Review

Wilson’s disease: the scourge of copper

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Major advances in our understanding of Wilson’s disease have occurred since it was first described in 1912 as a primary neurologic disease accompanied by cirrhosis and referred to as “hepatolenticular degeneration” (1). Wilson’s disease is an inherited disorder of copper metabolism with a variable clinical presentation. It is transmitted in an autosomal recessive manner: the altered gene is localized on the long arm of chromosome 13. Linkage studies have associated the locus to chromosome 13q 14.3 (2,3). It shares homology with the Menke’s disease gene and it codes for a copper-transport P-type adenosine triphosphatase (4,5). The resultant intrahepatic impairment of copper transport leads to a reduction in biliary copper excretion and accumulation of hepatic copper.

The excess intrahepatic copper results in hepatocellular injury and ultimately in the deposition of copper in nonhepatic tissues. The source of the copper in Wilson’s disease is a dietary intake that contains on average 1.0–2.0 mg of copper/day. The synthesis of ceruloplasmin, the copper-binding protein associated with Wilson’s disease is controlled on chromosome 3 and it is essential to realize that ceruloplasmin deficiency, a characteristic of the disease, is not the primary gene defect or abnormality, but rather an associated defect. DNA linkage studies can identify Wilson’s disease and permit early diagnosis. It is estimated that Wilson’s disease occurs worldwide with a prevalence of 1 in 30 000, and it has a heterozygous carrier rate of 1 in 90 (6). The risk of Wilson’s disease in siblings and parents or children of an index patient is 25% and 0.5%, respectively (2). Mutations in the Wilson’s gene are common and include small insertions or deletions. One mutation, histidine 1069 glutamine is the most commonly encountered. The wide spectrum of age of onset of the clinical features in Wilson’s disease may be related to the severity of the gene disruption by mutation. Milder mutations can be associated with late-onset hepatic or neurologic disease, and severe mutations can produce liver disease by age 3 years. The mutations provide an explanation for some of the wide phenotype variations encountered in Wilson’s disease.

Physiology

Copper is essential for a number of enzymes (lysyl oxidase is required for connective tissue, superoxide dismutase, a free radical scavenger, tyrosinase and the neurotransmitter dopamine-B hydroxylase). Dietary sources of copper include shell fish, nuts, soy products, gelatin and chocolate. The average daily intake exceeds the body’s requirements. Copper is transported to the liver and incorporated – into apoceruloplasmin to form ceruloplasmin. Copper is excreted mostly into the bile by an ATP-dependent carrier protein in the canalicular membrane; a minor amount is excreted in urine. The estimated total body copper is 50–150 mg. The normal serum concentration of ceruloplasmin is 20–45 mg/dl. Low levels are found in newborns and in Wilson’s disease (however, 5–15% of patients with Wilson’s disease have low normal values of 20–22 mg/dl). Also, Wilson’s disease heterozygotes have low levels of ceruloplasmin, less than 20 mg/dl in 10–20% of cases. Patients with the nephrotic syndrome, or those on penicillamine for other reasons, can also have low ceruloplasmin levels.

Clinical Features

A variety of clinical manifestations occur in Wilson’s disease, depending on the site of copper deposition (see Table 1).

Age

The age at which Wilson’s disease is first diagnosed varies, with reports ranging from 3 years to 61 years; however, it is extremely unusual for Wilson’s disease to manifest after the fourth decade of life (7,8). Hemolysis is usually apparent between ages 7 and 14 years. Fulminant hepatic failure or chronic liver disease appears between ages 5 and 33, the median age for both
Wilson’s disease

being 18 years in a recent study (9). Features of personality disorder or psychosis present in the teens, and neurologic symptoms are noted from age 14 to 40 years, median age 24 years. The spectrum of neurologic manifestations is wide: including tremor, dysarthria, ataxia, writing difficulties, asthenia, hypersalivation, nervousness, headache, dizziness and convulsions (10). The spectrum of psychiatric presentations in Wilson’s disease is considerable: altered work performance, impulsiveness and antisocial behavior may herald the onset of the disease, while anxiety personality changes, schizoid psychosis and paranoia can occur. In almost 10% of patients with Wilson’s disease (8), the initial manifestation is psychiatric.

Ocular findings
The commonest ocular finding in Wilson’s disease is the presence of a Kayser-Fleischer ring. The term refers to brownish-green discoloration in the zone of Descemet’s membrane in the limbic area of the cornea. It can be detected by the naked eye, especially in blue-eyed patients; however, slit-lamp microscopy is often required to aid identification. Other ophthalmologic manifestations of Wilson’s disease include the sunflower cataract (this does not impair vision and is only visible by slit-lamp biomicroscopy), and rarely night blindness, xerophthalmia or exotropic strabismus (11). Although Kayser-Fleischer rings are considered pathognomonic for Wilson’s disease, they can be detected in conditions of prolonged cholestasis (primary or secondary biliary cirrhosis, sclerosing cholangitis, and chronic familial cholestatic syndromes with impaired biliary copper excretion) (12–15). Rarely, patients with autoimmune chronic hepatitis or cryptogenic cirrhosis without cholestasis manifest Kayser-Fleischer rings (16). In Wilson’s disease, Kayser-Fleischer rings are often incomplete, and they commence at the start at the superior and inferior margins of the cornea, encircling it.

Kayser-Fleischer rings are present in nearly all patients with Wilson’s disease complicated by neurologic symptoms, whereas they occur in 55–70% of patients with only hepatic disease (6,9).

In a recent report in which the clinical and laboratory findings of 55 patients with Wilson’s disease were evaluated at diagnosis, but before treatment, the investigators noted that 12 patients had normal ceruloplasmin levels and no Kayser-Fleischer rings (9). They also reported that detectable Kayser-Fleischer rings were associated with significantly lower levels of ceruloplasmin. The presenting hepatic disease in the 12 patients included: fulminant hepatic failure, acute hepatitis, decompensated cirrhosis, abnormal hepatic biochemistry, and a case with hemolytic anemia. The authors concluded that commonly used clinical and laboratory parameters were insufficient to exclude a diagnosis of Wilson’s disease in patients with liver disease of unknown origin. They suggest that the diagnostic problems related to Wilson’s disease will be solved with certainty only when markers for the mutations of the Wilson’s gene are easily available.

Hepatic disease
Wilson’s disease can manifest with a vast range of liver disturbances, including an episode of self-limiting hepatitis, asymptomatic minor biochemical disturbances, or severe fulminant hepatic failure. The presenting features may even suggest chronic autoimmune hepatitis, or established cirrhosis with portal hypertension and its sequelae. Rarely, the patients present with asymptomatic hepatomegaly or hepatosplenomegaly. Associated hemolytic anemia often accompanies acute or fulminant hepatitis due to Wilson’s disease.

Neurological manifestations
The onset of neurologic abnormalities is usually in the second or third decade. Symptoms occurring before adolescence or after age 40 are most unusual. The dominant neurologic abnormality is a disorder of movement especially involving the bulbar or facial muscles (8). A Parkinson-like syndrome can occur, with akinetic rigidity. An intention tremor with ataxia may be seen. Also, on occasion, a dystonic syndrome with involuntary movements can occur. Paralysis, visual changes, and incontinence are not seen. Seizures are rarely noted.

Complications Associated with Wilson’s Syndrome
Fulminant hepatic failure (FHF)
This is a very serious sequela that can suddenly, without recognizable precipitating factors, complicate Wil-
son's disease. Fulminant hepatic failure in Wilson’s disease can be differentiated from viral or idiopathic fulminant hepatic failure by a number of biochemical findings. These include higher copper levels in the serum, urine and liver, less pronounced elevations of the aminotransferase levels, higher levels of total bilirubin (especially unconjugated bilirubin) and lower hemoglobin levels (17,18). A ratio of serum alkaline phosphatase to serum bilirubin of >2.0 and an aspartate aminotransferase: alanine aminotransferase ratio of <4.0 have been reported to differentiate Wilson's disease from other causes of FHF (19). The alkaline phosphatase:total bilirubin value provided 100% sensitivity and specificity in identifying Wilson's disease from other types of FHF (19). Histologic findings in patients who died with FHF are non-specific and reveal extensive hepatic necrosis, nodular regeneration and Mallory bodies in most cases.

Intravascular hemolysis is extremely common in patients with FHF associated with Wilson's disease. An associated low hemoglobin level often occurs. It is crucial to recognize FHF associated with Wilson's disease, because it has 100% mortality without liver transplantation (19); also, once it is recognized, prompt screening of the proband's relatives is possible. The mechanism for FHF is unknown. One view is that the accumulation of hepatic copper in the cytoplasm of the hepatocytes is gradually redistributed to the lysosomes. If this redistribution is impaired, hepatic cell necrosis ensues, with the release of copper into plasma leading to acute massive hemolysis (20).

Hemolysis
The excess free copper found in Wilson’s disease alters red cell membrane stability, via its oxidative effects, leading to hemolysis (21–26). Often, episodes of sudden massive hemolysis occur concurrently with the onset of fulminant hepatic failure (20). In animal models, copper caused hemolysis at a concentration of 75 μg/dl (24). Copper inhibits the transfer of glycerol into erythrocytes, and it may lower levels of glutathione in the erythrocytes (27,28). Unexplained anemia (with hemolysis) in children under age 15 years should be regarded as a possible initial manifestation of Wilson’s disease.

Chronic hepatitis
Chronic hepatitis is a clinical, biochemical and pathological syndrome associated with protracted inflammatory changes in the liver. It can be associated with chronic viral hepatitis (due to hepatitis C virus or hepatitis B virus) or a response to certain medications, or an autoimmune process or Wilson’s disease (29). A distinctive feature of Wilson’s chronic hepatitis is a mild elevation of aminotransferase chronic hepatitis is a mild elevation of aminotransferase associated with severe hepatocellular necrosis and inflammatory changes. Most of the characteristic biochemical markers of Wilson’s disease can be detected in these patients with a chronic hepatitis-like picture. Early treatment with D-penicillamine or trientine improves the biochemical markers and also improves the prognosis, in spite of the presence of severe hepatitis or cirrhosis in the more advanced cases.

Endocrine abnormalities
Endocrine abnormalities have been reported in Wilson’s disease (30–33). Hypoparathyroidism, amenorrhea, decreased thyroid-binding globulin, glucose intolerance, hyperphosphaturia, and rickets (in association with the Fanconi defect seen in Wilson’s disease) have all been reported. Moderate hypercalciumia may occur as part of the Fanconi defect and osteoporosis may also be present. Hypoparathyroidism may be due to parenchymal degeneration and atrophy of the parathyroids as a consequence of the copper deposition (30,34), but it is rarely encountered.

Renal stones
Renal stones have been noted in 16% of patients with Wilson’s disease (35). Calcium phosphate stones are the commonest calculi encountered.

Factors predisposing patients with Wilson’s disease to develop renal calculi include hypercalciumia, hyperuricosuria, abnormalities of acid-base excretion with a distal (type 1) renal tubular acidosis, and decreased citrate excretion. Patients often have accompanying aminoaciduria.

Diagnosis
A variety of clinical findings and biochemical measurements can be selectively utilized in the diagnosis of Wilson's disease (Table 2). Traditionally, a diagnosis of Wilson's disease was made based on Sternlieb's criteria, which required two or more of the following to be present:

1) Kayser-Fleischer rings
2) Typical neurological symptoms
3) Low serum ceruloplasmin
4) Increased hepatic copper content.

A recent report on 55 patients with Wilson's disease noted that 31 out of 55 had two of the first three criteria and 12 had low ceruloplasmin levels and raised hepatic copper levels (9). Twelve patients had normal ceruloplasmin levels and no Kayser-Fleischer rings. Only 18 out of 20 patients (90%) with neurological symptoms had Kayser-Fleischer rings. Clearly, the tra-
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**TABLE 2**

Current diagnostic tests for Wilson’s disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Result</th>
<th>False positive</th>
<th>False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayser-Fleischer rings</td>
<td>absent</td>
<td>present</td>
<td>cholestatic syndrome, cryptogenic cirrhosis</td>
<td>non-neurologic Wilson’s disease</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>20–40 mg/dl</td>
<td>&lt;20 mg/dl</td>
<td>hypoalbuminemia, fulminant hepatic failure</td>
<td>5% of Wilson’s disease have low normal levels</td>
</tr>
<tr>
<td>Hepatic copper concentration</td>
<td>&lt;50 μg/g dry wt</td>
<td>&gt;250 μg/g</td>
<td>cholestatic syndromes</td>
<td></td>
</tr>
<tr>
<td>24-h urinary copper</td>
<td>&lt;50 μg/24 h</td>
<td>&gt;100 μg/24 h</td>
<td>chelation therapy</td>
<td></td>
</tr>
<tr>
<td>Radio copper (^64Cu) incorporation into ceruloplasmin</td>
<td>low</td>
<td></td>
<td>heterozygous carrier</td>
<td></td>
</tr>
<tr>
<td>Histology*</td>
<td>glycogen excess steatosis excess Cu</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No pathognomonic specific morphology in Wilson’s disease (36)
(Modified from Am J Gastroenterol 1990; 85: 1453, Schoen RE, Sternlieb I.)

ditional diagnostic criteria require critical re-evaluation, and there is an urgent need for easily performed commercial tests to detect markers for the mutations of the Wilson’s disease gene. Screening procedures that use DNA probes may provide a useful tool to detect homozygous patients in infancy, thus enabling early effective therapy to be started.

**Treatment**

**Chelation**

D-penicillamine (1–2 g/day administered orally in divided doses on an empty stomach) is an effective long-term therapy. It chelates and excretes copper effectively. Patients with neurologic disease may worsen temporarily (37). Most patients respond to this therapy, but isolated patients continue to progress and deteriorate (37). Pyridoxine 50 mg daily should be prescribed to compensate for penicillamine’s weak antipyrrooxidine action. D-penicillamine not only decreases hepatic copper levels, but also improves hepatic histology and function; however, it does not reverse hepatomegaly, splenomegaly or cirrhosis (10). Nearly 25%–30% of patients show sensitivity to D-penicillamine in the form of rashes, fever, lymphadenopathy, leukopenia or thrombocytopenia (38). A smaller number develop serious penicillamine toxicity with arthralgias, nephrotic syndrome, lupoid-like reactions and pemphigus. D-penicillamine should not be discontinued, even during pregnancy (39). Triethylene tetramine (treintine) is an alternative therapy given in the same dosage (40). Tetra-thiomolybdate may be effective for severe neurologic complications of Wilson’s disease.

**Zinc**

The beneficial effect of daily doses of 75–300 mg of elemental zinc in patients with neurologic complications has been reported (41,42). Zinc decreases intestinal copper absorption, and it enhances mucosal and cellular metallothionin levels which sequester copper in intestinal cells.

**Dietary measures**

The avoidance of foods high in copper (shellfish, nuts, chocolate, soy products) is advocated.

**Liver transplantation**

Liver transplantation has a cardinal role in the management of fulminant hepatic failure and in selected cases of decompensated cirrhosis with clinical progression despite adequate chelation and supportive measures (43–45). In patients with progressive neurologic disease which is unresponsive or deteriorates on conventional therapy, the role of transplantation in the absence of severe hepatic disease is unproven (46). In a report of 55 patients who underwent liver transplantation, the 1-year survival was 79%. Of the seven patients given transplants for hepatic insufficiency who had additional neurologic and/or psychiatric manifestations at the time of orthotopic liver transplantation, four showed an improvement in neuro/psychiatric features. One patient given a transplant for intractable neurologic disease improved but died of a vascular complication. It is not known, however, whether copper may reaccumulate in the transplanted livers of patients with Wilson’s disease.

It is 85 years since the original report by Wilson appeared. During this period there has been a widening of the spectrum of the disease, associated with a genetic predisposition to excess copper absorption with a subsequent deposition of copper in a number of diverse tissues. We are tantalizingly close to perfecting a diagnostic genetic test to permit early detection of pa-
patients with homozygotic inheritance of this potentially disabling and fatal condition. Clearly early recognition and treatment will prevent many of the complications associated with Wilson’s disease. The future may see genetic substitution and correction of these abnormalities.

References

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