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CASE REPORT

Liver Failure with Coagulopathy, Hyperammonemia and Cyclic Vomiting in a Toddler Revealed to Have Combined Heterozygosity for Genes Involved with Ornithine Transcarbamylase Deficiency and Wilson Disease

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Abstract A girl with a 2 month history of cyclic episodes of vomiting, diarrhea, and lethargy lasting 2–3 days each presented with acute hepatopathy (ALT 3,500 IU/L) with coagulopathy (PT 55 s) and hyperammonemia (207 μmol/L) at age 1½ years. Biochemical and molecular analyzes revealed ornithine transcarbamylase (OTC) deficiency. While laboratory signs of mild hepatocellular dysfunction are common in OTC deficiency, substantial liver failure with coagulopathy is generally not seen, although four others cases have been reported, three of which presented with cyclic vomiting. Further evaluation in our case revealed elevated urine (198.8 μg/g creatinine) and liver (103 μg/g dry weight) copper content, and a heterozygous mutation in the Wilson disease gene, *ATP7B*. Our patient, now aged 5 years, has remained in excellent health with normal growth and development on fasting avoidance, a modified vegan diet, and sodium phenylbutyrate.

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These five cases demonstrate that generalized liver dysfunction/failure is a potential serious complication of OTC deficiency, although not a common one, and suggests that an ALT and PT should be obtained in OTC patients during episodes of hyperammonemia. Cyclic vomiting is a known presentation of OTC deficiency; it is not known if comorbid liver failure predisposes toward this phenotype. We propose that the heterozygote state in *ATP7B* increases the liver copper content, thus predisposing our patient with OTC deficiency to develop liver failure during a hyperammonemic episode. Our present case is an example of the opportunity of molecular diagnostics to identify putative modifier genes in patients with atypical presentations of genetic disorders.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CMV	Cytomegalovirus
EBV	Epstein–Barr virus
HSV	Herpes simplex virus
INR	International normalized ratio
OTC	Ornithine transcarbamylase
PT	Plasma thromboplastin
PTT	Partial thromboplastin time

Introduction

Ornithine transcarbamylase (OTC) deficiency, an inborn error of the urea cycle inherited in an X-linked manner, is the most common inherited cause of hyperammonemia (Pridmore et al. 1995). While hemizygous males generally suffer from life-threatening early-onset disease, disease manifestations in heterozygous females with unfavorable

X-inactivation are generally milder and of later-onset, often presenting in the first few years. OTC deficiency in females is frequently under-diagnosed (Pridmore et al. 1995), yet potentially fatal. Clinical presentation generally is of acute, often episodic, altered mental status in an otherwise normal young girl, although cyclic vomiting can also occur (Li et al. 2008). Diagnosis is suspected based on high blood ammonia, high serum glutamine, low serum citrulline, and high urine orotate, and confirmed by sequencing the OTC gene. While laboratory signs of mild hepatocellular dysfunction is common in OTC deficiency, substantial liver failure with coagulopathy is not commonly seen, although a few cases have been reported (Mustafa and Clarke 2006; Zammarchi et al. 1996).

Case Report

We report a Hispanic female with normal growth and development who first presented at age 20 months with intermittent vomiting, diarrhea, and lethargy over the preceding 2 months. Episodes were stereotypical, commencing always at 22:30 in the evening, lasting for 2–3 days each, and separated by a few days before the next episode occurred. Symptoms resolved between episodes. On presentation, laboratory studies revealed acute liver failure with peak values of PT 55 s, PTT 68 s, INR 4.3, ALT 3,500 IU/L, AST 2,500 IU/L, and ammonia 207 μmol/L (normal 22–48). Hepatomegaly and jaundice were absent. All symptoms and laboratory anomalies resolved on supportive therapy.

Biochemical analysis 9 days later revealed high plasma glutamine (1,512 μmol/L), low plasma citrulline (17 μmol/L), and high urine orotate (60 mmol/mol creatinine, normal < 1), consistent with OTC deficiency. Genetic evaluation revealed she is a heterozygote for the OTC mutation c.602 T>C, with an amino acid change at L201P. This is a known mutation associated with neonatal-onset disease (Shimadzu et al. 1998). Due to elevations in liver copper (103 μg/g dry weight, normal 10–35) and urine copper (198.8 μg/g creatinine, normal 6.7–18.6), DNA testing was also performed on the *ATP7B* gene, whose dysfunction causes Wilson disease. Results revealed a heterozygote state for a mutation in exon 6, 1934 T>G, with an amino acid change of M645R. Kayser–Fleischer rings were absent. Many other potential causes of liver failure were absent on testing, including hepatitis A, B, and C, adenovirus, CMV, EBV, HSV, antinuclear antibody, alpha-1-antitrypsin, and acetaminophen and salicylate levels.

Shortly after first presentation, the patient was placed on a low-protein (modified vegan) and low-copper diet, fasting avoidance, and sodium phenylbutyrate as a nitrogen-conjugating agent. On this therapy, she has been asymptomatic up to the present age of 5 years, except for a single episode of vomiting during an upper respiratory infection, with ALT elevated at 529, but normal PT (12) and borderline-elevated ammonia (52). Growth and development have remained normal.

Molecular evaluation on the mother revealed carrier status for both the OTC and Wilson disease mutations, although she never had any symptomatology consistent with hyperammonemia or episodes of liver failure. She has always been on a varied diet, including meat and dairy, without protein aversion. Testing of the mother revealed an elevated urine orotate (39), with normal levels for blood glutamine (559), ammonia (< 9), and ceruloplasmin (35), and for urine copper (15.6) (units and normal ranges essentially as listed above). Unfortunately, X-inactivation studies on both mother and child were not interpretable, with two possibilities in each, one essentially normal (83:17 mom, 68:32 child), and one highly skewed (100:1 in both).

Discussion

A literature search revealed four cases with OTC deficiency presenting with acute liver dysfunction with coagulopathy, presenting at ages 3, 10, 14, and 44 months (Mustafa and Clarke 2006; Zammarchi et al. 1996). These cases demonstrate that generalized liver dysfunction/failure is a potential serious complication of OTC deficiency, although likely not a common one, and suggests that an ALT and PT should be obtained in OTC patients during episodes of hyperammonemia.

Wilson disease is an inborn error of copper transport in which reduced excretion of copper into bile leads to copper accumulation in many tissues. It generally presents with neurological, psychiatric, and/or hepatic disease. Liver dysfunction, including liver failure, is the presenting feature in over 80% of cases presenting in the first decade (Gollan and Gollan 1998). Heterozygous carriers for Wilson disease are not known to develop liver failure, although copper content of the liver can be elevated in some (Hoogenraad 1997). We propose that the heterozygote state in *ATP7B* increases the liver copper content, thus acting as a modifier gene by predisposing our patient with OTC deficiency to develop liver failure during a hyperammonemic episode. Finding a heterozygous mutation in the Wilson gene, or in another gene involved in copper metabolism, in other patients with OTC deficiency, and episodic acute liver failure would support our hypothesis. The four above-mentioned cases with OTC deficiency and liver failure reported normal plasma ceruloplasmin (Mustafa and Clarke 2006; Zammarchi et al. 1996), and blood copper was reported as normal in one of those cases (Zammarchi et al. 1996). However, blood copper was also normal in our

patient (105 mcg/dl, normal 76–193), and our patient's ceruloplasmin was only mildly low (16 mg/dl, normal 24–71), which is a common finding in infants with liver dysfunction of varied etiologies.

Our patient's mother is heterozygous for mutations in both genes but, unlike her daughter, the mother never presented with clinical disease. These differences parallel the differences in body fluid metabolite testing, in that the child had elevated blood glutamine and urine copper, but not the mother. The reasons are not clear, but may be due to differences in additional modifying genes and/or X-inactivation proportions for the OTC gene (lyonization). Unfortunately, we were unable to test the latter possibility.

Cyclic vomiting refers to repetitive stereotypical episodes of vomiting separated by intervals without vomiting. While most cases meet criteria for cyclic vomiting syndrome (Li et al. 2008), a condition associated with combinations of specific mtDNA polymorphisms (Zaki et al. 2009), another definable etiology is identified in a substantial minority of cases with a cyclic vomiting pattern. Among the etiologies that should be considered in cases with cyclic vomiting is deficiency of the intra-mitochondrial enzyme OTC (Li et al. 2008). In the four above-mentioned cases with OTC deficiency and liver failure, vomiting was present in three cases that were described as "intermittent" (Mustafa and Clarke 2006), in "recurrent episodes" (Zammarchi et al. 1996), and "persistent" (Zammarchi et al. 1996). OTC can be distinguished from cyclic vomiting syndrome by the presence in the former of true altered mental status and/or aversion to high-protein foods (Hoogenraad 1997). We do not know if the presence of comorbid liver failure predisposes OTC-deficient girls to present with a cyclic vomiting presentation, but the limited number of case reports suggest this as a possibility. Another condition that presents as altered mental status, vomiting and hyperammonemic liver failure is Reye syndrome. However, the presentation associated with that historical term is now known to include cases with many clinically definable metabolic disorders, including urea cycle defects and mitochondrial disorders. Interestingly, liver dysfunction is the most prominent effect of copper toxicity, and this toxicity is thought to at least in part involve mitochondrial dysfunction (Mehta et al. 2006).

Our present case is an example of the opportunity of molecular diagnostics to identify putative modifier genes in patients with atypical presentations of genetic disorders.

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One Sentence Take-Home Message

Liver failure is an occasional complication of partial OTC deficiency; potential associations may include cyclic vomiting and/or heterozygosity for the Wilson gene.

References

Gollan JL, Gollan TJ (1998) Wilson disease in 1998: genetic, diagnostic and therapeutic aspects. J Hepatol 28:28–36

Hoogenraad T (1997) Wilson's disease. In: Major problems in neurology. WB Saunders, London, p 209

Li BU, Lefevre F, Chelimsky GG et al (2008) NASPGHAN consensus statement on the diagnosis and management of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 47:379–393

Mehta R, Templeton DM, O'brien PJ (2006) Mitochondrial involvement in genetically determined transition metal toxicity II. copper toxicity. Chem Biol Interact 163:77–85

Mustafa A, Clarke JTR (2006) Ornithine transcarbamylase deficiency presenting with acute liver failure. J Inherit Metab Dis 29:586

Pridmore CL, Clarke JT, Blaser S (1995) Ornithine transcarbamylase deficiency in females: an often overlooked cause of treatable encephalopathy. J Child Neurol 10:369–374

Shimadzu M, Matsumoto H, Matsuura T et al (1998) Ten novel mutations of the ornithine transcarbamylase (OTC) gene in OTC deficiency. Hum Mutat 1:S5–S7

Zaki EA, Freilinger T, Klopstock T et al (2009) Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. Cephalalgia 7:719–728

Zammarchi E, Donati MA, Filippi L, Resti M (1996) Cryptogenic hepatitis masking the diagnosis of ornithine transcarbamylase deficiency. J Pediatr Gastroenterol Nutr 22:380–383