Significant Hepatic Involvement in Patients with Ornithine Transcarbamylase Deficiency

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Objective To determine the frequency of significant liver injury and acute liver failure (ALF) in patients with ornithine transcarbamylase deficiency (OTCD), the most common urea cycle defect.

Study design In this historical cohort study, charts of 71 patients with OTCD at 2 centers were reviewed to assess the prevalence of ALF (international normalized ratio [INR] ≥2.0), liver dysfunction (INR 1.5-1.99), and hepatocellular injury (aspartate aminotransferase/alanine aminotransferase ≥250 IU/L).

Results More than one-half (57%) of the 49 patients with symptomatic OTCD had liver involvement; 29% met the criteria for ALF, 20% had liver dysfunction, and 8% had isolated hepatocellular injury. The prevalence of ALF was highest in the patients with more severe OTCD, including those with markedly elevated ammonia levels (>1000 μmol/L). Some patients with severe liver involvement (INR ≥2.0 and aspartate aminotransferase/alanine aminotransferase >1000 IU/L) had only moderate hyperammonemia (ammonia 100-400 μmol/L). ALF was the initial presenting symptom of OTCD in at least 3 of 49 symptomatic patients with OTCD.

Conclusion Episodes of hepatocellular injury, liver dysfunction, and ALF were identified in a high proportion of children with symptomatic OTCD. The more severely affected patients had a higher likelihood of ALF. The diagnosis of a urea cycle defect should be considered in patients with unexplained ALF, liver dysfunction, or hepatocellular injury. *(J Pediatr 2014;164:720-25)*.

Accurate diagnosis of an underlying etiology is crucial to outcome in acute liver failure (ALF).[1] ALF is of indeterminate cause in up to 50% of cases in children[2] and ~15% of cases in adults.[1] Genetic metabolic disorders are important causes of ALF in children, accounting for 9.7% of final diagnoses in a large international multisite observational study[2] and 42.5% of final diagnoses in patients presenting at age <1 year to a single center.[3] Metabolic disorders presenting with ALF include galactosemia, tyrosinemia type 1, fatty acid oxidation defects, Wilson disease, and mitochondrial hepatopathies, among others.[4,5] Narkewicz et al[2] emphasized that a systematic evaluation for treatable causes in children with ALF, including metabolic diseases, is not routine practice in many centers.

Urea cycle defects (UCDs) occur in approximately 1 in 30 000 live births.[6] These disorders are not considered prominent among the metabolic diseases that cause severe hepatic dysfunction and ALF,[4,5] despite past reports of hepatocellular injury and ALF in individuals with ornithine transcarbamylase (OTC) deficiency (OTCD),[7-11] the most common UCD. OTCD is an X-linked genetic disorder that affects both males and females. Severely affected males present with marked hyperammonemia in the newborn period. There is variable clinical expression in heterozygote females and in males with residual OTC enzyme activity; individuals of either sex may remain asymptomatic throughout their lifetime with no episodes of hyperammonemia, and symptomatic individuals with at least 1 episode of hyperammonemia can present at any age.[12] Hepatic histology in OTCD may show microvesicular steatosis, focal cell necrosis, aggregates of clear hepatocytes, portal-to-portal bridging fibrosis, abnormal mitochondria, abnormal peroxisomes, or may appear normal.[13-19]

Other UCDs have been associated with hepatocellular injury and liver failure as well.[20-28] Sundaram et al[29] reported that 2 of 148 (1.4%) infants aged <3

ALF	Acute liver failure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HCC	Hepatocellular carcinoma
INR	International normalized ratio
NIH	National Institutes of Health
OTC	Ornithine transcarbamylase
OTCD	Ornithine transcarbamylase deficiency
PT	Prothrombin time
PTT	Partial thromboplastin time
UCD	Urea cycle defect

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Portions of this study were presented at the annual meetings of the Urea Cycle Disorder Consortium in Pacific Grove, CA, February 27, 2011 and Washington, DC, July 13, 2012, and also as a poster at the meeting of the Society for Inherited Metabolic Disease, in Charlotte, NC, March 31-April 3, 2012.

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months with ALF were diagnosed with a UCD, 1 with OTCD. Despite these reports, OTCD and other UCDs are rarely considered in children and adults presenting with severe liver injury or ALF unless profound hyperammonemia is present, which has resulted in delayed or postmortem diagnosis.[11] The goal of the present study was to determine the frequency of significant liver injury and ALF in patients with OTCD.

An illustrative case is a 19-month-old female who was transferred to University of California Los Angeles Medical Center for evaluation for liver transplantation because of ALF of unknown origin. She had presented to an outside hospital with fever, vomiting, and lethargy, and was found to have an alanine aminotransferase (ALT) level of 906 IU/L, an international normalized ratio (INR) of 3.9, a partial thromboplastin time (PTT) of 46 seconds, and an ammonia level of 161 μmol/L. Evaluation for infectious hepatitis, autoimmune hepatitis, Wilson disease, and acetaminophen toxicity was negative. Liver biopsy evaluation revealed acute hepatocellular injury with mild lobular necrosis. Further testing detected elevated urine orotic acid and uracil levels. Pharmacologic treatment of OTCD was initiated on day 10 of hospitalization. Abnormal laboratory values normalized after treatment (**Figure 1**). The diagnosis of OTCD was confirmed by genotyping, which identified a heterozygous c.67C>T (p.R23X) mutation. Liver tissue was not available for enzyme analysis.

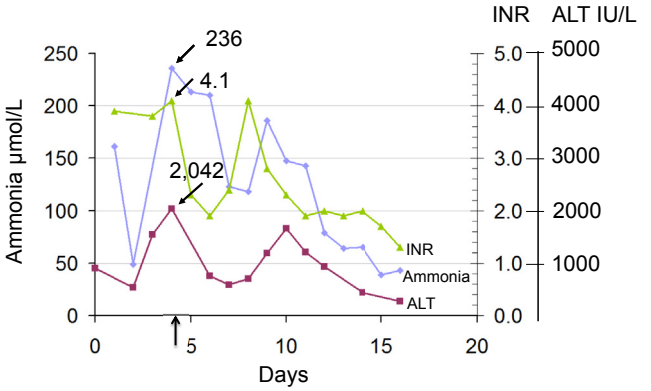

Figure 1. Time course of plasma ammonia, ALT, and INR in a severe OTCD female during her initial hospitalization at 19 months of life. Dietary treatment was instituted on day 7, and full medical therapy on day 10. The vertical black arrow indicates the time point collected for the chart review in this hyperammonemic episode (**Table IV**, case 8).

Methods

This historical cohort study was conducted at 2 large metabolic disease centers, Children's Hospital Colorado and University of California Los Angeles Medical Center. The study was approved by the Institutional Review Board at each center. Records of all individuals with OTCD who were followed at these centers between 2000 and 2011 were reviewed. These subjects were identified by site records and ongoing clinical care, and through enrollment in the National Institutes of Health (NIH)-funded, multisite Longitudinal Study of Urea Cycle Disorders at these 2 centers, which is an Institutional Review Board–approved natural history study,[30] for which written informed consent was obtained. Many individuals followed clinically for OTCD were also subjects in the NIH study, whereas some asymptomatic individuals were not seen clinically, but were subjects in the NIH study. These 2 groups constituted all known subjects followed for OTCD at the 2 centers.

OTCD was established in each subject by biochemical test results, molecular diagnosis, or enzymology. For each subject, the following historical information was recorded: age at presentation, sex, OTC mutation if known, clinical presentation, OTC enzyme activity in the liver, and liver histology. To assess liver injury, the following tests were recorded at least once for every subject: aspartate aminotransferase (AST), ALT, prothrombin time (PT), PTT, and INR. Values were obtained from clinic visits, Longitudinal Study research visits, or hospitalizations. If available, measurements of total and direct bilirubin, factor V, factor VII, factor VIII, D-dimers, fibrinogen, and plasma ammonia were recorded as well. For each subject, the time at which the available liver injury–related laboratory results were collected was the time of the highest recorded PT or INR (or AST/ALT if PT/INR was not obtained). Some of the recorded tests might have been obtained at an earlier or later time point that same day. Liver injury–related tests were also recorded on every identified occasion when the AST/ALT or PT/INR values met the criteria defined in this study for ALF, liver dysfunction, or hepatocellular injury. When possible, outside medical records, including evaluations before the identification of UCD, were reviewed.

For the purpose of this study, ALF was defined as acute liver injury with an INR $\geq$2.0 or PT $\geq$20 seconds in the absence of disseminated intravascular coagulation[2,29]; liver dysfunction, as an INR $\geq$1.5 and <2.0 or PT $\geq$15 seconds and <20 seconds; and hepatocellular injury, as AST or ALT $\geq$250 IU/L. Lack of response of elevated INR or PT to vitamin K was not included as a criterion for ALF, because this is a retrospective study, and vitamin K was not administered uniformly.

In this study, the subjects were assigned to 1 of 5 groups based on clinical severity of UCD. Subjects were considered asymptomatic with respect to OTCD if they had not experienced any episodes of hyperammonemia requiring medical intervention. The subjects with symptomatic OTCD were classified into 4 groups: neonatal males, severe males and females, moderate males and females, and mild males and females. Neonatal males, who lack residual enzyme activity, were the most severely affected, developing symptoms of hyperammonemia in the first 2 days of life. Severe males and females developed symptoms of hyperammonemia after 2 days of life, required maximal medical and dietary therapy, and had frequent hospitalizations. Moderate males and females required medical and/or dietary therapy and had less frequent hospitalizations. Mild males and females did not