

Triose-phosphate isomerase deficiency

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[Abstract](#)

[Keywords](#)

[Name of the disease and its synonyms](#)

[Diagnostic criteria/Definition](#)

[Incidence](#)

[Clinical description](#)

[Management and treatment](#)

[Methods for biological diagnosis](#)

[Genetic counseling](#)

[Prenatal diagnosis](#)

[References](#)

Abstract

Triose-phosphate isomerase (TPI) deficiency is a severe multisystemic disease with autosomal recessive inheritance. It is mainly characterized by early-onset chronic hemolytic anemia, always present, and progressive neurological involvement that starts between 6 and 30 months of age. Other clinical signs can be observed, in particular, diaphragm paralysis that requires assisted ventilation, cardiomyopathy and an increased susceptibility to infections. The incidence is not known and only 30 or so cases have been described in the world. The TPI gene is located on chromosome 12, diverse mutations have been identified. Prenatal diagnosis can be obtained by enzymatic assay and/or molecular biology.

Keywords

Triose phosphate isomerase deficiency, autosomal recessive inheritance hemolytic anemia, neurological involvement

Name of the disease and its synonyms

Triose-phosphate isomerase deficiency

Diagnostic criteria/Definition

Triose-phosphate isomerase (TPI) deficiency is a severe multisystemic disease with autosomal recessive inheritance that essentially consists of chronic hemolytic anemia and progressive neurological involvement, often associated with an increased susceptibility to infections. It evolves towards early death or severe neurological involvement.

Incidence

The incidence is unknown but seems to be very low. Since the first description in 1965

by Schneider, approximately 30 cases have been reported. However, the frequency of heterozygotes in the general population appears to be between 3 and 8%. This difference leads us to think that TPI deficiency is either lethal before birth or poorly recognized.

Clinical description

The symptoms comprise:

– constant and early hemolytic anemia (with neonatal onset in 50% of the cases, before 3 months in 75% of them and always before 14 months). Moderate macrocytosis is present without any specific biological signs. This chronic anemia remains moderate but

is aggravated by acute attacks of hemolysis, which are favored by infections;

– progressive neurological involvement begins between 6 and 30 months of age. Its expression is variable: it usually is manifested by neuromuscular involvement starting in the legs with hypotonia, motor defect, amyotrophy and abolition of the deep tendon reflexes.

Diaphragm paralysis can occur and requires assisted ventilation.

In some patients, these neuropathic signs seem to be the only manifestations and intelligence is unaffected. In others, central involvement has been reported: pyramidal signs, dystonia and dyskinesia with severe tremor and mental retardation.

For the few patients investigated by these means, electroencephalogram and computed tomography were normal, as was the cerebrospinal fluid examination. MRI can show only non specific white matter hypersignals. The electromyogram showed signs of denervation with nerve conduction-velocity conservation, suggestive of spinal motor neuron involvement. In addition, one can observe:

– frequent infections, with immune- and leukocyte-function anomalies;
– cardiomyopathy.

The outcome is often dismal, with early death, before the age of 6 years, due to respiratory or cardiac failure; prolonged survival is possible but generally with major neurological involvement. However, rare adult cases with less severe involvement have been reported.

Management and treatment

The treatment of hemolytic anemia remains symptomatic and consists of transfusions during episodes of acute hemolysis. Splenectomy and corticosteroids are not effective. Neurological management is the same as that for a progressive neuromuscular disease. Assisted ventilation can be required for diaphragm paralysis.

Methods for biological diagnosis

TPI, a glycolytic enzyme, is present in all the cells of the organism. The diagnosis of a TPI deficiency relies on the specific dosage of the enzyme in red blood cells: in affected homozygous subjects, the level is very low, between 5 and 10% of the normal; in Heterozygotes (who are clinically normal) its concentration is about 50% of the normal.

Genetic counseling

TPI deficiency is transmitted by autosomal recessive inheritance. TPI is encoded by a single structural gene localized to chromosome 12 that has been cloned. Diverse mutations of the gene have been detected in patients with TPI deficiency. Carriers of TPI variants with more moderate clinical signs have been described.

Prenatal diagnosis

- Prenatal diagnosis can be obtained by dosage of TPI in cultured amniotic cells, chorionic villi or a fetal blood sample. The latter method appears to be the best.

- It can be obtained also by molecular biology (screening for the known TPI gene mutations)

References

Ationu A, Humphries A, Bellingham A, Layton M. Metabolic correction of triose phosphate isomerase deficiency in vitro by complementation.

Biochem Biophys Res Commun. 1997 Mar 17;232(2):528-31.

Bellingham AJ, Lestas AN, Williams LH, Nicolaides KH. Prenatal diagnosis of a red-cell enzymopathy: triose phosphate isomerase deficiency.

Lancet. 1989 Aug 19;2(8660):419-21

Bellingham AJ, Lestas AN. Prenatal diagnosis of triose phosphate isomerase deficiency.

Lancet. 1990 Jan 27;335(8683):230.

Eber SW, Pekrun A, Bardosi A, Gahr M, Krietsch WK, Kruger J, Matthei R, Schroter W. Triosephosphate isomerase deficiency: haemolytic anaemia, myopathy with altered mitochondria and mental retardation due to a new variant with accelerated enzyme catabolism and diminished specific activity.

Eur J Pediatr. 1991 Sep;150(11):761-6

Olah J, Orosz F, Keseru GM, Kovari Z, Kovacs J, Hollan S, Ovadi J. Triosephosphate isomerase deficiency: a neurodegenerative misfolding disease.

Biochem Soc Trans. 2002 Apr;30(2):30-8

Poinsot J, Alix D, Rosa R, Checoury A, Badoual J, Parent P, Castel Y. Triosephosphate isomerase deficiency. Familial survey and prenatal detection]

Arch Fr Pediatr. 1987 May;44(5):365-8.

Poinsot J, Parent P, Alix D, Toudic L, Castel Y. [A case of congenital non-spherocytic hemolytic anemia caused by triose phosphate isomerase deficiency. Prenatal diagnosis]

J Genet Hum. 1986 Nov;34(5):431-7.

Poll-The BT, Aicardi J, Girot R, Rosa R. Neurological findings in triosephosphate isomerase deficiency Ann Neurol. 1985 May;17(5):439-43

Repiso A, Boren J, Ortega F, Pujades A, Centelles J, Vives-Corrans JL, Climent F, Cascante M, Carreras J. Triosephosphate isomerase deficiency. genetic, enzymatic and metabolic characterization of a new case from Spain. Haematologica. 2002 Apr;87(4):ECR12

Rosa R, Prehu MO, Calvin MC, Badoual J, Alix D, Girod R. Hereditary triose phosphate isomerase deficiency: seven new homozygous cases. Hum Genet. 1985;71(3):235-40.

Valentin C, Cohen-Solal M, Maquat L, Horanyi M, Inzelt-Kovacs M, Hollan S. Identical germ-line mutations in the triosephosphate isomerase alleles of two brothers are associated with distinct clinical phenotypes

Valentin C, Pissard S, Martin J, Heron D, Labrune P, Livet MO, Mayer M, Gelbart T, Schneider A, Max-Audit I, Cohen-Solal M. Triose phosphate isomerase deficiency in 3 French families: two novel null alleles, a frameshift mutation (TPI Alfortville) and an alteration in the initiation codon (TPI Paris). Blood. 2000 Aug 1;96(3):1130-5.

Schneider AS., Valentine W.N., Baughan MA., *et al.* Hereditary hemolytic anemia with triose-phosphate isomerase deficiency. N Engl J Med 1965, 272, 229-235.