ILLUSTRATIVE CASE

When Developmental Delay and Failure to Thrive Are Not Psychosocial

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CASE

A 5-month-old Caucasian male presented to the emergency department after his primary care physician referred him for workup of noted failure to thrive (FTT) and severe global developmental delay (DD) that did not respond to hypercaloric formula and physical therapy. The patient was born at 39 weeks' gestation to a 26-year-old primigravida mother via spontaneous vaginal delivery. The mother had not received prenatal care until ~33 weeks' gestation and endorsed both alcohol and marijuana use throughout the pregnancy. An antenatal ultrasound was performed at that time and revealed polyhydramnios. His birth weight was 3290 g, which was appropriate for gestational age. Shortly after birth, the patient had hypotonia, nystagmus, and failed hearing screens both at birth and at 3 months of age. At 4 months of age, physical and occupational therapy were started. Additionally, he was started on a concentrated formula of Enfamil Premium 22 kcal/oz, which provided 115 calories/kg/day, considering catch-up growth requirement. Despite this, he was unable to appropriately gain weight.

In the emergency department, patient measurements were as follows: weight 5720 g (<5%), length 62 cm (<5%), and head circumference 43 cm (50%). Pertinent physical examination findings included generalized hypotonia, decreased deep tendon reflexes, marked scoliosis, and bilateral rotatory and horizontal nystagmus. The patient was unable to support his head or to track objects across the midline. He showed increased head lag in sitting position.

Family history was not significant for consanguinity.

WHAT IS THE RELATIONSHIP BETWEEN FTT AND DD? WHAT IS THE INITIAL ASSESSMENT OF A PATIENT WITH THESE CHARACTERISTICS?

Children with FTT have a higher incidence of developmental delay. FTT can result in severe short- and long-term sequelae on neurodevelopmental outcome. This leads to a higher risk of cognitive deficits and behavioral disorders.[1] Cognitive function is below normal in approximately half of children with FTT. This presents as DD early in life. It is unclear whether these outcomes are directly related to FTT or are secondary to other factors that lead to growth failure.[2,3] For this reason, early diagnosis and intervention are extremely important.

The initial assessment of patients with DD should confirm the existence of developmental deficits, recognize the affected domains, and try to identify the specific etiology. An initial assessment should include a complete history

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and physical examination. History should be comprehensive and include detailed family history and prenatal and perinatal information. This leads to the diagnosis of 20% of the cases of DD.[4]

In a child with FFT, the initial evaluation should pay special attention to nutritional details. The most common cause of FTT is an inadequate dietary intake. A psychosocial evaluation is critical because psychosocial stressors have been shown to be the predominant cause of poor intake in children of all ages.[5] Further individualized evaluation is mandatory if this is not the case.[3,6]

Case Continuation

Because initial nutritional and physical therapy interventions were not successful, further evaluation was warranted in this patient. The patient was admitted to the general pediatric ward, and pediatric neurology was consulted. Auditory evoked potential failed to show reproducible waves. Visual evoked potentials and electroencephalography were normal. Serum thyroid-stimulating hormone, free thyroxin, and total creatine kinase levels were within normal limits. Homocysteine, lactate, and ammonia levels were normal. A karyotype was normal. Nutritional support and physical therapy were continued.

WHEN IS FURTHER EVALUATION WARRANTED?

Further evaluation is required when initial assessment does not lead to a diagnosis and initial interventions fail to generate significant improvement.[1,7] These investigations should be tailored based on the patient's individual characteristics. At this point, the input from different subspecialists should be considered. Additionally, neuroimaging is recommended in patients with micro- or macrocephaly, seizures, loss of psychomotor skills, and neurologic signs. The role of these tests is unclear under other circumstances.[7]

If the DD is disproportionate to the severity of the FTT, with any clues on history (such as history of consanguinity or developmental regression) and physical examination (hypotonia, nystagmus, hepatosplenomegaly), inborn errors of metabolism (IEM) should be considered in the differential diagnosis.[8] It is estimated that IEM are responsible for 1% to 5% of cases of DD. These numbers vary depending on the specific population assessed.[9] Early diagnosis is essential because the outcomes for children with IEM may be time-dependent. Delay in the diagnosis can lead to irreversible complications and even death.[10] Although newborn screening was created to aid in early diagnosis and treatment of congenital diseases, such as IEM, not all disorders are included in this screen. Additionally, there are many variables with newborn screening including false-positive and false-negative results and the state in which the patient was born.[11]

In this particular case, despite history of delayed prenatal care, signs were not compatible with an intrauterine infection or teratogen exposure (birth weight, length, and head circumference were appropriate for gestational age).

Case Continuation

Additional metabolic evaluation included plasma amino acids, urine organic acids, free and total carnitine, quantitative acyl-carnitine, screening for congenital disorder of glycosylation, urine creatine panel screen, and very long chain fatty acid screen considering peroxisomal disorders. A lumbar puncture was performed and revealed normal lactate, amino acids, and monoamine neurotransmitters in cerebrospinal fluid.

A brain MRI was obtained. The results were significant for diffuse symmetric increased T2 signal changes involving the bilateral cerebellar white matter, anterior pons, and supratentorial deep and subcortical white matter. The infra- and supratentorial region demonstrated no obvious myelination. These features were reported as compatible with an underlying leukodystrophy-dysmyelinating disease (Fig 1).

Considering the MRI findings and the clinical presentation, the differential diagnosis included dysmyelinating disorders such as 18q deletion syndrome, Salla disease, vanishing white matter disease, and Pelizaeus-Merzbacher syndrome. Sequencing for myelin proteolipid protein 1 (PLP-1) gene confirmed the diagnosis of Pelizaeus-Merzbacher syndrome. The patient's mother was then tested for the mutation because the most common type of this disease follows an X-linked inheritance pattern of transmission. She was negative for the mutation, indicating that this was a de novo mutation.

QUESTION: WHAT IS PELIZAEUS-MERZBACHER SYNDROME, AND HOW IS IT MANAGED?

Pelizaeus-Merzbacher syndrome is included in a group of disorders characterized by progressive degeneration of myelin due to abnormal growth or development. These disorders are called leukodystrophies. Also included in this group are Refsum disease, Canavan disease, Krabbé disease, Alexander disease, metachromatic leukodystrophy, adrenoleukodystrophy, vanishing white matter disease, and cerebrotendinous xanthomatosis.[12]

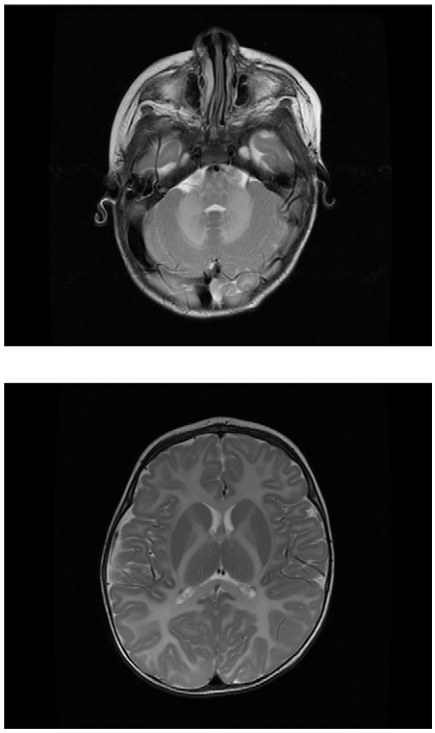

FIGURE 1 Diffuse symmetric increased T2 signal changes involving the bilateral cerebellar white matter, middle cerebellar peduncle, anterior pons, and supratentorial deep and subcortical white matter.

Pelizaeus and Merzbacher first described this disorder during the 19th century.[13,14] The prevalence of this disease in the United States has been estimated between 2 and 5 cases per 1 million people.[15] It is caused by a mutation of the PLP1 gene located on the long arm of the X chromosome (Xq22.2). Multiple mutations to the PLP1 gene are possible, with duplication being the most common.[16,17] The PLP1 gene encodes 2 major myelin proteins, proteolipid protein (PLP) and myelin DM20 proteolipid protein (DM20). Both are major structural myelin proteins required for adequate axonal myelination. The mutation in this disease generates abnormal cellular signaling process leading to cellular death.[16]

In general, clinical manifestations include nystagmus, hypotonia in infancy and spasticity, athetosis, tremor, and ataxia later in life. The clinical presentation varies in severity, which determines different phenotypes (classic, connatal, transitional form, X-linked spastic paraplegia type 2, and *PLP1* null syndrome). The prognosis for those with the severe forms of the disease is poor. On the other hand, individuals with the mild form may have activity levels and life span close to normal. The chief symptom includes spastic paraplegia in these individuals.[15]

There is no specific treatment for this disease and supportive care via a multidisciplinary approach is recommended. Aspiration precautions, assistive devices, and physical therapy are important supportive measures. Although they may not improve the prognosis, they may significantly modify the quality of life.[16]

CONCLUSIONS

This case presents FTT and DD secondary to Pelizaeus-Merzbacher syndrome. It highlights the importance of promptly initiating a workup for underlying organic etiologies for FTT and DD when nutritional and social assessments fail to reveal potential contributing factors or when history and physical examination provide clues to an organic etiology (such as hypotonia, nystagmus, developments regression among others). It also emphasizes having a high index of suspicion for IEM when evaluating children with DD and/or FTT because early identification is extremely important to prevent sequelae and implement early supportive measures and follow-up.

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