Child Neurology: Triosephosphate isomerase deficiency

Corrie Harris, MD, Bailey Nelson, MD, Darren Farber, MD, Scott Bickel, MD, Heather Huxol, MD, Alexander Asamoah, MD, PhD, and Ronald Morton, MD

Correspondence

Dr. Harris
Corrie.Harris@Louisville.edu

Neurology® 2020;95:e3448-e3451. doi:10.1212/WNL.0000000000010745

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 1965,¹ 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

From the Divisions of Pediatric Hospitalist Medicine (C.H., H.H.), Pediatric Neurology (D.F.), Pediatric Pulmonology (S.B., R.M.), and Pediatric Genetics (A.A.), University of Louisville School of Medicine (B.N.), KY.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Clinical features of our patient with triosephosphate isomerase deficiency

(A) At age 12 months, the child sits without support, cannot pull to a stand, and increased tone in lower extremities is noted. (B, C) At age 3 years, the child is ventilator- and wheelchair-dependent with progressive muscle weakness involving proximal muscles preferentially. (D, E) At age 12–18 years, the child remains interactive with quadriplegia, diffuse hypotonia, bilateral facial weakness, muscle wasting of all extremities, and contractures of upper extremities. Note macrocephaly secondary to extramedullary hematopoiesis.

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.

Figure 2 Sequence change in the patient's *TPI* gene at codon 315 from G to C designated as c.315G > C (p.Glu105Asp)

Figure 3 Anaerobic glycolysis, phase one

Triosephosphate isomerase (TPI) catalyzes the interconversion of glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP). TPI deficiency results in the accumulation of cellular DHAP and toxic biproducts. GAP available to enter the second phase of glycolysis is reduced, decreasing oxidative conversion of GAP to pyruvate and resultant ATP formation.

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.² CNS involvement includes intellectual disability, epilepsy, dystonia, and dyskinesia.² 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.^{3,4} This variant causes the most severe symptoms, typically resulting in death in infancy or early childhood.⁵ 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.^{3,4}

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.⁴ 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.⁶ Also, TPI is catalytically active only in its dimeric form.⁴ 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.⁴ Mutant TPI protein may misfold, resulting in toxic protein aggregates that trigger neurologic dysfunction.⁶ These pathogenic mechanisms may contribute to neurodegeneration in addition to decreased red cell survival.⁶

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.⁷

Homozygotes of the Glu105Asp variant, as in our patient, tend to exhibit the most severe symptoms, resulting in death in infancy or early childhood.⁴ 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.^{8,9} 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](https://www.neurology.org/N) for full disclosures.

Acknowledgment

The authors thank Luke Drury, Laboratory Directory, PreventionGenetics, Marshfield, Wisconsin, for providing Sanger sequencing data; and the patient, parents, and facility staff for their cooperation.

Study funding

No targeted funding reported.

Appendix Authors

Name	Location	Contribution
Corrie Harris, MD	University of Louisville, KY	Acquisition of information, drafting and revising the manuscript
Bailey Nelson, MD	University of Louisville, KY	Conceptualized paper, acquisition of information, drafting the initial manuscript
Darren Farber, MD	University of Louisville, KY	Revising the manuscript for intellectual content

Appendix (continued)

Name	Location	Contribution
Scott Bickel, MD	University of Louisville, KY	Drafting figures, technical support, revising manuscript for intellectual content and format
Heather Huxol, MD	University of Louisville, KY	Revising the manuscript for intellectual content
Alexander Asamoah, MD, PhD	University of Louisville, KY	Acquisition of information, revising the manuscript for intellectual content, provided substantial editing
Ronald Morton, MD	University of Louisville, KY	Revising the manuscript for intellectual content

References

- Schneider AS, Valentine WN, Hattori M, Heins HL. Hereditary hemolytic anemia with triose phosphate isomerase deficiency. *N Engl J Med* 1965;272:229–235.
- Poll-The BT, Alcardi J, Girot R, Rosa R. Neurological findings in TPI deficiency. *Ann Neurol* 1985;17:439–443.
- Tanak KR, Zerez CR. Red cell enzymopathies of the glycolytic pathway. *Semin Hematol* 1990;27:165–185.
- Orosz F, Olah J, Ovadi J. Triosephosphate isomerase deficiency: facts and doubts. *IUBMB Life* 2006;58:703–715.
- Aissa K, Kamoun F, Sfaihi L, et al. Hemolytic anemia and progressive neurologic impairment: think about triosephosphate isomerase deficiency. *Fetal Pediatr Pathol* 2014;33:234–238.
- Orosz F, Olah J, Ovadi J. Triosephosphate isomerase deficiency: new insights into an enigmatic disease. *Biochim Biophys Acta* 2009;1792:1168–1174.
- Conway AJ, Brown FC, Hurtle EJ, et al. Bone marrow transplantation corrects haemolytic anaemia in a novel ENU mutagenesis mouse model of TPI deficiency. *Dis Model Mech* 2018;11:dmm034678.
- Linarello RE, Shetty AK, Thomas T, Warrier RP. Triosephosphate isomerase deficiency in a child with congenital hemolytic anemia and severe hypotonia. *Pediatr Hematol Oncol* 1998;15:533–536.
- Wilmshurst JM, Wise GA, Pollard JD, Ourvriier RA. Chronic axonal neuropathy with triosephosphate isomerase deficiency. *Pediatr Neurol* 2004;30:146–148.

Neurology®

Child Neurology: Triosephosphate isomerase deficiency

Corrie Harris, Bailey Nelson, Darren Farber, et al.

Neurology 2020;95:e3448-e3451 Published Online before print September 1, 2020

DOI 10.1212/WNL.0000000000010745

This information is current as of September 1, 2020

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/95/24/e3448.full
References	This article cites 9 articles, 1 of which you can access for free at: http://n.neurology.org/content/95/24/e3448.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Neuromuscular Disease http://n.neurology.org/cgi/collection/all_neuromuscular_disease Hematologic http://n.neurology.org/cgi/collection/hematologic Metabolic disease (inherited) http://n.neurology.org/cgi/collection/metabolic_disease_inherited
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.