BETA-KETOTHIOLASE DEFICIENCY : REPORT OF TWO CASES

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SUMMARY : *Beta-kethothiolase deficiency is a rare metabolic disorder of branched chain amino acids, which is characterised by an increased plasma glycine level, metabolic acidosis and ketosis. The clinical expression of beta-kethothiolase deficiency is highly variable. Typical manifestations are severe ketoacidosis and excessive excretion of 2-methyl-3-hydroxybutyrate and tiglylglycine with or without 2-methylacetoacetic acid and butanone in urine. This report describes two children with beta-ketothiolase deficiency presenting with acidotic respiration and vomiting. Our experiences with these cases indicate that early detection and treatment of this disorder are important, as patients may achieve normal development with early intervention.*

Key Words : *Acetyl - CoA C - Acetyltransferase, Mitochondrial.*

INTRODUCTION

Beta-ketothiolase deficiency is an autosomal recessive, rare inborn error of isoleucine and ketone body metabolism, which is first described by Daum et al. in 1972 (1). Although the pattern of metabolites suggested that the defect was in mitochondrial 2-methylacetoacetyl-CoA thiolase (commonly called beta-ketothiolase or 3-oxothiolase), direct demonstration of the enzyme deficiency occurred in 1982 (2).

The clinical manifestations range from an asymptomatic course to severe life threatening ketoacidosis with coma and cardiomyopathy(3,4,5). The attacks are usually precipitated by high protein ingestion or by systemic infections(6). There is abnormal urinary excretion of 2-methyl-3-hydroxybutyric acid, tiglylglycine and in some cases also 2-methylacetoacetic acid and butanone (3,5,6). At present there are more than 20 published cases of beta-ketothiolase deficiency (3,5).

This report describes a 24-month-old girl and a 9-month old boy with beta-ketothiolase deficiency.

CASE REPORTS

Case 1: A twenty-four-month-old girl was admitted to hospital with the complaints of high fever, convulsion, vomiting, hematemesis and respiratory distress of two days duration. A year ago she had been admitted to another hospital because of severe acidosis and anemia. Peritoneal dialysis had been instituted. The parents were first degree consanguineous. Past history disclosed normal physical and motor development. The patient had a healthy four-year-old sister. Physical examination revealed that she was critically ill, unconscious and had acidotic respiration. Deep tendon reflexes were hyperactive in the lower extremities. She weighed 10 kg (between the 3rd and 10th percentile) and measured 82 cm in length (between the10th and 25th percentile).

Laboratory investigations revealed hemoglobin of 11.7gr/dl, white blood cells 18000/mm3 with 74% polymorphonuclear leucocytes, 26% lymphocytes. The platelet count was normal. Urinary analysis yielded 2+ ketonuria. The blood pH was 6.9 and HCO_3 was 3.1 mEq/lt. Serum lactic acid was elevated. Paper chromatography of the blood and urine samples for amino acids were normal,quantitative blood and urine amino acid levels were also found normal with HPLC. Urinary organic acid analysis by gas chromatography and mass spectrometry (GC-MS) showed a pattern consistent with the diagnosis of beta-ketothiolase deficiency (Table 1).

Table 1 : Urinary organic acid pattern of the patients

Organic acid (mmol/mol creatinine)	Patient 1	Patient 2
Lactic acid	308	-
3- OH-butyric acid	22.66	125.91
Adipic acid	40.3	-
2- Methylacetoacetic acid	Very elevated	-
2- Methyl-3-Hydroxybutyric acid	Very elevated	28.72
Tiglylglycine	Very elevated	853.34

Following intravenous alkali replacement therapy and peritoneal dialysis the patient's clinical condition improved. She was subsequently discharged on a low -protein diet. She is now symptom free and is being followed-up.

Case 2: The second patient was a nine month-old-boy who was referred to our hospital because of high fever, tachypnoea and unconsciousness. There was no remarkable feature in the history except parental consanguinuty. Physical examination was normal except for acidotic respiration and mild hepatomegaly. His physical and motor development was considered normal. The patient weighed 7.6 kg (between the 10th and 25th percentile) and measured 70 cm in length (between the 50th and 75th percentile).

The laboratory investigations revealed blood pH of 7.1 and HCO3 4.9 mEq/lt., hemoglobin 11.3 gr/dl, white blood cells 13.900 /mm3 with 48% polymorphonuclear leucocytes and 52 % lymphocytes, and 2+ ketonuria. The tests for serum lactic and pyruvic acids, biotinidase activity, carnitine and amino acid levels were all in the normal range. Urinary organic acid analysis of the patient by gas chromatography and mass spectrometry (GC-MS) was also consistent with the diagnosis of beta-ketothiolase deficiency (Table 1).

Intravenous alkali replacement therapy was repeated three times until the desired serum HCO_3 level was reached. He was also discharged from the hospital on a low-protein diet. He had no attacks for about one year and is being followed up.

DISCUSSION

The number of patients with beta-ketothiolase deficiency that have been reported is small and the number in whom the specific enzyme defect has been documented is even smaller (3,5). On the other hand a considerable degree of heterogeneity of expression has been observed, suggesting that different abnormalities in the gene may be responsible for the variable clinical presentation of this disease (3,5). Today, the identification of heterozygosity is possible by enzyme assays on patients' fibroblasts, and immunoblot analyses. Molecular analysis of mitochondrial acetoacetyl-CoA thiolase

deficiency is now possible, as the cDNA for this enzyme has been cloned. (6)

The clinical features of beta-ketothiolase deficiency are quite variable. The most common features are failure to thrive, intermittent severe metabolic acidosis, ketosis, vomiting, diarrhea and coma following infections. It may also resemble salicylate toxicity. In the two patients reported here, there was severe acidosis as the initial manifestation of the disease. Both of the patients had normal mental and motor development. Furthermore, their subsequent course has been normal. This is consistent with other experiences with this disorder (7). A number of patients have had no abnormalities other than the occurrence of acute episodes, and intellectual development has been normal (2,4). Some patients were clinically silent and detected only by enzyme assay (8,9). With prompt correction of the severe acidosis and ketosis during the first episode, the prognosis and subsequent growth and development are excellent for patients who are treated with moderate protein restriction.

Our experience with these cases indicates that early detection, treatment of acute metabolic crisis and the implementation of a protein restricted diet are important, as the patients may achieve normal development with early intervention. Establishment of a correct diagnosis not only gives a chance to control the disorder but also gives the parents an opportunity of having a healthy child in subsequent pregnancies by prenatal diagnosis.

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