Triosephosphate isomerase deficiency with elevated sweat chloride test: report of a case

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A 15-month-old girl with severe hemolytic anemia and progressive respiratory failure is presented. She was well until the age of six months when she developed a pulmonary infection. During the next six months, she had frequent respiratory infections and her paleness became evident. At the age of 12 months, she was observed to have easy fatigability and muscle weakness, and she received her first blood transfusion. She was referred to our hospital at the age of 15 months. The physical examination revealed a malnourished girl with hypotonia, nystagmus, generalized muscle weakness and severe breathing difficulty requiring ventilatory support The hemoglobin (Hb) was 9.7 g/dl; hematocrit (Hct) 29%, mean corpuscular volume (MCV) 101 fl and reticulocyte count 15%. Peripheral blood smear revealed macrocytosis and stomatocytosis (30% of the red cells) and polychromasia. Sweat chloride test was 90 and 94 mEq/L on two separate occasions. The serum vitamin E level was 0.26 mg/dl (N: 0.44-0.68). She was found to be heterozygous for factor V Leiden mutation. Although malnutrition, low serum vitamin E and elevated sweat chloride test were suggestive of cystic fibrosis, this diagnosis failed to account for all the findings in the patient. A search for a red cell enzyme deficiency revealed that the red cell triosephosphate isomerase (TPI) activity was low. DNA analysis showed the 315 G-C (105 Glu-Asp) TPI mutation, thus confirming the diagnosis of TPI deficiency.

Key words: triosephosphate isomerase deficiency, elevated sweat chloride.

Triosephosphate isomerase (TPI) enzyme catalyzes the interconversion of dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3 phosphate in the energy-generating glycolytic pathway. Although the enzymatic defect can be partially bypassed via the hexose monophosphate shunt, its deficiency results in a rare autosomal recessive disease characterized by markedly reduced enzyme activity in all tissues accompanied by metabolic block in glycolysis with accumulation of intracellular DHAP, particularly in red cells. Clinically, patients present with hemolytic anemia, increased susceptibility to infections and progressive and severe neuromuscular symptoms. As yet, there is no promising treatment and the disease usually culminates in death[1]. We report a new case with TPI deficiency who, in addition to the characteristic findings of TPI, had a greatly elevated sweat chloride test and low vitamin E levels and was prone to develop thrombosis. Implications of these findings in the differential diagnosis are discussed. The patient also had heterozygosity for factor V Leiden mutation.

Case Report

A 15-month-old girl was admitted to the intensive care unit because of progressive respiratory failure. Her parents were first cousins and she had a seven-year-old healthy sister. Her past history revealed that she was well and had normal developmental milestones

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until six months of age when she was diagnosed to have anemia and pulmonary infection. After this point, respiratory infections recurred frequently. She was transfused at another facility once at 12 months of age when she also started to have easy fatigability and muscle weakness. She was never able to sit without support or to crawl. Physical examination in this hospital at 15 months of age showed a severely malnourished girl weighing 6.9 kg (< 3rd percentile). She had striking hypotonia, generalized muscle weakness and prominent breathing difficulty with patchy infiltrates on both lungs. Blood gas determination showed carbon dioxide retention, whereupon she was intubated for ventilatory support. The hemoglobin (Hb) was 9.7 g/dl: hematocrit (Hct) 29%, white blood cell count 12,000/mm^3; mean corpuscular volume (MCV) 101 fl; platelets 314,000/mm^3; and reticulocytes 15%. Peripheral blood smear showed macrocytosis, polychromasia and marked basophilic stippling. It was remarkable in addition for the presence of stomatocytosis (30%) of the red cells). Hb electrophoresis, direct and indirect Coombs tests, autohemolysis, osmotic fragility, serum B12 and folic acid levels and urinary orotic acid excretion were normal. Red cell G6PD, pyruvate kinase, and pyrimidine 5'-nucleotidase levels were within normal limits. Of note, however, was an abnormal hydrogen peroxide hemolysis test and a low α-tocopherol level, 0.26 mg/dl (N: 0.44-0.68), which prompted a search for cystic fibrosis (CF). Sweat chloride was 90 and 94 mEq/L on two occasions with a two week interval. Steatocrit was negative and an ultrasonographic examination of the pancreas was normal. In order to have definitive evidence to affirm or refute the diagnosis, a mutation analysis was undertaken and exons of cystic fibrosis transmembrane regulator (CFTR) on chromosome 7 were analyzed. A large part of the CFTR gene, including exons 3, 7, 9, 10, 11, 14a, 14b, 17b, 18, 19, 20, 21 and 22, were screened and no mutation was detected. Immunologic evaluation, including immunoglobulin levels, lymphocyte subsets, blastic transformation, and neutrophil chemotaxis, was normal. Similarly, a search for a mitochondrial DNA abnormality was negative.

A diagnosis of TPI deficiency was entertained on clinical grounds and was confirmed by an enzymatic assy showing a significantly low TPI level (459.7 IU/g Hb N: 1317.0-2905.0). The mutation on chromosome 12p13 was at cDNA 315 G-C and had the amino acid chain designation 105 Glu-Asp.

Interestingly, the patient was noted to have thrombosis at venipuncture sites, and she was found to be heterozygous for factor V Leiden mutation. The patient was unable to be fed orally and total parenteral nutrition (TPN) was instituted at the second month of hospital stay.

Sweat chloride test was repeated at four week intervals, and a final sweat chloride test two months after the first one was 20 mEq/L. On the fifth month of admission, the patient died of respiratory failure.

Discussion

Our patient exhibited all the characteristic features of TPI deficiency, and the diagnosis was confirmed by enzymatic assay and mutation analysis. The exact mechanism leading to clinical manifestations in TPI deficiency remains obscure. Although accumulation of DHAP was claimed to be responsible[2], other enzymatic deficiencies associated with increased concentrations of DHAP do not result in a similar clinical picture[3].

The most interesting features in our patient with respect to the previously published patient were the high sweat chloride test, marked stomatocytosis and the incidental finding of heterozygosity for factor V Leiden mutation. Many of the findings, including parental consanguinity, recurrent pulmonary infections, low vitamin E levels and hemolytic anemia[4,5], suggested the diagnosis of CF. As the diagnosis of TPI deficiency was confirmed by biochemical and molecular analysis, the question then arose whether the elevated sweat chloride was a sign of coexisting CF, even though the absence of chronic diarrhea and chronic changes in the chest X-ray did not support this diagnosis.

The extensive molecular search that was performed failed to detect any mutations. The final low sweat chloride determination also supports the notion that the elevation in sweat chloride was probably not due to CF. Yet another possibility is that the elevated sweat chloride might have been due to the presence of severe malnutrition, as sweat chloride normalized, probably because of TPN[4,5].

Another interesting finding in our patient was marked and persistent stomatocytosis in the peripheral blood smear. We introduce this pathology as one of the features of the hemolytic components of the disease. However, this finding needs to be supported by other observations in the future.

Presence of factor V Leiden mutation, which is the most common pathology underlying the hypercoagulable state in Turkish patients, with a frequency of 32 percent in children with thrombosis versus 7.1 percent normal controls[7,8], shows that even in patients with known pathologies, a search for this distinct entity should be instituted.

The case presented in this report, in addition to being another example of a very rare autosomal recessive deficiency, implies that some cases, especially those with hemolytic anemia due to vitamin E malabsorption, may have been misdiagnosed as CF. Therefore, we suggest that, especially in cases where molecular analysis fails to detect any mutation and where hemolytic anemia and stomatocytosis are part of the clinical picture, TPI level should be determined in order to rule out this rare deficiency.

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