First Report of 3-Oxothiolase Deficiency in Iran

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Introduction: Mitochondrial acetoacetyl-CoA thiolase (3-oxothiolase) deficiency is a rare metabolic disorder involving ketone body metabolism. The enzymatic defect is the deficiency of mitochondrial acetoacetyl-CoA thiolase and the responsible gene is on chromosome 1q22.3-q23.1 (1-3) with autosomal recessive inheritance. There is considerable heterogeneity in clinical features, while a unique presentation is the attacks of massive ketosis and acidosis. Rarely, patients have neonatal onset; however, most of them begin first in late infancy or childhood. The attacks are usually triggered by infections and other causes of increased metabolism. Dehydration, lethargy, hyperventilation, coma, and death might occur during these episodes. Noticeable patients have a history of sibling deaths in early years of age (4, 5).

The frequency of attacks decreases with age. Other features are hyperglycemia, vomiting, seizures, mental retardation, central hypotonia, ataxia, and speech problems (4). Specific organic aciduria is the diagnostic key of this disorder. The main metabolites are 2-methyl-3-hydroxybutyric acid, tiglylglycine, and 2-methylacetoacetic acid. They are excreted constantly in patient’s urine and have trace levels in normal urine (4, 5). There is no definite treatment for the disorder. According to considerable heterogeneity in clinical presentations, the treatment schedules are individualized. During fever or gastrointestinal disturbance, prolonged fasting is hazardous and intravenous glucose is beneficial and may prevent the ketoacidotic crisis. Large volume of water and electrolytes are prudent during the furious acidotic episode. Intravenous carnitine administration during attacks followed by long-term orally intake to esterify and remove tiglyl CoA and the other accumulated CoA esters are practical. It is appropriate to limit the use of isoleucine in some patients (6).

2. Case Presentation

A 6-month-old boy presented with intractable vomiting and a history of three-day symptoms of common cold. On examination, he was conscious, febrile, tachypneic, dehydrated, and hypotonic with an acetone-like breath odor. The patient was the first child of consanguineous parents. There was no family history of similar disease. He had normal growth and development prior to the recent disorder. Initial laboratory studies showed severe metabolic acidosis (PH: 7.06, bicarbonate: 8.5) and severe ketonuria. Blood glucose, electrolytes, liver enzymes, and thyroid function tests had normal results. Routine sepsis workup and CSF analysis revealed negative results for infections. The patient had high level of plasma lactate (27 and 35 mmol/L in two separate occasions) and normal level of blood ammonia. Urine organic acids analysis by gas chromatography/mass spectrometry (GC/MS) indicated a very high level of 2-methyl-3-hydroxybutyric acid.
periventricular white matter lesions on MRI scan of the 19-month-old patient had cognitive and motor developmental T2 hyperintensities involving the globi pallidi (15). A diagnostic (12). Recently, O'Neill et al reported a five-year-old patient with time. Severe neurologic delay was reported recently with the posterolateral putamen, but this pattern is not diagnostic (12). The disease is usually detected in late infancy or childhood. Our patient had 6 months of age at presentation. Infections are the most common triggering causes of attacks; n our patient, the common cold was the triggering factor. Ketoacidotic attacks are the most common clinical manifestations. Intelligence may be normal occasionally but in others, developmental delay or speech disorders exist (9-11). Although our patient had developed recurrent abnormal movements of tongue, salivary drooling, and dystonia in upper and lower extremities at seven months of age. Dystonia relatively responded to levodopa and trihexyphenidyl; however, it recurred by discontinuation of drugs.

3. Discussion

The 3-oxothiolase deficiency is a rare disorder and less than 100 cases are reported by now (2). There is no previous report of this disorder in Iran. Our patient was a typical case of the disease. These patients are marked by recurrent attacks of severe ketosis mostly caused by ketolysis defects, the main probable mechanism of excessive production of acetoadipate (7). There is significant variety in reported cases, but the specific characteristics are the episodes of massive ketosis and acidosis. Sometimes attacks are marked by vomiting and are occasionally accompanied by dehydration, lethargy, hyperventilation, and coma (4, 8). The disease is usually detected in late infancy or childhood. Our patient had 6 months of age at presentation. Infections are the most common triggering causes of attacks; n our patient, the common cold was the triggering factor. Ketoacidotic attacks are the most common clinical manifestations. Intelligence may be normal occasionally but in others, developmental delay or speech disorders exist (9-11). Although our patient had developed regression in developmental milestones after the first attack of his disease, he recovered partially with time. Severe neurologic delay was reported recently in four cases and the development was slow before the initial acidotic episodes in all of them. Severe central nervous system involvement was reported in all of them. Severe neurologic delay was reported recently in four cases and the development was slow before the initial acidotic episodes in all of them. Severe central nervous system involvement was reported in all of them. Severe central nervous system involvement was reported in all of them. Severe central nervous system involvement was reported in all of them. Severe central nervous system involvement was reported in all of them. Severe central nervous system involvement was reported in all of them. 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