Brain & Development 36 (2014) 537–540

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Metabolic encephalopathy in beta-ketothiolase deficiency: The first report from India

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Received 30 June 2013; received in revised form 22 July 2013; accepted 22 July 2013

Abstract

Beta-ketothiolase deficiency, or mitochondrial acetoacetyl-CoA thiolase (T2) deficiency, is a rare autosomal recessive disorder affecting isoleucine catabolism and ketone body metabolism. A patient from South India presented with acute ketoacidosis at 11 months of age. During the acute crisis the C5OH (2-methyl-3-hydroxybutyryl) carnitine and C5:1 (tiglyl) carnitine were elevated and large amounts of 2-methyl-3-hydroxybutyrate, tiglylglycine, and 2-methylacetoacetate were excreted. Brain CT showed bilateral basal ganglia lesions. Potassium ion-activated acetoacetyl-CoA thiolase activity was deficient in the patient's fibroblasts. The patient is a homozygote for a novel c.578T>G (M193R) mutation. This is the first report of T2 deficiency confirmed by enzyme and molecular analysis from India.

Keywords: T2 deficiency; 2-Methyl-3-hydroxybutyrate; Tiglylglycine; C5OH; *ACAT1*; Ketoacidosis

1. Introduction

Beta-ketothiolase deficiency (OMIM 203750), also known as mitochondrial acetoacetyl-coenzyme A (CoA) thiolase (T2, gene symbol *ACAT1*) deficiency, is a rare autosomal recessive disorder that affects the metabolism of isoleucine and ketones. T2 deficiency is clinically characterized by severe ketoacidosis triggered by ketogenic stresses such as infections and fasting [1]. The disorder is usually suspected when increased excretion of 2-methyl-3-hydroxybutyrate, tiglylglycine, and 2-methylacetoacetate is detected by urinary organic acid analysis and/or elevated levels of 2-methyl-3-hydroxybutyrylcarnitine (C5OH) and tiglylcarnitine (C5:1) are detected in blood plasma using tandem mass spectrometry [1–4]. However, some patients do not show such typical profiles in these analyses [2–4].

Here we provide the first report of a T2-deficient patient from India, with typical urinary organic acid and blood acylcarnitine profiles, who presented with severe metabolic acidosis and metabolic encephalopathy.

2. Case report

An 11-month-old male child (GK95, GK number is an internal identifier for T2 deficient patients) was admitted in the pediatric intensive care unit with a history of fever, cough, and rapid breathing. The child

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http://dx.doi.org/10.1016/j.braindev.2013.07.007

was born to parents who are first cousins and he is the first child to the parents. The development at 11 months was appropriate. Ten days prior to the admission he had diarrhea and dehydration and was treated with intravenous fluids. Following 2 days of febrile episodes, he developed tachypnea, poor perfusion and tachycardia, and unconsciousness. Initial laboratory tests indicated metabolic acidosis with an arterial pH of 6.9, Pco_2 of 10 mmHg, and bicarbonate level of 4.4 mM. The blood glucose was low at 1.8 mmol/L. Urine ketones were strongly positive (180 mg/dL). Serum lactate was normal. On the second hospital day, he had generalized tonic–clonic seizures and was treated with levetriacetam 20 m/kg and then started on maintenance dose of 10 mg/kg/dose. Brain CT showed hypodensities in the bilateral lentiform nucleus and caudate head, suggestive of metabolic encephalopathy (Fig. 1). The child was intubated and kept on a ventilator on the second hospital day. There was no improvement with sodium bicarbonate correction and the child was put on dialysis for 2 days. Fluid and electrolyte balance was maintained and the child received a glucose infusion stepwise in 2 mg/kg/min increments up to 12–15 mg/kg/min with monitoring of blood glucose levels. Following dialysis, the biochemical parameters improved. The child was extubated on the fourth hospital day. Acylcarnitine analysis showed a C5OH concentration of 3.08 μM (cut-off value 1.0) and a C5:1 concentration of 1.69 μM (cut-off value 0.3). Urinary organic acid analysis showed elevated levels of 2-methyl-3-hydroxybutyrate, 2-methylacetoacetate, and tiglylglycine. A tentative diagnosis of T2 deficiency was made. The child regressed, with loss of social smile, recognition, and the ability to sit or crawl. Management following the acute stage included a low-protein (1.5 g/kg), high-carbohydrate diet supplemented with 50 mg/kg carnitine. The child was discharged on the 15th hospital day on the same diet with the antiepileptic drug and baclofen for dystonia.

One week after discharge, dystonia of all four limbs, predominant in lower limbs and mild irritability were noted. A month later, irritability subsided and the child could follow objects and started recognizing the parents. Physiotherapy was started. At 15 months of age, social smile with partial head control was attained but central hypotonia persisted. Dystonia of the trunk with intermittent arching was also noted by 15–16 months of age. Trihexyphenydyl was used at dose of 4 mg twice a day. At 18 months, good head control was achieved and the child could sit and stand with support. At 24 months, he could walk with support; social interac-

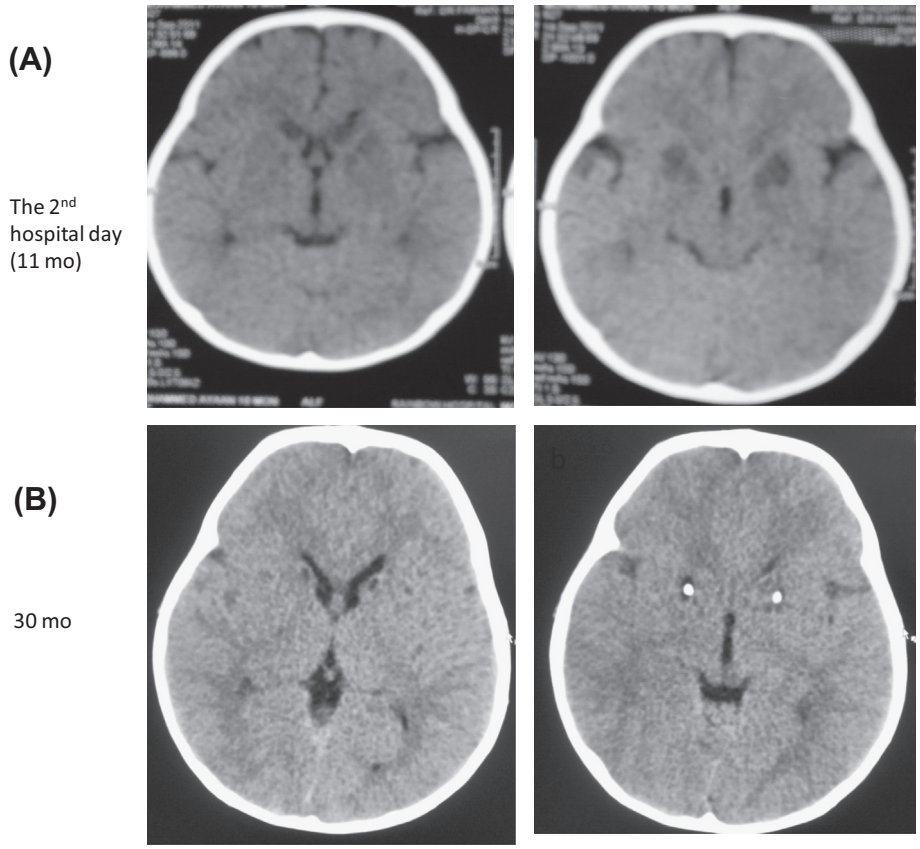

Fig. 1. Brain CT findings in patient GK95. (A) Plain axial images show symmetrical hypodensities involving bilateral basal ganglia, suggestive of metabolic encephalopathy. (B) Plain axial images show bilateral symmetrical calcification involving the anterior part of the lentiform nucleus with surrounding low-density areas.