabolic acidosis, which were not observed in the infant in this vignette.[6,7]

Defects in the lysine degradation pathway are characteristic of pyridoxine-dependent epilepsy **(Option B)**, a vitamin-responsive form of neonatal epilepsy associated with *ALDH7A1* gene mutations.[8] Pyridoxine-dependent epilepsy is caused by a deficiency of alpha-aminoadipic semialdehyde dehydrogenase in the lysine degradation pathway, resulting in an accumulation of alpha-aminoadipic semialdehyde, piperideine-6-carboxylate, and pipecolic acid. Though associated with dystonia and developmental delay, pyridoxine-responsive seizures do not typically present with facial dysmorphisms or other systemic symptoms.[6]

Deficient phosphomannomutase 2 (PMM2) enzyme activity is an autosomal recessive congenital disorder of glycosylation **(Option D)**. PMM2 mutations result in abnormally glycosylated proteins in organs and tissues.[9] Characteristic physical features of PMM2 deficiency include an underdeveloped cerebellum, inverted nipples, and abnormal fat distribution, which were not present or described in the infant in this case.[9] Beyond the neonatal period, cases of PMM2 deficiency are associated with hypotonia, liver failure, renal cysts, craniofacial dysmorphisms, seizures, pericardial effusions, and coagulopathy.[9]

Infants with an increased plasma concentration of citrulline may also exhibit lethargy and seizure activity, which is characteristic of urea cycle defects (UCDs) **(Option E)**. Increased citrulline levels are associated with UCDs, such as argininosuccinic acid synthetase deficiency and argininosuccinic acid lyase deficiency.[6,7,10] However, UCDs are strongly associated with an increased plasma ammonia concentration, which was not detected or described in the infant in this vignette.[6,7]

Did you know?

The triad of cortical malformations of the perisylvian and perirolandic regions, hypomyelination, and subependymal germinolytic cysts on fetal brain MRI is highly suggestive of a diagnosis of ZSD.[3]

What are the characteristic brain MRI features of infants with metabolic disorders?

For a review of metabolic syndromes with characteristic structural malformations of the brain, refer to: Kaur et al. Genetic etiologies of neonatal seizures. *Neoreviews.* 2020;21(10):e663–e672 [8]

What other metabolic disorders should be suspected in an infant with neonatal seizures?

For a comprehensive overview of the metabolic etiologies of neonatal seizures and the approach to their diagnosis, refer to: Niemi, A. Neonatal presentations of metabolic disorders. *Neoreviews.* 2020;21(10):e649–e662 [6]

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