Idiopathic copper toxicosis1,2

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ABSTRACT Liver diseases of infancy and childhood are generally rare and within the spectrum of these disorders, only a few subtypes are related to abnormal hepatic copper accumulation. Idiopathic copper toxicosis has been defined as such a subtype; although this disease is characterized by distinct clinical and pathologic features, its exact etiology is still controversial. On the basis of a review of the literature, supplemented by our own observations of 138 cases endemic to western Austria, we hypothesize that idiopathic copper toxicosis is caused by a synergy of an autosomal-recessive inherited defect in copper metabolism and excess dietary copper. Increased awareness of the disease should enable early diagnosis and lead to successful treatment, thereby improving the overall poor prognosis of affected patients. Am J Clin Nutr 1998(suppl):67:1082S–6S.

KEY WORDS Liver cirrhosis, childhood, copper, genetics, idiopathic copper toxicosis

INTRODUCTION Hepatic copper accumulation has been observed in a variety of pediatric liver diseases including Wilson disease (WD) (1), Indian childhood cirrhosis (ICC) (2), the non-Indian disease termed idiopathic copper toxicosis (ICT) (3), and disorders associated with chronic cholestasis. Disorders associated with chronic cholestasis result in increases in liver copper secondary to disturbed bile metabolism and do not usually give rise to copper concentrations as high as those found in the other conditions (4). WD, ICC, and ICT are believed to be primary copper-associated liver diseases with distinguished epidemiologic, clinical, and biochemical characteristics as well as distinct histologic features.

WD is an autosomal-recessive disorder linked to chromosome 13 (5); presenting symptoms include hepatic, neurologic, and ophthalmologic involvement; low serum concentrations of copper and ceruloplasmin; and an increase in urinary copper excretion (6). The histologic findings evolve from steatosis to chronic active hepatitis, ultimately leading to macronodular cirrhosis. Symptomatic liver disease has never been observed before the age of 5 y and because of an inborn error in copper metabolism, the manifestation of WD is independent of dietary copper intake (1). ICC, as detailed by Tanner (7) in this supplement, is a fatal and rapidly progressive liver disease attributed to high dietary copper ingestion from the use of brass vessels for the preparation of milk for infants (6). The purpose of this paper is to review the present knowledge of the analogous non-WD occurring outside of India, ICT, and to discuss factors of etiologic significance, with special emphasis on the role of dietary copper and genetic susceptibility.

TERMINOLOGY AND EPIDEMIOLOGY The nomenclature of ICT is rather confusing. On the basis of clinical and morphologic analogies to ICC, many reports were labeled as studies of ICC-like liver disease occurring in various ethnic groups or countries outside India, resulting in a considerable number of different names for this rare entity (8–11). Sternlieb (3) was the first to suggest a specific nomenclature and introduced the term idiopathic copper toxicosis. Another name, copper-associated childhood cirrhosis (CACC), was suggested by Horslen et al (12). Finally, Baker et al (13) proposed copper-associated liver disease in childhood to be applied for both ICC and the analogous non-Indian disorder in an attempt to unify the terminology of non-Wilsonian pediatric liver diseases overtly related to primary copper hepatotoxicity.

A complete compilation of cases of ICT is hampered by this lack of agreement on terminology for the disease, by the reappearance of the same subjects in several publications, and by obvious misdiagnoses in some cases. Thus, as pointed out in a comment by Ludwig et al (14), in some patients hepatic copper toxicosis has been misdiagnosed as unusual manifestations of WD (15, 16). In contrast, a Hungarian child with extraordinarily high hepatic copper concentrations (17) and repeatedly cited as having ICT was recognized later as having α1-antitrypsin deficiency (14). Considering these difficulties, over the past 25 y ≈30 cases of ICT have been identified in several countries, including Australia (18), Germany (19–21), Ireland (13), Italy (22), Kuwait (11), Mexico (23), Singapore (15), the United Kingdom (12, 13), and the United States (8, 10, 14, 16). These were reports of sporadic cases occasionally describing a familial occurrence (8, 15). Recently, another 138 cases termed Tyrollean infantile cirrhosis were identified in the Tyrol (western Austria) (24). This series of cases contrasts with previous reports in the

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high number of affected infants in 102 sibships encountered between 1900 and 1974. Furthermore, it also shows an endemic clustering of the disease within a geographically circumscribed rural area.

CLINICAL FEATURES AND DIAGNOSIS

The age of onset of clinical symptoms of ICT described in the literature varies from 2 mo (24) to 10 y (22). Three age groups of onset can be distinguished (Table 1): infantile onset of the disease, with manifestation of symptoms before or around the age of 2 y (10, 11, 13, 18–21); later onset, peaking at ~5 y (8, 12, 15); and exceptionally delayed onset at the age of 10 y (22). Symptoms at presentation include hepatosplenomegaly and abdominal distention in most cases, accompanied occasionally by fever, malaise, lethargy, ascites, anemia, and, relatively rarely, recurrent jaundice. Complications are generally consequences of hepatic failure or portal hypertension, such as coagulopathy, encephalopathy, renal failure, gastrointestinal bleeding, and systemic infections.

The clinical course of most cases is characterized by an insidious disease onset, rapid progression, and death within 2 wk to 11 mo (24). However, as shown by Ludwig et al (14), a clinical presentation of chronic hepatitis lasting for several years and culminating in hepatic failure does not exclude a diagnosis of ICT. Survivors are rarely reported. Three patients have been treated with orthotopic liver transplantation (13, 14, 16); whereas an English infant recovered fully (13), chronic graft rejection complicated the posttransplant course in a 14-y-old girl (14). Two children seem to have responded to an unspecified therapy (15, 20). Two patients benefited from the early introduction of D-penicillamine (12, 22). Symptoms of liver disease appeared relatively late in these patients, at the ages of 7 and 10 y, and the patients performed well in response to chelation therapy, with stabilized liver function over a 2-y observation period.

Markers of copper metabolism have proven to be of major diagnostic importance; most intriguing are the abnormally high copper concentrations that have been described in liver of between 190 and 3360 µg/g dry wt (the normal concentration is < 50 µg/g) (8, 10–16, 18–23). Increased urinary copper excretion has also been observed, but prospective investigations have been performed in only a few patients (12, 22). When tested, serum copper and ceruloplasmin concentrations were either normal or slightly raised and may therefore be less diagnostic for ICT although providing crucial information for exclusion of WD (10, 12–15, 22). Further insights into copper metabolism may be gained from copper kinetic analyses using the stable isotope 65Cu. As shown by Horslen et al (12) in a 7-y-old patient with non-Wilsonian copper toxicosis, the percentage enrichment of plasma 65Cu, in contrast with that in WD, reflected that of normal individuals. In all cases for which data are available, biochemical markers of hepatic injury such as aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time have been shown to be abnormal (8–10,12–14); however, such changes may not exactly reflect the underlying stage of pathology (9). Furthermore, in one patient, autoimmune and immune activation phenomena with a borderline increase of antibody titers to smooth muscle, an elevation of immunoglobulin G, and an increase in lymphocytes positive for interleukin 2 receptor were observed (13).

Such laboratory investigations may provide important hints of the presence of ICT; however, a correct diagnosis requires histologic confirmation. Therefore, liver biopsy is indicated not only to quantitate the hepatic copper load, but also to verify the characteristic morphologic changes. These include a destruction of the normal liver architecture by a marked panlobular and pericellular fibrosis associated with a usually mild inflammatory infiltrate. Because nodular regeneration is generally lacking, this histologic appearance has also been described as micro-micronodular cirrhosis (8). The architectural changes are accompanied by prominent ballooning degeneration of hepatocytes and an abundance of Mallory bodies (8, 10–14, 19, 20, 22, 25, 26), a feature almost pathognomonic for ICT when detected in infants. Additional and inconsistent findings include central vein edema or fibrosis resembling veno-occlusive disease and a variable degree of cholestasis (8, 19). It is important to note that in contrast with the full-blown alterations detected in most cases in which biopsies were performed at preterminal stages (10, 11, 13, 19, 20, 26) or at autopsy (25), a more subtle and rather unspecific liver histopathology may be present earlier in disease development. Most importantly, Mallory bodies may be scarce or even absent (10, 11).

In addition to conventional histology, histochemical staining for copper or copper-associated proteins has shown granular deposits in hepatocytes and mesenchymal cells in nearly all cases investigated (8, 10, 12, 19, 20). The hepatic copper content may be correlated with the intensity of the rhodamine and orcein staining; therefore, a low or moderately elevated copper load together with the limited sensitivity of histochemical methods may explain the negative or weakly positive staining results for copper or copper-associated protein (11, 14). Other methods for detection of hepatic copper or proteins involved in copper metabolism, such as scanning or transmission electron microscopy (10, 19) and enzyme histochemistry for Mg-ATPase, cytochrome-c oxidase, or acid phosphatase, have been applied in only a few studies (19, 20).

ETIOLOGIC FACTORS

Copper has been implicated as a key factor in the development of ICT. The observations leading to this conclusion are summarized in Table 1: first, abnormally high liver copper concentrations in all cases in which measurements were made; second, identifiable sources of environmental copper exposure in some cases; and third, analogies with respect to epidemiology, clinical presentation, and histopathology between many cases, particularly the large series from the Tyrol (24), and ICC. In both the Tyrolean disease and ICC, the early introduction of copper-contaminated milk from copper or brass vessels has been etiologically linked to hepatic copper overload (6, 24). The pathogenic importance of copper can be further deduced from the successful treatment of two ICT patients with the copper chelating agent D-penicillamine (12) and the disappearance of the disease from the Tyrol after 1974 [in the late 1960s, sociocultural changes led to the replacement of traditional copper cooking utensils, thus eliminating excess copper exposure in this population (24)].

Several arguments inherent to the case reports and inferred from epidemiologic studies, however, contradict the conclusion that environmental or dietary copper is solely responsible for the illness. For example, a retrospective study performed in three Massachusetts towns with copper concentrations in drinking water of between 8.5 and 8.8 mg/L and covering 64 124 child-years of exposure did not reveal a single death from any form of
pediatric liver disease (27). Remarkably, these reported copper concentrations exceed both those currently recommended by the World Health Organization [2 mg/L (28)] and those observed in published cases of ICT [0.3–6.8 mg/L (27)]. Another striking observation was made in the Tyrol, where 231 siblings remained healthy although they had been exposed to the same copper-enriched diet as 112 diseased infants (24). Genealogic investigations of these Tyrollean cases, including a large pedigree of 23 families with 38 affected children, and segregation analysis strongly suggested that the disease was transmitted in an autosomal-recessive mode of inheritance. This finding underlined the evidence for a hereditary background of ICT inferred from the data from Massachusetts (27) and also confirmed the conclusions drawn from several case reports supporting a genetic predisposition (8, 10, 11, 13, 15). Arguments for an inherited disorder were provided by studies on patients with consanguineous parents (10, 11) and the familial occurrence of the disease in two sibships (8, 15).

On the basis of a compilation of 16 cases, Horslen et al (12) proposed a hypothesis for the pathogenesis of ICT. The variable age of disease manifestation, the clinical course of the disease, the ultrastructure of the liver, and the history of excessive copper exposure were considered to be criteria for defining two subgroups of disease, called types I and II CACC. Type I CACC was suggested to closely resemble ICC, with early manifestation of the disease attributable to a high dietary copper intake. Type II

<table>
<thead>
<tr>
<th>Nation</th>
<th>Sex</th>
<th>Age at disease manifestation</th>
<th>Age at death</th>
<th>Liver copper</th>
<th>Copper in tap water</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (16)</td>
<td>Male</td>
<td>5 y</td>
<td>Treated</td>
<td>2083</td>
<td>ND</td>
<td>Unknown</td>
</tr>
<tr>
<td>Australia (18)</td>
<td>Male</td>
<td>4 y</td>
<td>Treated</td>
<td>708</td>
<td>ND</td>
<td>0.05</td>
</tr>
<tr>
<td>Singapore (15)</td>
<td>Female</td>
<td>6 y</td>
<td>Treated</td>
<td>992</td>
<td>ND</td>
<td>0.05</td>
</tr>
<tr>
<td>United States (8)</td>
<td>Male</td>
<td>8 y</td>
<td>Treated</td>
<td>1970</td>
<td>ND</td>
<td>Unknown</td>
</tr>
<tr>
<td>Italy (22)</td>
<td>Male</td>
<td>10 y</td>
<td>Treated</td>
<td>1900</td>
<td>ND</td>
<td>Unknown</td>
</tr>
<tr>
<td>Germany (19,20)</td>
<td>Female</td>
<td>7 mo</td>
<td>10 mo</td>
<td>1485</td>
<td>0.4–5.5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mexico (23)</td>
<td>Male</td>
<td>5 y</td>
<td>Treated</td>
<td>2319</td>
<td>ND</td>
<td>One brother died at 9 y with jaundice; one paternal uncle died at 20 y with jaundice</td>
</tr>
<tr>
<td>United States (10)</td>
<td>Male</td>
<td>29 mo</td>
<td>Treated</td>
<td>1500</td>
<td>1.3</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kuwait (11)</td>
<td>Female</td>
<td>1.3 mo</td>
<td>15 mo</td>
<td>425</td>
<td>Breast-fed</td>
<td>Consanguineous parents</td>
</tr>
<tr>
<td>Ireland (13)</td>
<td>Male</td>
<td>10 mo</td>
<td>11 mo</td>
<td>1245</td>
<td>3.9–8.0</td>
<td>—</td>
</tr>
<tr>
<td>United Kingdom (13)</td>
<td>Female</td>
<td>14 mo</td>
<td>16 mo</td>
<td>1310</td>
<td>2.3–6.3</td>
<td>1/4 Siblings affected</td>
</tr>
<tr>
<td>United Kingdom (12)</td>
<td>Male</td>
<td>7 y</td>
<td>Treated</td>
<td>2319</td>
<td>ND</td>
<td>One brother died at 9 y with jaundice; one paternal uncle died at 20 y with jaundice</td>
</tr>
<tr>
<td>Germany (21)</td>
<td>Male</td>
<td>13 mo</td>
<td>Unknown</td>
<td>1990</td>
<td>12–28.6</td>
<td>Unknown</td>
</tr>
<tr>
<td>United States (14)</td>
<td>Female</td>
<td>10 y</td>
<td>Treated</td>
<td>190–307</td>
<td>Not elevated</td>
<td>Unknown</td>
</tr>
<tr>
<td>Austria (24)</td>
<td>Male</td>
<td>2–24 mo</td>
<td>2–36 mo</td>
<td>ND</td>
<td>10.5–63.3</td>
<td>6 Consanguineous matings; 112/343 siblings affected; autosomal recessive inheritance</td>
</tr>
<tr>
<td>Austria (24)</td>
<td>Female</td>
<td>69 female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 ND, not done.
2 Value is for copper in feeding milk prepared in untinned brass and copper vessels.
IDIOPATHIC COPPER TOXICOSIS

CACC was suggested to appear after 4 y of age without an identifiable source of excess nutritional copper. Although not explicitly excluded for type I CACC, an autosomal-recessive inheritance was assumed to be more likely involved in type II CACC because of the proven consanguinity of the parents in two families (10, 11) and affected siblings in two sibships (8, 15). As a confirmation of their concept, the authors also referred to the autosomal-recessive copper toxicosis observed in Bedlington terriers, which may be an animal model for type II CACC (29).

This classification scheme may be weakened by reports published by Aljajeh et al (11) and Baker et al (13). In both of these studies, patients in the younger age group with no evidence of a history of excess dietary copper were reported. Furthermore, the cases in the Tyrol fulfill all the criteria of type I CACC yet show unequivocally that this subtype also requires a genetic predisposition for disease manifestation (24). In conclusion, the available data indicate strongly that for ICT, exposure to abnormally high dietary copper causes overt liver disease only in the presence of a genetic susceptibility.

The candidate gene for ICT has yet to be identified but will most likely encode a protein involved in the regulation of copper metabolism. Although ICT appears as a distinct entity that is clinically and morphologically separated from WD, the possibility that ICT is caused by yet unknown allelic variations within the WD gene and requires excess dietary copper for its manifestation cannot be ruled out (30, 31). On the other hand, mutations in the genetic matrix of several other proteins associated with copper, such as metallothionein, superoxide dismutase, ceruloplasmin, or an as yet unknown molecule, might be implicated. The reasonable number of possible and obligate heterozygous siblings, as evident from pedigree analysis in the Tyrol (24), and methodologic advances in total genome screening (32) should facilitate identification of the respective genetic defect.

CONCLUSIONS

ICT appears in infancy and early childhood as severe liver disease with normal or raised serum ceruloplasmin concentrations invariably accompanied by elevated hepatic copper concentrations. The underlying liver pathology is characterized by marked hepatic fibrosis associated with a prominent presence of Mallory bodies scattered throughout the parenchyma. Despite being rare, ICT should be considered as a differential diagnosis in pediatric patients with otherwise unexplained liver disease because early recognition may offer successful therapeutic options. The current evidence that disease manifestation requires a convergence of a hereditary predisposition and high copper intake also implies the possibility of preventive interventions to identify and subsequently eliminate environmental sources of excess copper for the benefit of other siblings.

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