Child Neurology: Triosephosphate isomerase deficiency

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Triosephosphate isomerase (TPI) deficiency is a rare autosomal recessive disease of infancy and childhood classified as a glycolytic enzymopathy. Clinical features include hemolytic anemia, progressive neuromuscular dysfunction, and increased susceptibility to infection with specific pathogenic variants resulting in severe disease and death by age 8. Since initially described in 1965, fewer than 50 clinically affected patients have been described in the literature. We describe a 20-year-old patient with a severe pathogenic variant in the TPI gene who has outlived all reported cases, residing in a long-term care facility for most of her life with aggressive medical interventions.

Clinical case

The proband was born at term after an uncomplicated pregnancy to a gravida 1 mother. Her birthweight was 3,409 g. She was diagnosed with hepatomegaly, nonspherocytic hemolytic anemia, and jaundice that required phototherapy in the neonatal intensive care unit. She experienced her first hemolytic crisis requiring blood transfusion at 4 months of age. Bone marrow biopsy at 5 months of age was consistent with congenital dyserythropoietic anemia. Her growth and development were normal. At age 13 months, she was hospitalized with pneumonia and respiratory failure that required intubation. Developmental motor delay was noted, which worsened during her acute illness. Multiple failed trials at extubation resulted in tracheostomy placement. Physical examination during this admission revealed an alert interactive child who could reach for and grasp objects and sit without assistance, but could not pull to a stand (figure 1A). diffuse muscle weakness and increased tone was noted in all extremities, lower greater than upper, with normal deep tendon reflexes. Initial laboratory evaluations including complete blood count, comprehensive metabolic panel, thyroid studies, serum creatine phosphokinase level, botulinum toxin, carnitine, and CSF analysis were normal. Blood, urine, and CSF cultures were negative for infection. Brain and spine MRI were normal. Evaluation for a primary neuromuscular disorder was negative, including normal EMG and nerve conduction studies, muscle biopsy, Tensilon test, and DMPK trinucleotide repeat testing for congenital myotonic dystrophy. Our patient remained ventilator-dependent, and experienced slow progression of motor weakness and developmental delay. At age 4 years, her physical examination revealed macrocephaly, bifacial weakness including ptosis, nystagmus, and upper and lower extremity spasticity. Diffuse progressive muscle weakness with proximal muscles more severely affected, brisk upper and absent lower extremity deep tendon reflexes, and an action tremor of the upper extremities were noted. Additional evaluation including SMA gene testing, urine organic and plasma amino acid analyses, Canavan disease, Kennedy disease, and lysosomal storage diseases enzyme testing was negative. Repeat brain MRI was normal except frontal bossing and macrocrania were noted due to extramedullary hematopoiesis. At 20 years of age, our patient has developed quadriparesis with generalized hypotonia, muscle atrophy, loss of deep tendon reflexes of upper and lower extremities, and uses a wheelchair for mobility (figure 1, D and E). Progressive facial weakness has resulted in dysarthria, dysphagia, and tongue fasciculations. She experiences chronic mild hemolysis exacerbated by acute illness. Physical disease...
manifestations have exceeded intellectual impairment, with a diagnosis of moderate intellectual disability at age 19. The patient has 2 unaffected siblings, a healthy brother and sister.

NextGen sequencing for congenital dyserythropoietic anemia panel comprising the genes CDAN1, GATA1, KIF23, KLF1, and SEC23B was normal. Blood for hemolytic red blood cell panel done at 15 years of age showed triose phosphate isomerase deficiency. Blood for Sanger sequencing performed in a commercial laboratory showed that the patient is homozygous for the most common variant p.Glu105Asp (c.315G>C) that was previously described as p.Glu104Asp associated with TPI deficiency (figure 2).

Discussion

TPI deficiency is a rare autosomal recessive multisystem genetic disorder characterized by non-spherocytic hemolytic anemia that begins from birth and over time progresses to neuromuscular dysfunction, increased susceptibility to infections, cardiomyopathy, respiratory failure, and ultimately death in early childhood. Our patient survived respiratory failure at age 13 months with chronic mechanical ventilatory support. The prevalence of TPI deficiency is unknown but fewer than 100 cases exist worldwide. TPI deficiency may also remain unrecognized, as TPI activity is not typically assayed in cases of hemolytic anemia.
Clinical findings typically begin in infancy and include hemolytic anemia requiring blood transfusion. Progressive neurologic dysfunction becomes evident by 6–24 months of age, and rapid neurologic decline occurs with more significant disease in the legs, hypotonia, motor deficit, and loss of deep tendon reflexes. CNS involvement includes intellectual disability, epilepsy, dystonia, and dyskinesia. Patients typically experience increased susceptibility to infection, cardiomyopathy, and death in early childhood from infection or respiratory failure.

Numerous mutations in the gene coding for the TPI enzyme are known to result in TPI deficiency. The pathogenic variant, Glu105Asp substitution (previously described as p.Glu104Asp), is the most frequent, accounting for approximately 80% of clinical TPI cases. This variant causes the most severe symptoms, typically resulting in death in infancy or early childhood. Additional pathogenic variants have been identified, so far with infrequent occurrence, mostly in compound heterozygous form with Glu105Asp, and result in a less severe disease course.

TPI is one of the enzymes in the glycolytic pathway. Glycolysis is the anaerobic metabolic process in which glucose is converted, through a series of steps, to pyruvic acid, during which energy is released in the form of ATP in cells. Red blood cells lack mitochondria and are therefore dependent on this anaerobic process to create ATP. Defects in any of the enzymes in the glycolytic pathway result in bioenergetic deficiency and chronic hemolytic anemia. However, defects of only 3 of the glycolytic enzymes (TPI, phosphoglycerate kinase, and glucose-6-phosphate isomerase) are associated with neurologic manifestations. TPI deficiency is the most rare and results in disease more severe than any other glycolytic enzyme deficiency. TPI catalyzes the interconversion of glyceraldehyde 3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) (figure 3). A deficiency in TPI results in accumulation of the substrate DHAP. Accumulated DHAP may decompose to form advanced glycation end products that are toxic to cells in large concentrations. Also, TPI is catalytically active only in its dimeric form. Evidence suggests that reduction in the stability of the dimeric enzyme due to TPI pathogenic variants and thermolability may be a crucial component in the etiology of illness. Mutant TPI protein may misfold, resulting in toxic protein aggregates that trigger neurologic dysfunction. These pathogenic mechanisms may contribute to neurodegeneration in addition to decreased red cell survival.

Treatment of patients with TPI deficiency is supportive, but enzyme replacement therapy and cord blood transplantation may offer hope for children diagnosed early in infancy. Homozygotes of the Glu105Asp variant, as in our patient, tend to exhibit the most severe symptoms, resulting in death in infancy or early childhood. To date, only 2 patients have been described in the literature homozygous for this mutation who lived past age 2 years; 1 alive at 5 years and 1 at 8 years of age. TPI deficiency is autosomal recessive, but it is possible that there are modifier genes yet to be identified and environmental factors that interact with the TPI pathogenic variants that have influenced the course of disease in our patient. Aggressive supportive care including mechanical ventilator support, physical, occupational, and speech therapies, and aggressive management of infections and anemia starting at an early age in a chronic care facility may have helped slow down the rapid neurologic regression that has been described in previous cases. She uses a wheelchair and...
is ventilator-dependent, but at age 20 our patient continues to have meaningful interactions with care facility staff and her family.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix

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References
