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Triosephosphate isomerase deficiency in a Tunisian case series

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Triosephosphate isomerase deficiency (TPID) is the most severe glycolytic enzyme defect associated with a progressive neurologic dysfunction. It typically causes hemolytic anemia, neurodegeneration, and recurrent bacterial infections. TPID is caused by a homozygous or a compound heterozygous mutation in the TPID gene. The most frequent variant is Glu104Asp. We report a case series from three unrelated Tunisian families affected by TPID caused by a homozygous Glu104Asp mutation. These reported cases had severe hemolytic anemia. Informed consent was obtained from patients' parents.

Key words: *triosephosphate isomerase deficiency, homozygous mutation, hemolytic anemia, pediatrics*

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Triosephosphate isomerase (TPI) deficiency (TPID) is a rare multisystem disorder characterized by congenital hemolytic anemia and progressive neuromuscular dysfunction beginning in early childhood [1–6]. Most of described cases die from respiratory failure in childhood [3]. The neurologic syndrome is variable. However, it commonly includes a lower motor neuron dysfunction with hypotonia, muscle weakness and atrophy, and hyporeflexia. Some patients may show additional signs such as dystonic posturing and/or spasticity. Laboratory studies show a defect of TPI activity (< 30%) and increased dihydroxyacetone phosphate level, particularly in red blood cells [4].

TPID is an autosomal recessive disorder caused by a mutation in the *TPI1* gene (OMIM 190450) on chromosome 12p13.31. The most common variant is a point mutation at codon 104 changing Glu to Asp, manifested in homozygous or compound heterozygous states. This variant accounts for around 80% of clinical TPID and causes the most severe phenotype [7].

We report three unrelated Tunisian families with TPID caused by a homozygous Glu104Asp mutation of the *TPI1* gene.

CASE REPORTS

Informed consent was obtained from patients' parents.

Family A

A 13-month-old female infant (VII-2; *figure*) presented to the pediatrics emergency department with dyspnea and fever. She was born from a twin pregnancy. Her parents were healthy and non-consanguineous.

Her medical history consisted of jaundice at birth requiring a transfusion at one day of age. At six months of age, she was diagnosed with autoimmune hemolytic anemia of unknown etiology. At the age of ten months, she was hospitalized with severe acute bronchiolitis requiring invasive ventilation.

At admission, the physical examination showed respiratory failure with stable neurological and hemodynamic status. The patient started urgent treatment with oxygen and antibiotics. Nevertheless, the respiratory state rapidly worsened, and the infant was intubated. Two days later, the infant developed seizures (treated with benzodiazepine). Thus, a brain scan and a lumbar puncture were performed and the findings were normal. The blood tests showed hyperlactatemia, with no other abnormalities. But the electroencephalography showed diffuse slow-wave activity without paroxysm. An MRI was done and revealed bilateral signal abnormalities in the globus pallidus. An immunological assessment was done and the findings were normal (blood count; N-methyl-D-aspartate antibodies; G and M immunoglobulins; the level of $CD4^+$ lymphocytes, the $CD4^+/CD8^+$ ratio, lymphocyte phenotyping). A molecular analysis of the *TPI1* gene was performed and showed the homozygous missense mutation at c.315 G>C (Glu104Asp). The infant died two months after her admission.

The assessment of her twin (VII-3; *figure*) detected a TPID with the same gene mutation. Three months after the death of her sister, she was hospitalized with the same symptoms. She died one week after the admission.

Family B

A 4-year-old child (III-4; *figure*) was admitted to the pediatrics emergency department with an altered state of consciousness and fever. The child was born after a normal full-term pregnancy. During gestation, no molecular tests were performed. Yet, his sister was diagnosed at the age of two with TPID and then died.

The parents were found to be heterozygous for the Glu104Asp variant of the *TPI1* gene.

From the age of one year, delayed neurological development and hemolytic anemia were diagnosed. In the second year of life, the patient was unable to walk without assistance. Distal weakness, hypotonia, and amyotrophy were noted.

At admission, this child was comatose, requiring mechanical ventilation. A cerebral CT-scan and a lumbar puncture were performed and the results were normal. DNA analysis showing the homozygous *TPI1* gene mutation at c.315 G>C (Glu104Asp) confirmed the diagnosis of TPID.

Family C

A 15-month-old child was admitted to the pediatrics emergency department with an altered state of consciousness and dyspnea. The child was born after a normal full-term pregnancy. At 6 months of age, he was diagnosed with glucose-6-phosphate dehydrogenase deficiency. His medical history included a psychomotor regression with a break in the weight curve (at 3 months of age). At admission, the child was comatose with irregular breathing requiring mechanical ventilation. A brain scan and a lumbar puncture were performed and the results were normal. The electroencephalography showed a mildly slowed rhythm and poorly structured acivity which was suggestive of metabolic encephalopathy. Due to hemolytic anemia and alteration of the state of consciousness, the diagnosis of TPID was suspected. A molecular analysis of the *TPI1* gene was performed and showed a missense mutation at c.315 G>C (Glu104Asp) in homozygous state. The child died 7 days after his admission.

DISCUSSION

We have reported TPID in three unrelated families. This deficiency was initially reported in 1965, and since then, fewer than 50 cases are described in the literature [1, 8]. The clinical manifestations were typical, and the diagnostic circumstances were similar to the cases reported in the literature [3–6, 9]. Hemolysis and progressive neurologic disease (neuromuscular impairment with spasticity or mental retardation) are noticed in almost all reported cases of TPI deficiency [5, 6, 9]. Neurological symptoms become obvious by two years of age, with motor disturbances as the most common features.

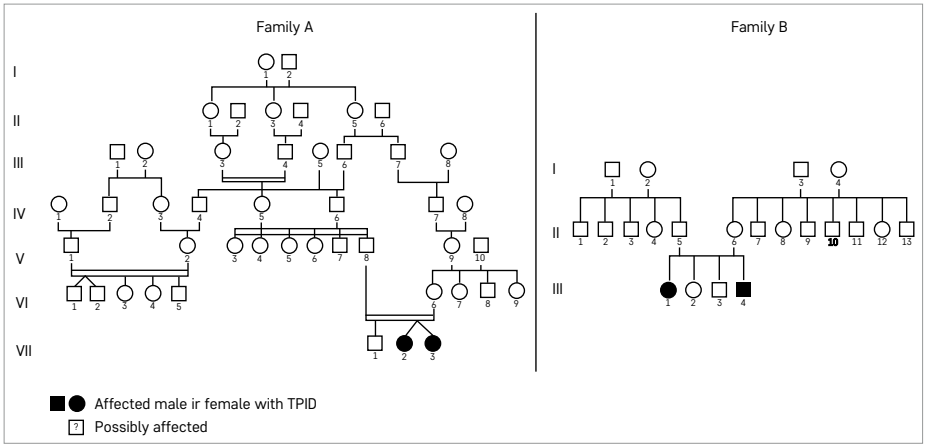
As in our cases, the outcome is commonly poor. Patients with TPI deficiency often do not survive past childhood due to respiratory failure. In a few rare cases, affected subjects have lived into adulthood; they had no severe nerve damage or muscle weakness [9].

No specific therapy exists for TPID. Symptomatic management is necessary. Mechanical ventilation in case of respiratory failure caused by diaphragmatic paralysis is possible. Blood transfusions may be indicated in the case of hemolytic anemia during episodes of hemolysis. Bone marrow transplantation is reported in rare cases [10].

The genetic transmission of the disease is autosomal recessive. Various mutations in the *TPI1* gene have been identified. The mechanisms of these mutations are thought to be a decrease in the catalytic activity of the dimers, or their dissociation into inactive monomers [11–14]. The Glu104Asp substitution is the most common pathogenic mutation accounting for approximately 80% of TPID cases [7].

Little is still known about the pathogenesis of TPID [15]. The TPI functions achieve the rapid equilibration of the triose-phosphates. These triose-phosphates are produced by aldolase in glycolysis and interconnected to lipid metabolism. The impairment of TPI activity does presumably not affect the energy metabolism at the system level; however, it results in the accumulation of dihydroxyacetone phosphate followed by its chemical conversion into the toxic methylgly-

Figure
Family tree diagram showing the affected subjects in two families



oxal, leading to the formation of advanced glycation products [3, 15].

Reported observations of compound-heterozygous cases are rare and imply that reduced TPI activity may not be sufficient to cause the disease symptoms and lower catalytic activity may be required to explain the clinical outcome [16]. Other studies suggest that the Arg189 salt bridge is critical for organizing the TPI enzyme catalytic site [17]. These researches have demonstrated that reduced TPI levels are associated with human TPID [18]. Concerning the neurological symptoms, it has been established that a synaptic vesicle is the cause of neurologic dysfunction in TPID cases. These troubles are less pronounced with catalytically inactive TPI [18].

TPID is an autosomal recessive disorder. Therefore, it has a 25% risk of recurrence in the case of two heterozygous parents. Prenatal diagnosis is proposed to ensure an early diagnosis. In addition to molecular diagnosis, TPI enzyme activity in amniotic fluid cells and fetal blood cells is measurable.

CONCLUSION

We reported 5 cases of TPID in 3 unrelated Tunisian families. In this cases, the clinical presentation consisted of a triad: progressive neurologic dysfunction, hemolytic anemia, and recurrent infections. Pediatricians have to be aware of this pathology namely to guarantee an early assessment of the genetic status of the family members.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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