Case Study

GLUTARIC ACIDEMIA TYPE II IN A FILIPINO SCHOOL AGE CHILD

Dr. Leniza G. De Castro-Hamoy [1, 2,3], Dr. Juan Carlo C. Viado [1], Dr. Novette Regina M. Lagunzad [1,3]

Author's Affiliation:
1- Department of Pediatrics, Medical Center Manila (ManilaMed), Ermita, Manila.
2- Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila.
3- Department of Pediatrics, College of Medicine, University of the Philippines Manila.

Correspondence:
Leniza G. de Castro-Hamoy, Email: lgdecastrohamoy@up.edu.ph Contact: +63283101780

Received on: 04-Mar-2020 Accepted for Publication: 20-July-20

ABSTRACT

Glutaric Acidemia type II is a rare hereditary metabolic disorder involving fatty acid oxidation and amino acid metabolism. Symptoms can range from severe neonatal life-threatening events which may include physical abnormalities and acidosis to milder, late-onset presentations.

Aims: The aims of this report are to raise the awareness of physicians regarding the metabolic causes of encephalopathy and rhabdomyolysis, to discuss the value of molecular panel testing, and showcase the importance of a genetic diagnosis to aid prognostication and treatment.

Case Description: This is a case of a 9-year-old healthy young boy who experienced metabolic crisis with rhabdomyolysis precipitated by a prior history of acute gastroenteritis. Urine organic acid analysis was suggestive of a fatty acid oxidation disorder and a fatty acid oxidation panel confirmed a homozygous pathogenic variant identified in ETFDH consistent with multiple Acyl-CoA dehydrogenase deficiency. He was started on riboflavin and CoQ10 supplementation and advised dietary modification to allow intake of a healthy amount of fats.

Conclusion: This is the first reported case of Glutaric Acidemia type II in the Philippines and underlies the importance of multidisciplinary approach to diagnosis and management of rare clinical presentations and conditions. It also showcases the role of diagnostic panels when a particular group of metabolic disorders is suspected but the exact enzyme defect cannot yet be identified.

Keywords: glutaric aciduria type 2, rhabdomyolysis, myopathy, riboflavin-responsive MADD

INTRODUCTION

Glutaric aciduria II (GA2, OMIM # 231680), also called multiple acyl-coenzyme A (acyl-CoA) dehydrogenase deficiency (MADD), is an autosomal recessive inborn error of fatty acid, amino acid, and choline metabolism. The prevalence rate of MADD is 1 to 9/1,000,000 but there is a great variation among different countries.[1] Based on the Philippine Pediatric Society registry and as confirmed with the Institute of Human Genetics which manages the metabolic registry (oral communication, May 2019), this is the first reported case in the Philippines.[2] Three genes are involved in glutaric acidemia type II, namely *ETFA* (15q23-q25), *EFTB* (19q13.3-q13.4) and *ETFDH* (4q32-q35). Symptoms result from deficiencies in the electron transfer flavoprotein (ETFA or ETFB subunits) or ETF flavoprotein dehydrogenase (ETFDH) seen in the inner mitochondrial matrix, which are essential in metabolizing proteins and fats.[3,4,5]

There are three described phenotypes of MADD -- neonatal onset with, or without, congenital anomalies (MADD-S, severe), and mild and/or late onset (MADD-M, mild). Classical MADD or MADD-S may present with hypoglycemia, hyperammonaemia and acidosis with hypotonia and hepatomegaly in the early life. Congenital abnormalities involving the kidneys, genitalia and neuronal migration defects are noted in infancy yielding a poor prognosis. MADD-M patients manifest in adolescence or adulthood with acute Reye-like illness with ketoacidosis and lipid storage myopathy triggered by infections or fasting, and are associated with better outcomes. Some mutations in the *ETFDH* gene have been associated with riboflavin-responsiveness. The ETFDH (or ETFQ:O) protein mediates electron transport from flavoprotein dehydrogenases to the ubiquinone

pool.[6] Riboflavin is a precursor of flavin adenine dinucleotide (FAD), a cofactor of ETFDH, hence riboflavin has been hypothesized to play a role in proper protein folding or stabilization of ETFDH variant protein conformation.[7]

This case report describes a school-aged child with clinical manifestations and molecular confirmation consistent with mild, riboflavin-responsive MADD.

CASE DESCRIPTION

A previously healthy 9-year-old Filipino male presented with encephalopathy and lower extremity weakness. He had a 3-week history of multiple bouts of loose bowel movement and vomiting with resolution after hydration and antibiotic therapy. He developed undocumented fever, severe abdominal pain, bilateral lower extremity weakness, and decreased sensorium a few hours prior to admission. Complete blood count revealed leukocytosis with neutrophilic predominance. Serum lactate dehydrogenase (10,307 U/L), serum aspartate aminotransferase (AST; 5,295 U/L), serum alanine aminotransferase (ALT; 830 U/L), and serum ammonia (152 umol/L) were significantly elevated. Hypoglycemia was noted on capillary blood glucose testing. At the time, the impression was acute liver injury probably secondary to ischemia, rule out Reye syndrome. He was transferred to our institution for further work-up and management.

He is the younger among 2 children, born to non-consanguineous parents of Filipino descent. Family history of fatty liver on the maternal side and of diabetes mellitus on both maternal and paternal sides were noted. The rest of the history was non-contributory.

At the emergency room, the patient was received stretcher-borne, drowsy but arousable, not in cardio-respiratory distress. The patient was afebrile, normotensive, had tachycardia with regular heart rhythm, and clear breath sounds. There was no jaundice noted. Abdominal examination revealed epigastric tenderness on light palpation with palpable liver edge 1-2 cm below the subcostal margin. He had no cranial nerve and sensory deficits but there was significant symmetric muscle weakness with motor grading of 3/5 in all extremities. Meningeal signs were absent.

Imaging studies such as cranial computed tomography scan and chest X-ray were unremarkable. Serum ceruloplasmin, antinuclear antibodies, immunoglobulin G, anti-smooth muscle antibody, and anti-liver-kidney microsomal antibody were within normal limits. He had rhabdomyolysis with a peak creatine kinase (CK) level of 50,842 U/L (elevated 726-fold). Serum aminotransferases (AST significantly higher than ALT) and lactic dehydrogenase were elevated. Urine organic acid analysis revealed a moderately increased adipate with slightly increased decenedioate and suberate, and positive hexanoylglycine and suberylglycine, suggestive of a fatty acid oxidation disorder. Due to unavailability of plasma acylcarnitine analysis during this time, tandem mass spectrometry analysis of dried blood spot samples was done which showed an increase in medium chain and very long-chain acyl-CoA dehydrogenase metabolites namely decanoylcarnitine (C10), dodecanoylcarnitine (C12), and ratios of octaboylcarnitine/acetylcarnitine (C8/C2) and tetradecenoylcarnitine/acetylcarnitine (C14:1/C2).

The initial consideration was a fatty acid oxidation disorder, probably very long chain acyl Co-A dehydrogenase deficiency on the basis of the clinical presentation of acute muscle weakness, rhabdomyolysis precipitated by a history of acute gastroenteritis, high ammonia and organic acid analysis results.

The patient received aggressive hydration with 5% dextrose in 0.9% normal saline, with frequent monitoring of CK levels. Adequate caloric support was provided through nasogastric tube feeding.

By the 5th hospital day, his sensorium improved, he regained his motor strength and his CK had decreased to 657 U/L. Other abnormal laboratory parameters also gradually normalized. He was eventually discharged well and advised lifestyle and diet modification, as well as avoidance of fasting and special precautions to increase caloric intake during exercise or episodes of concomitant illness. A fatty acid oxidation disorder panel was sent

(Invitae, USA), and sequence analysis and deletion/duplication testing of the 31 genes tested revealed a homozygous pathogenic variant, c.250G>A (p.Ala84Thr) identified in *ETFDH* gene, confirming the diagnosis of Glutaric Aciduria type II.

He was advised to start a healthier diet with fat content at the recommended intake for his age, and was started on Riboflavin 300 mg/day and CoQ10 60 mg/day. They were also advised regarding avoidance of fasting, early consult and higher calorie intake during sick days. Genetic counseling was done regarding recurrence risk for autosomal recessive inheritance. Twelve months since his presentation to the emergency room, he has been asymptomatic with no recurrence of muscle weakness.

DISCUSSION

Rhabdomyolysis is defined as muscle symptoms with 11-fold increase of serum creatine kinase. Biochemically, an insult in the ion channels can activate a series of myolytic cascading events leading to necrosis of the muscle fibers and release of its contents such as myoglobin, creatine kinase, aldolase, and lactate dehydrogenase into the bloodstream. The causes of rhabdomyolysis overlap with that of muscle weakness and may range from traumatic injury to infectious and genetic etiologies. When initial testing for common acquired causes does not reveal a diagnosis, inherited myopathies should be considered and these include inborn errors of metabolism such as glycogen storage disorders, fatty acid oxidation disorders, and mitochondrial disorders, as well as congenital myopathies and mutations in LPIN1.[8]

Biochemical tests such as urinary organic acid analysis and plasma acylcarnitines aid in the diagnosis of metabolic myopathies. For patients with MADD, urine organic acid analysis findings show combinations of increased dicarboxylic acids, glutaric acid, ethylmalonic acid, 2-hydroxyglutarate, and glycine conjugates, similar to the findings in our patient.[5] The plasma acylcarnitine profile may reveal short, medium and long chain metabolites.[4] Muscle biopsy, now recommended only when genetic test results are inconclusive, may show lipid accumulation and enlargement of the mitochondria.[8] Molecular DNA testing can confirm the diagnosis and in our case was very informative in terms of predicting prognosis.

The c.250G>A (p.Ala84Thr) variant identified in *ETFDH* gene in our patient has been reported as the most common mutation in late-onset/ riboflavin-responsive MADD and is common in South East Asian countries like Southern China and Taiwan where there is a strong Southern Min background.[9,10,11] Chen, Zhang et. al. proposed that the geographic distribution of the variant being consistent with the migration route of the southern Min Chinese in Southeast Asia is suggestive of a founder effect in this population. While this patient does not have any reported Chinese ethnicity, the Philippines actually has a significant number of Chinese immigrants, wherein 98.1% are of Min background, and majority specifically from Quanzhou.[12] The usual dose of riboflavin supplementation reported for riboflavin-responsive patients is 90-400mg/day, which results in significant improvements in the biochemical and clinical parameters as seen in our patient.

CONCLUSION

It is important to have a high index of suspicion for metabolic disorders in patients with unusual presentations such as encephalopathy and rhabdomyolysis. Prompt and correct diagnosis will enable us to give appropriate intervention and prevent future episodes of life-threatening rhabdomyolysis. The availability of diagnostic panels is helpful in narrowing down possible metabolic causes in a timely manner when it is difficult to identify the specific enzyme defect. This case further supports the good genotype phenotype correlation in MADD and its importance in counseling regarding outcomes and response to therapy.

ACKNOWLEDGEMENT

The authors would like to thank the Pediatric team of the Medical Center Manila (ManilaMed) for the multi-disciplinary medical management

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