Case Report

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A Five-Year-Old Boy with GAII Administered with High-Dose Riboflavin: A Case Report

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ABSTRACT

Background: Inborn errors of metabolism can cause a number of morbidities and mortality in pediatric population. Glutaric aciduria II (GAII) or multiple acyl-CoA dehydrogenase deficiency (MADD) is an ultra-rare (i.e. <1:50 000) disorder of mitochondrial fatty acid oxidation (FAO) and amino acid metabolism. It is inherited in an autosomal recessive manner. Congenital deficiency of electron transfer flavoproteins and ETF dehydrogenase genes cause an illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several aminoacides. Newborn screening (NBS) using tandem mass spectrometry (MS/MS) permits detection of neonates with glutaricaciduria-Type II.

Case Presentation: We reported a five-year-old boy with muscle weakness of lower limb and inability to walk (myopathy), seizure due to hypoglycemia (as a result of prolonged fasting), hepatomegaly and rhabdomyolysis that treated with high dose riboflavin and he is well in follow up.

Conclusion: Early diagnosis of mild cases and treatment with high dose riboflavin may have better prognosis.

Introduction

Glutaric aciduria II (GAII) or multiple acyl-CoA dehydrogenase deficiency (MADD) is classically caused by a congenital defect in mutations in the electron transfer flavoprotein alpha-subunit (ETFA), electron transfer flavoprotein β-subunit (ETFB) or electron transfer flavoprotein dehydrogenase (ETFDH) genes, which encode for the mitochondrial electron transfer flavoprotein (ETF) and ETF: QO proteins.[1]

Flavin adenine dinucleotide synthase (FADS) deficiency caused by mutations in flavin adenine dinucleotide synthetase 1 (FLAD1) was recently reported as a novel riboflavin metabolism disorder resembling MADD.[2] In this disease, disrupted transfer of reduced flavin adenine dinucleotides toward the mitochondrial respiratory chain results in

an impaired mitochondrial fatty acid β-oxidation (FAO) and accumulation of toxic metabolites.[3] MADD-patients are historically classified into three groups: neonatal-onset congenital anomalies (type I/II) or with a later onset, relatively mild phenotype (type III).[4]

Patients with a neonatal onset suffer from life-threatening symptoms which include metabolic derangements, cardiomyopathy, leukodystrophy, hypotonia[3] and also severe hypoglycemia and metabolic acidosis leading to rapid death.[5]

The clinical course of later onset patients ranges from recurrent hypoglycemia to cyclic vomiting, lipid storage myopathy, exercise intolerance, chronic fatigue[3] and acidosis especially after meals rich in fat and/or proteins.[5] It also can be fatal in rare cases and usually associated with metabolic stress.[6] An acrid odor may be a clue to the diagnosis.

Diagnosis: GAII typically presents with characteristic organic aciduria with increased excretion of numerous metabolites, reflecting multiple pathway involvement. Abnormalities of fatty acid oxidation (FAO) are reflected by C4-C18 dicarboxylic aciduria. Other metabolites include glutaric acid, isovaleryl, isobutyryl and 2-methylbutyryl glycine and ethylmalonic acid. Diagnostic confirmation of GAII is DNA studies. Both ETF and ETF-QO activities can be measured in a variety of tissues including skin fibroblast and amniocytes.[7]

Treatment: Treatment of GAII is difficult because supplying energy from fatty acids is impossible due to the functional loss of the electron transfer flavoprotein. Acetyl-CoA, provided by exogenous ketone bodies such as NaßHB3, is the only treatment option in severe cases. Short-term therapy attempts have shown positive results.[8] A considerable group of patients has been described to respond positively to high dose of riboflavin (100-300mg/daily).[7]

Case Presentation

A 5-year-old boy presented with muscle weakness of lower limb and inability to walk from one month before. He had a history of neonatal admission because of respiratory distress, hepatomegaly, hypoglycemia, metabolic acidosis, pancytopenia, and hyperlipidemia (Triglyceride: 4423mg/dl, Cholesterol: 375mg/dl). He had two attacks of seizure due to hypoglycemia following long fasting from two years ago. Biopsy of liver was done two years ago because of hepatomegaly and elevated levels of liver enzyme. Macrovesicular steatosis suggesting of glycogen storage disease type I was reported. Laboratory tests of his recent admission are presented in Table 1.

Table 1. Laboratory tests of the patient

Test	Result
Blood	
Serum glutamic-pyruvic transaminase	990 U/L
Aspartate aminotransferase	3060 U/L
Lactate dehydrogenase	2690 U/L
Creatin phosphokinase	20000 U/L
Blood sugar	35 mg/dl
Cholesterol	153 mg/dl
Triglyceride	215 mg/dl
Uric acid	10 mg/dl
Lactate	98 mg/dl
Ammonia	592 µg/dl
Calcium	9.3 mg/dl
Phosphorus	1.9 mg/dl
Creatinine	0.5 mg/dl
Urine Randome	
Phosphorus	26
Creatinine	15
Sodium	250
Potassium	33

Table 2. Acylecarnitine Profile and Urine Organic Acids

Test	Result	Reference range
Plasma acylecarnitine profile		
Free carnitine	1.78 µmol	7.6-32
C4	0.51 µmol/L	< 0.28
C14	0.19 µmol/L	0.15
C16	0.42 µmol/L	< 0.02
C16:1	0.37 µmol/L	< 0.07
C18	0.22 µmol/L	< 0.1
C18:1	0.43 µmol/L	< 0.16
C18:2	0.25 µmol/L	< 0.14
Urine organic acid		
Ethylemalonic acid	88.2 mmol/mol cr	< 32
Glutaric acid	140 mmol/mol cr	< 7
2-hydroxyglutaric acid	97.9 mmol/mol cr	< 14

In urine analysis, the urine ketone was negative. Blood 3 positive due to rhabdomyolysis, tubulopathy, elevated phosphorus excretion (FEP: 46%) and transient renal tubular acidosis was detected.

Echocardiography was normal. With suspicion of FAO disorder metabolic test was done and he also took dextrose water 10% 1.5*maintenance and sodium benzoate for treatment of hyperammonemia. Supportive care was done due to rhambdomyolysis.

Based on acylecarnitine profile and urine organic acids, the diagnosis of GAII was established (Table 2).

Riboflavin treatment (100mg every 12 hours) started for him. He was discharged with relative improvement, recommendation of avoiding long fasting, use of raw corn starch (1gr/kg) at bedtime and riboflavin. At two years' follow-up he was well.

Discussion

Long term success has not been reported for early onset glutaric aciduria type 2. Because ETF and ETF-QO are flavoproteins, long term treatment with high-dose riboflavin in some milder cases has been successful.[7] Our patient was treated with high-dose riboflavin (100mg BID) and is well after 2 years.

Conclusion

GAII is a rare disorder of mitochondrial fatty acid oxidation and amino acid metabolism. The infant with classic GAII presents with life threatening illness in the first days of life. The clinical picture is reminiscent of those of the typical organic acidemias, propionic acidemia, methyl malonic acidemia and isovaleric acidemia, but the severity of illness in this disease is so great. Early diagnosis of mild cases and treatment with high-dose riboflavin may be effective and lifesaving.

Conflict of Interests

Authors have no conflict of interests.

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