Case Report

VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY IN A CHILD

DEFICIT DI ACIL-COA DEIDROGENASI A CATENA MOLTO LUNGA IN UN BAMBINO

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Abstract: This report concerns a patient affected by Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency, a rare inherited metabolic disease with different severity levels that can arise at all ages. VLCAD is involved in metabolic pathway of β-oxidation regarding energy production during prolonged fast.
A 18-months old boy experienced a febrile crisis, during which a severe hypoketotic hypoglycaemia emerged, leading him to a multi organ failure that ultimately caused death.
Immediate administration of a therapy, even during diagnostic phase, is crucial in this kind of metabolic inherited diseases.

KEYWORDS: VLCAD, Fatty acid, Beta oxidation.

Abstract: Presentiamo il caso di un paziente con deficit di Acil-CoA deidrogenasi a catena molto lunga (VLCAD), un raro errore congenito del metabolismo con diversi gradi di severità, che può esordire a ogni età. L'enzima VLCAD è coinvolto nella via metabolica della β-ossidazione degli acidi grassi che interviene nella produzione di energia durante il digiuno prolungato. Il paziente all'età di 18 mesi durante una crisi febbrile presentò un episodio di ipoglicemia severa ipochetotica, con deficit di produzione energetica, che lo portò a deficit multi organo e successivamente all'exitus.
In questo tipo di errore congenito del metabolismo è necessario che la terapia venga iniziata immediatamente, anche solo in fase di sospetto diagnostico non ancora confermato.

PAROLE CHIAVE: VLCAD, Beta ossidazione, Acidi grassi.

Introduction

Very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency is the rarest inborn error of mitochondrial fatty acid beta-oxidation, with an autosomal recessive mode of inheritance. Mitochondrial β-oxidation is involved in energy production, especially during prolonged fast when fatty acids are mobilized from adipose tissue and then oxydated in liver, skeletal muscle and cardiac muscle. Moreover, liver β-oxidation of fatty acid produces ketones which are utilized by brain. Metabolic pathways include: cellular uptake of fatty acid, their activation to Acyl CoA esters, transesterification to acylcarnitines, translocation across the inner mitochondrial membrane, re-esterification to Acyl-CoA esters and then β-oxidation that generates electrons and acetyl CoA which is transformed in ketones.
VLCAD is present in the mitochondrial inner membrane and catalyzes the first reaction in β-oxidation of Acyl-CoA chains ranging in length from 14 carbons up to 20 carbons. Therefore, this enzyme deficiency would have important effects on other metabolic pathways, not only regarding energy production during a prolonged fast, but also for toxic effects of long chain intermediates accumulating within mitochondria.
VLCAD deficiency can be classified clinically into 3 forms: a severe early-onset form with high incidence of cardiomyopathy and high mortality; an intermediate form with childhood onset, usually with hypoketotic hypoglycaemia and more favourable outcome; and an adult-onset, myopathic form with isolated skeletal muscle involvement, rhabdomyolysis, and myoglobinuria after exercise or fasting (1).
In neonatal period the most common clinical picture can be hypoglycaemia, accom-

panied with irritability and lethargy, rapidly responding to glucose infusion. The presence of VLCAD may not be noticed until severe events occur (hypoketotic hypoglycaemia, heart failure, rhabdomyolysis).
Diagnosis is made by analysis of acylcarnitines in plasma and urine by tandem mass spectrometry that shows high level of C14:2, C14:1, C16:1 and C18:1 acylcarnitine species and by urinary organic acid assay, that could show excretion of dicarbossilic acids. To confirm the biochemical diagnosis, molecular analysis can be performed.
VLCAD long term management is based on avoiding prolonged fast, frequent feeding, high carbohydrate intake and low fat diet. Intravenous (I.V.) glucose, medium chain triglyceride and carnitine administration is generally effective during acute episodes of stress (illness, hyporexia).

Case Report

The patient was 18 months old, born after a normal pregnancy from unrelated parents; he had two healthy siblings and familiar history was negative for hypoglycaemia, cardiomyopathy, muscle weakness or other important diseases. He was a healthy child that never experienced febrile episodes or acute illness. Two days before admission, he had cough and he was inspected by a physician, who diagnosed a pharyngitis. The day after, cough was still present, and hyporexia, pallor and weakness appeared. The night after, his condition aggravated, with higher sense of weakness, seizures and rapid loss of consciousness.
He entered in another hospital where I.V. glucose 5% solution infusion started and blood tests showed low levels of glucose (<50 mg/dl). Finally, he was admitted in our hospital. The patient was nondysmorphic and well- nourished, his physical examination showed hypotony, hyporeflexia and hepatomegaly and he was unconscious. He had fever (39oC). His blood tests showed a very low level of glucose (24 mg/dl), despite of infusion with glucose solution started some hours before, GOT was 145 UI/L (vn 5-45), GPT 220 UI/L (vn 5-45), CPK was 2341 UI/L (vn 25-185), lactate 85 mg/dl (vn 20 mg/dl) associated with metabolic acidosis. No ketones were found in urine.
I.V. glucose 10% solution infusion started and we provided high caloric intake with carbohydrate administration via nasal-gastric tube. ECG was normal, but echocardiogram demonstrated left ventricular hypertrophy with reduction of ejection fraction. A brain TC and NMR were performed for the occurrence of coma and they showed cerebral oedema. Clinical clues suggested us a β-oxidation defect, therefore we carried out the relevant tests. Urine organic acid analysis showed a dicarboxylic aciduria, which is a clue to a mitochondrial fatty acid oxidation problem. Also, plasma acylcarnitine profile revealed that the C14:1 acylcarnitine levels were high. He died for multiorgan failure three days after admission despite of high caloric intake provided from carbohydrate and medium chain triglyceride and carnitine administration. The patient's parents did not give their consent to perimortem tests, therefore neither enzymatic nor molecular analyses were possible. Post-mortem examination performed three days later revealed diffuse lipid accumulation in liver.

Conclusions

Discovery of fatty acid oxidation is relatively recent. The first disorder was described in the early 1970s in patients with skeletal muscle weakness or exercise induced rhabdomyolysis associated with decreased muscle carnitine or carnitine palmytoiltransferase (2). Discovery of VLCAD deficiency dates back to 1992, but since then, our knowledge of this disease has greatly improved.
The phenotype of the disease ranges from hypoketotic hypoglycaemia to metabolic and cardiac failure or to rhabdomyolysis in adults (3-7), so it can show up at any age.
It would be possible to prevent metabolic insufficiency, liver and cardiac failure and death only performing I.V. glucose and high carbohydrate intake, easy and life-saving therapies, since the early hours of acute illness. This case demonstrates that, although VLCAD deficiency is the rarest among the β-oxidation enzyme deficiencies, we should be able to diagnose it on time and carry out rapidly the necessary therapy.

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