Coagulopathy in Patients With Late-Onset Ornithine Transcarbamylase Deficiency in Remission State: A Previously Unrecognized Complication

abstract

The late-onset type of ornithine transcarbamylase (OTC) deficiency is almost asymptomatic before an abrupt onset of metabolic crisis in adolescence. This study focused on coagulopathy in OTC deficiency. We collected laboratory data regarding coagulation from OTC-deficient patients in Kyushu University Hospital in Japan or from cases reported from previous articles. Five patients with late-onset OTC deficiency, admitted to Kyushu University Hospital at the first metabolic attack or who presented at the outpatient clinic in the hospital, were analyzed, and 3 additional cases of OTC deficiency with coagulopathy in previous articles were included. As a result, the blood ammonia levels in these patients were remarkably high at the time of the metabolic attack, and prothrombin times were far below the normal level. The prothrombin times remained significantly abnormal on remission, despite almost normal levels of blood ammonia, serum aspartate aminotransferase, and alanine aminotransferase. Coagulation abnormality is a previously unidentified complication of OTC deficiency in remission state. This information will aid in the identification of patients with OTC deficiency before a lethal metabolic crisis occurs during adolescence. Pediatrics 2013;131:e327–e330

AUTHORS: Kenji Ihara, MD, PhD,a Makoto Yoshino, MD, PhD,b Takayuki Hoshina, MD, PhD,a Nawomi Harada, PhD,b Kanako Kojima-Ishii, MD, PhD,a Mika Makimura, MD, PhD,a Yuki Hasegawa, MD, PhD,c Yoriko Watanabe, MD, PhD,b Seiji Yamaguchi, MD, PhD,a and Toshiro Hara, MD, Phda

aDepartment of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; bDepartment of Pediatrics and Child Health, Kurume University School of Medicine; and cDepartment of Pediatrics, Shimane University School of Medicine

KEY WORDS
coagulopathy, late-onset type, ornithine transcarbamylase deficiency

ABBREVIATIONS
ALT—alanine aminotransferase
AST—aspartate aminotransferase
OTC—ornithine transcarbamylase
PIVKA-II—des-g-carboxyprothrombin
PT—prothrombin time
VK—vitamin K

www.pediatrics.org/cgi/doi/10.1542/peds.2012-0030
doi:10.1542/peds.2012-0030

Accepted for publication Jul 31, 2012

Address correspondence to Kenji Ihara, MD, PhD, Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan. E-mail: k-ihara@pediatr.med.kyushu-u.ac.jp

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.
Ornithine transcarbamylase (OTC) deficiency, an X-linked disorder, is the most frequent urea cycle disorder characterized by an acute clinical manifestation of hyperammonemia, accounting for >60% of all urea cycle disorders.\(^1\) The classic type of OTC deficiency demonstrates a severe hyperammonemia during infancy and sometimes proves fatal, whereas the late-onset type is almost asymptomatic before an abrupt onset of metabolic crisis in adolescence.\(^2\) The early diagnosis of the late-onset type is sometimes difficult because the first crisis usually appears in either adolescent or adult patients who have exhibited normal growth and development. Specific findings of abnormal metabolites in urine such as orotic acid or uracil are critical for making an accurate diagnosis of OTC deficiency.\(^5\)

In contrast, the biochemical markers in routine examinations are usually within the normal ranges. Consequently, the identification of specific markers in routine biochemical analysis would be clinically beneficial for patients with OTC deficiency. Coagulopathy in OTC deficiency is usually accompanied by acute liver failure, and slight changes in the coagulation data in a remission state have been overlooked as nonspecific findings. Hence, coagulopathy is not recognized as a consequence of OTC deficiency by itself.

This report focused on the presence of any underlying coagulation abnormality in OTC deficiency during a metabolically compensated state. We retrospectively collected laboratory data on coagulation from the clinical records of OTC-deficient patients of Kyushu University Hospital in Japan. A bibliographic search was also conducted to determine whether any coagulopathy had previously been noticed before the abrupt onset of metabolic attack in cases of OTC deficiency.

**METHODS**

Patients with OTC deficiency, admitted to Kyushu University Hospital at the first metabolic attack or who presented at the outpatient clinic in the hospital from January 1993 to December 2010, were enrolled in this study. A systematic search of the PubMed database was conducted for all articles from 1990 through 2012 with the terms “OTC deficiency,” “coagulopathy,” “coagulation,” or “prothrombin time” in the title, abstract, or key words to determine whether any articles described coagulation abnormality before and after the onset of metabolic attack in OTC-deficient patients.

**RESULTS**

Five patients were identified at our hospital as follows: patient 1 was a 10-year-old boy with OTC deficiency underlying asymptomatic coagulopathy of unknown etiology before the onset of metabolic crisis. Two patients (patients 2 and 4) were diagnosed during the asymptomatic period because the brother of patient 2 and the maternal uncle of patient 4 died of OTC deficiency at the first metabolic attack. Patients 3 and 5 experienced the first attack during infancy (10 months) and childhood (10 years), respectively. The database search identified 3 publications, and 3 cases of OTC deficiency from these articles with the description of the coagulation at remission state are shown in Table 1 (patients 6–8).\(^6\)–\(^8\)

Six of these 8 patients were male. Five patients were successfully treated and maintained normal growth and development for years. One patient died a sudden death at 19 years of age. The 2 patients described in the literature developed a metabolic attack at 24 years of age and died at the first attack. The levels of blood ammonia of these patients were remarkably high during the metabolic attack, whereas other laboratory data such as aspartateaminotransferase (AST) and alanineaminotransferase (ALT) levels were indistinctive. In contrast, prothrombin times (PTs) were below the normal level at the metabolic attack and were also considerably abnormal during remission. The blood ammonia, serum AST, ALT, or albumin levels were close to normal ranges while the patients were being managed by using either mild restriction of protein intake or oral arginine supplementation (Table 1).

**DISCUSSION**

Coagulation abnormalities have rarely been recognized in association with OTC deficiency. Coagulopathy may occur if the metabolic attacks cause severe liver damage or disseminated intravascular coagulation, but such critical conditions were not found in any of these patients. These cases also demonstrated the presence of abnormalities in coagulation even during remission. The findings suggest that coagulopathy may be a useful sign for detecting an underlying OTC deficiency, especially in boys with nonspecific clinical symptoms such as cyclic vomiting or psychological problems. To the best of our knowledge, no common genetic coagulopathy has yet been identified in the Japanese population; therefore, it is likely that this coagulation abnormality may be specific to OTC deficiency.

The pathogenesis of such a coagulation abnormality is unclear. This coagulopathy does not seem similar to that in fulminant hepatic failure with the collapse of protein synthesis in the liver. The coagulopathy in OTC deficiency might be under the same mechanism that occurs with vitamin K (VK) deficiency because elevation of serum des-γ-carboxyprothrombin (PIVKA-II) levels was sometimes detected, and VK administration seemed effective for these patients. The coagulation factors II, VII, IX, and X are activated in a VK-dependent manner during carboxylation at the γ-terminus-glutamate in
### TABLE 1 Clinical, Molecular, and Laboratory Data of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Proband</strong></td>
<td>Himself</td>
<td>Brother&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Transmission type</strong></td>
<td>ND</td>
<td>Maternal</td>
</tr>
<tr>
<td><strong>OTC gene mutation</strong></td>
<td>R40H</td>
<td>R40H</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Age 10 y</td>
<td>PP 8 mo</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>BDx</td>
<td>BDx</td>
</tr>
<tr>
<td><strong>Age at first attack</strong></td>
<td>Age 10 y</td>
<td>Age 12 y</td>
</tr>
<tr>
<td><strong>Representative data at attack</strong></td>
<td>AST/ALT, U/L</td>
<td>13–33/8–30</td>
</tr>
<tr>
<td><strong>PT, % [INR]</strong></td>
<td>≥70% [0.90–1.10]</td>
<td>58 [1.40]&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>APTT, s</strong></td>
<td>26.0–41.0</td>
<td>42.1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ammonia, μmol/L</strong></td>
<td>7–39</td>
<td>175&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Serum albumin, g/dL</strong></td>
<td>&lt;40</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Frequency of severe attack</strong></td>
<td>Once</td>
<td>3 times</td>
</tr>
<tr>
<td><strong>Long-term treatment</strong></td>
<td>A, P</td>
<td>A</td>
</tr>
<tr>
<td><strong>Outcome (age)</strong></td>
<td>Healthy adolescent (16 y)</td>
<td>Healthy adolescent (17 y)</td>
</tr>
</tbody>
</table>

A, oral arginine supplement; APTT, activated partial thromboplastin time; B, oral sodium benzoate treatment; BDx, biochemical diagnosis based on the hypersecretion of orotic acid and uracil in urine without elevation of any specific amino acid in blood; C, oral citrulline treatment; GDx, genetic diagnosis by the analysis of the OTC gene; INR, international normalized ratio; ND, not described or not available; P, intake protein restriction; PP, during the prenatal period; RR, reference range.

<sup>a</sup> Dead.
<sup>b</sup> Deletion, T892del/G893del in exon 9.
<sup>c</sup> In pregnancy.
<sup>d</sup> The laboratory data out of RRs.
<sup>e</sup> Hepaplastin test (normal range: 70%–150%).
their N-terminal domains, whereas in the absence of VK or in the presence of VK antagonists, hepatic VK-dependent carboxylase activity is inhibited, and PIVKA-II is released into the blood. It is possible that abnormal metabolites in association with OTC deficiency, such as orotic acid, might inhibit the hepatic VK-dependent carboxylase. In fact, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, which is a congenital error in the metabolism of ornithine accompanied with substantial elevations of orotic acid, is also associated with coagulopathy. In addition, a large amount of polyunsaturated fatty acids reduced the expression of γ-glutamyl carboxylase in apolipoprotein E knock-out mice. Taken together, orotic acid or other unknown abnormal products in common with hyperornithinemia-hyperammonemia-homocitrullinuria syndrome may affect the lipid metabolism and reduce the γ-glutamyl carboxylase activity and, consequently, cause coagulopathy. Further investigation is needed to understand the pathophysiology of coagulation in OTC deficiency. Moreover, the discovery of novel factor-specific inhibitors may provide valuable information for the design of new anticoagulation drugs with mechanisms of action distinct from warfarin or novel oral anticoagulants.

**CONCLUSIONS**

The current results suggest that coagulation abnormality is a previously unidentified complication of late-onset OTC deficiency in a metabolically compensated state. This information would be beneficial for undiagnosed patients to avoid lethal metabolic crises during adolescence.

**ACKNOWLEDGMENT**

We thank Professor Brian Quinn for help with the manuscript.

**REFERENCES**

Coagulopathy in Patients With Late-Onset Ornithine Transcarbamylase Deficiency in Remission State: A Previously Unrecognized Complication

Kenji Ihara, Makoto Yoshino, Takayuki Hoshina, Nawomi Harada, Kanako Kojima-Ishii, Mika Makimura, Yuki Hasegawa, Yoriko Watanabe, Seiji Yamaguchi and Toshiro Hara

Pediatrics 2013;131;e327
DOI: 10.1542/peds.2012-0030 originally published online December 3, 2012;
Coagulopathy in Patients With Late-Onset Ornithine Transcarbamylase Deficiency in Remission State: A Previously Unrecognized Complication
Kenji Ihara, Makoto Yoshino, Takayuki Hoshina, Nawomi Harada, Kanako Kojima-Ishii, Mika Makimura, Yuki Hasegawa, Yoriko Watanabe, Seiji Yamaguchi and Toshiro Hara
Pediatrics 2013;131:e327
DOI: 10.1542/peds.2012-0030 originally published online December 3, 2012;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/131/1/e327