Glutaric Aciduria Type II Presenting as Myopathy and Rhabdomyolysis in a Teenager

Manish Prasad, MBBS, MD, MRCPCH1, and Shanawaz Hussain, MBChB, BSc (Hons), MRCPCH2

Abstract

Late-onset glutaric aciduria type II has been described recently as a rare but treatable cause of proximal myopathy in teenagers and adults. It is an autosomal recessive disease affecting fatty acid, amino acid, and choline metabolism. This is usually a result of 2 defective flavoproteins: either electron transfer flavoprotein (ETF) or electron transfer flavoprotein–ubiquinone oxidoreductase (ETF:QO). We present a 14-year-old boy with a background of autistic spectrum disorder who presented with severe muscle weakness and significant rhabdomyolysis. Before the onset of muscle weakness, he was very active but was completely bedridden at presentation. Diagnosis was established quickly by urine organic acid and plasma acylcarnitine analysis. He has shown significant improvement after starting oral riboflavin supplementation and is now fully mobile. This case highlights that late-onset glutaric aciduria type II is an important differential diagnosis to consider in teenagers presenting with proximal myopathy and rhabdomyolysis and it may not be associated with hypoglycemia.

Keywords

myopathy, rhabdomyolysis, glutaric aciduria type II, multiple acyl Co-A dehydrogenase deficiency

Received September 4, 2013. Received revised October 9, 2013. Accepted for publication November 20, 2013.

Glutaric aciduria type II was first reported by Przyrembel et al1 in 1976, in an infant with hypoglycemia and profound metabolic acidosis in the absence of ketosis.

Glutaric aciduria type II or multiple acyl-CoA dehydrogenase deficiency is an autosomal recessive disorder affecting fatty acid, amino acid, and choline metabolism and defects in mitochondrial electron transfer.1 It is caused by a deficiency of either the alpha- or beta-subunits of the electron transfer flavoprotein (ETFA, ETFB) or electron transfer flavoprotein–ubiquinone oxidoreductase.2 Clinical presentation is highly variable and 3 major forms have been described (see Table 1): type I, the neonatal-onset (lethal) form with congenital anomalies, nonketotic hypoglycemia, metabolic acidosis, excretion of large amounts of fatty acids, and amino acid–derived metabolites and the patient may die in the newborn period; type II, a neonatal-onset form without congenital anomalies; and type III, a late-onset form.2

By contrast, the symptoms of the late-onset form differ in the disease course, and the age at presentation is highly variable. Presentations are characterized by recurrent episodes of vomiting, lethargy, hypoglycemia, metabolic acidosis, and hepatomegaly, particularly during metabolic stress. Muscle involvement may present in the form of pain, weakness, and lipid-storage myopathy. Of note, characteristic urine organic aciduria profile may only be detectable during periods of metabolic stress.3

We present a teenager with the late-onset form of glutaric aciduria type II, which is a rare but treatable cause of significant proximal myopathy. We also discuss the differential diagnosis and importance of considering late-onset glutaric aciduria type II in the differential in teenagers presenting with proximal myopathy and rhabdomyolysis as it is a potentially treatable disorder.

Case History

A 14-year-old boy with severe autism presented with a history of progressive weakness, anorexia, and significant rhabdomyolysis at presentation (creatine kinase 22 000 IU/L). His weakness had started 1 year prior to his presentation as well as weight loss and poor appetite. Parents attempted to help to improve his weight by feeding him a high-fat diet. This had...
progressed over the last 3 months, necessitating him to be wheelchair bound and at the time of presentation he was completely bedridden. He had lost significant weight at presentation (42 kg, 0.4th centile). He was born to healthy nonconsanguineous parents with no positive family history of myopathy or any muscle disorder.

On assessment, he was noted to have generalized wasting of his muscles and pain on flexion of his hips. His reflexes were difficult to elicit, and plantar reflexes were both flexor bilaterally. Because of his underlying severe autism, his power was difficult to assess. He also had a faint rash around his eyes and conjunctival injection.

Given his high creatine kinase level, a test for urine myoglobin was positive and his serum myoglobin was elevated at 4848 mg/L. He was started on hyperhydration and furosemide to prevent any secondary renal damage. His renal function remained intact. An underlying diagnosis of dermatomyositis was considered and an urgent muscle MRI was done. The muscle MRI was normal; however, he was noted to have persistently high plasma lactate (7.3 mmol/L). An urgent metabolic consult was made where it was thought the high plasma lactate could be secondary to muscle cell breakdown. At the same time, an urgent plasma acylcarnitine and urine for organic acids were sent.

His urine organic acids showed moderate ketonuria with increased dicarboxylic acids and increased 2-hydroxyglutarate, 4-hydroxyphenyllactate, and a significant peak of orotic acid diagnostic of multiple acyl-coenzyme A dehydrogenase deficiency (glutaric aciduria type II). Further analysis of plasma acylcarnitines showed an increase in a number of acylcarnitines (C4-C18:1), confirming the diagnosis of glutaric aciduria type II (Table 2).

As soon as the diagnosis was made, he was started on riboflavin 100 mg (twice daily), as well as a high carbohydrate diet. His diagnosis was made on urine organic acid and plasma acylcarnitine profile, which subsequently improved after commencement of the riboflavin (Table 2). At the 4-week follow-up, he had dramatically regained weight (49.5 kg, 9th centile) and his strength had improved, though he was still requiring his wheelchair for mobility. At the 4-month follow-up, he was able to mobilize fully at home only requiring a wheelchair for school with continuing improvement in weight. His mobility and school performance including behavior continued to improve with an associated dramatic reduction in his creatine kinase over time. At 1 year, parents reported normal mobility and exercise tolerance.

### Discussion

Our case illustrates an uncommon but treatable cause of proximal myopathy and significant rhabdomyolysis. Hereditary...
metabolic myopathies are a heterogeneous group of conditions and often pose a diagnostic challenge in view of diverse etiologies. Important differentials to consider include endocrine, infectious, neuromuscular junction, iatrogenic (steroids), inflammatory, and metabolic disorders.3

Metabolic myopathies are caused by defects in cellular energy metabolism. It comprises 3 main categories that are glycogen storage diseases, fatty acid oxidation defects, and mitochondrial disorders due to respiratory chain impairment.

Metabolic myopathies generally present with progressive muscle weakness, episodic muscle aches and cramps, fatigue, and occasionally with extensive rhabdomyolysis with myoglobinuria.4

It is no surprise that dermatomyositis was initially suspected in our patient. Review of literature suggests that metabolic myopathies such as glutaric aciduria type II can often be confused as inflammatory myopathies.4 In fact, some of these patients can also satisfy the criteria for diagnosis of polymyositis proposed by Bohan and Peter.3

Our patient at presentation had significant rhabdomyolysis as depicted by a creatine kinase level of 22 000 IU/L. Although rhabdomyolysis with a raised creatine kinase level is commonly associated in late-onset glutaric aciduria type II patients presenting with muscle aches and weakness, to our knowledge such significantly raised creatine kinase level has not been described before. Interestingly although rhabdomyolysis can be present in other causes of acquired myopathies, particularly inflammatory causes, rhabdomyolysis with myoglobinuria is generally more suggestive of metabolic myopathies.5

The age at presentation of glutaric aciduria type II is highly variable, ranging from late infancy and childhood6 to adolescence and even reported as late as 78 years.2,7,8 Of note, significant neck extension weakness, which is often out of proportion to the overall proximal muscle weakness,2 was not apparent on our case.

Diagnosis of glutaric aciduria type II can be established by analysis of urine organic acids and acylcarnitine profile. Urinary organic acid profiles in late-onset glutaric aciduria type II is characterized by elevated amounts of glutaric acid, ethylmalonic acid, isovaleric acid, a-methylbutyrate, isobutyrate, aliphatic dicarboxylic acids, and their derivatives, as evident in our case.1,13 However, in the milder late-onset glutaric aciduria type II form, the abnormal urinary organic aciduria may only be evident during episodes of stress or exacerbation. Interestingly, retrospective analysis of our patient’s newborn screening blood test showed a normal carnitine and acylcarnitine profile.

Acylcarnitine profiling by tandem mass spectrometry screening of serum or dried blood spot samples characteristically shows increased concentrations of short-, medium-, and long-chain acylcarnitines (C4-C12), as shown in our patient.5

All 3 clinical forms can be caused by a defect in any of the 3 genes associated with glutaric aciduria type II.14 Recent reports also suggest a genotype-phenotype correlation in patients with glutaric aciduria type II.14 However, it may be appropriate to start with mutational analysis of ETF-DH, in view of the relatively frequent reports of late onset cases with ETF-DH mutations.10,15 Genetic counseling was offered to the family but further mutational analysis for ETF-DH was not carried out by the genetics team as the diagnosis had already been on urine organic acids and blood acylcarnitine analysis.

This patient has shown dramatic and sustained improvement on a low-fat, low-protein, and high-carbohydrate diet supplemented with oral riboflavin and carnitine. This is consistent with the few previously reported cases of teenagers with late-onset glutaric aciduria type II, who showed no improvement on corticosteroids and carnitine but significantly improved after introduction of riboflavin and dietary changes.7 Oral riboflavin has been consistently reported to improve the condition of patients with glutaric aciduria type II dramatically, with almost complete resolution of symptoms and signs in milder cases.11-13 Supplementation with carnitine has also been suggested in view of the findings of low carnitine in these patients.6

Even in severe neonatal cases, oral riboflavin and dietary management regime has been associated with improvement, underlying the importance of early diagnosis and treatment.18,19

Conclusion
This case highlights that late-onset glutaric aciduria type II is an important differential to consider in teenagers presenting with proximal myopathy and rhabdomyolysis and may not be associated with hypoglycemia. This is a rare presentation that may be confused with neurologic and inflammatory conditions. Unnecessary invasive investigations such as muscle biopsy can be avoided as the diagnosis can be made rapidly by a dried blood spot test for acylcarnitine profile or urine organic acid analysis.

Acknowledgments
The authors wish to acknowledge the help of the metabolic department in the care of the patient.

Author Contributions
SH authored the first draft along with MP. The scientific aspects of the case were researched by MP.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval
Ethical approval was not required for this case study, though parental consent was obtained.

References


