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Wilson disease: Epidemiology and pathogenesis

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INTRODUCTION

Wilson disease (hepatolenticular degeneration) results from a defect in hepatocellular copper transport, leading to the accumulation of copper in the liver and other tissues, including the brain. Over time, the damage from the accumulation of copper results in the hepatic, neurologic, and psychiatric manifestations of Wilson disease.

This topic will review the epidemiology and pathogenesis of Wilson disease. The clinical manifestations, diagnosis, and treatment of Wilson disease are discussed separately. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history" and "Wilson disease: Treatment and prognosis".)

EPIDEMIOLOGY

Wilson disease is found worldwide, with an estimated prevalence of 1 case per 30,000 live births in most populations [1], although data from population screening by molecular sequencing in the United Kingdom suggest a potentially higher prevalence, perhaps as frequent as 1 case in 7021 [2]. Assuming a prevalence of 1 in 10,000 to 30,000, approximately one person in 90 carries an abnormal copy of the *ATP7B* gene. However, in some isolated populations, the prevalence is much higher. One of the highest reported prevalences was from a small mountain village on the island of Crete, where Wilson disease was diagnosed in 1 in 15 births [3]. The increased prevalence was likely due to high rates of consanguinity in the isolated area.

Additionally, a study using data from a large French cohort found that approximately one person in 31 is a heterozygous carrier [4], and this corresponds to an expected disease prevalence of one case in 1000 live births. The discrepancy between the heterozygous carrier frequency and the observed prevalence of Wilson disease suggests incomplete penetrance, but further study of disease-specific mutations is needed [5].

Some studies suggest that males and females are equally affected by Wilson disease, though females are more likely than males to develop acute liver failure due to Wilson disease [6-8]. However, a large registry study of 627 patients with Wilson disease found that there was a slight male predominance (52 percent) [9]. At the time of diagnosis, among patients who were symptomatic, males were more likely than females to have neuropsychiatric disease (75 versus 58 percent) and were less likely to have hepatic disease (25 versus 41 percent). (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Acute liver injury/failure'.)

COPPER METABOLISM

Overview — Dietary copper intake is approximately 1 to 2 mg per day [10]. Copper is absorbed in the stomach and duodenum, binds mainly to circulating albumin, and is taken up by various tissues [11-13]. The daily requirement for copper is approximately 0.75 mg. Excess copper is predominantly excreted into the bile, where it ends up as fecal copper. Renal losses account for only 5 to 15 percent of the daily excretion of copper. (See "Overview of dietary trace elements", section on 'Copper'.)

Copper transport — The transport of copper within hepatocytes is regulated by *ATP7B*, the copper-transporting intracellular protein affected in Wilson disease. *ATP7B* is expressed mainly in hepatocytes and is normally found in two subcellular locations: in the trans-Golgi network and in cytoplasmic vesicles [14-16]. In the trans-Golgi network, *ATP7B* mediates the transport of copper for the incorporation of six copper atoms into apoceruloplasmin (the ceruloplasmin peptide without copper) to form ceruloplasmin (copper containing holoceruloplasmin). Ceruloplasmin is then secreted into the bloodstream.

Copper in ceruloplasmin is not exchangeable under physiologic conditions (copper in this molecule is necessary for its function in iron metabolism as a "ferroxidase") and accounts for approximately 90 percent of the circulating copper. In the cytoplasmic vesicles, *ATP7B*-mediated copper transport sequesters excess copper in these pre-lysosomal vesicles, which are then excreted into bile via exocytosis across the hepatocyte apical canalicular membrane. There is

some suggestion that the *ATP7B* protein may itself localize to the canaliculus for the function of copper transport into bile; however, this is controversial.

Disorders in copper transport result in disease related to either copper deficiency or copper excess:

- Menkes disease is a fatal X-linked genetic disorder characterized by progressive neurodegeneration. In Menkes disease, there is a defect in *ATP7A*, a homologous protein to *ATP7B*, that reduces the transport of copper across the intestinal epithelium (effectively causing copper malabsorption) and internally in other tissues where it leads to a copper deficiency state [17,18]. (See "Overview of dietary trace elements", section on 'Menkes disease'.)

- In Wilson disease, there is decreased incorporation of copper into apoceruloplasmin and decreased transport of copper from the liver into bile, leading to copper excess in tissue despite low circulating levels of ceruloplasmin (the major form of circulating copper). (See 'Pathogenesis' below.)

The genes encoding the defective proteins for these two disorders are highly homologous, and identification of the gene for Menkes disease, *ATP7A*, led to the identification of the homologous gene for Wilson disease, *ATP7B* [19-21]. (See 'Genetic defect in Wilson disease' below.)

GENETIC DEFECT IN WILSON DISEASE

Wilson disease is an autosomal recessive disorder and is the result of mutation in *ATP7B*, a gene encoding a copper transport protein, ATP7B, on chromosome 13. (See 'Copper metabolism' above.)

Using positional cloning and information deduced by homology with the Menkes disease gene (*ATP7A*), the sequence of the Wilson disease protein was determined and named "*ATP7B*" [19,20]. (See "Overview of dietary trace elements", section on 'Menkes disease'.)

ATP7B mutation — *ATP7B* is a P-type ATPase expressed mainly in the liver but is present in some other tissues at lower amounts. ATP7B binds copper at its N-terminal domain and is responsible for the transmembrane transport of copper using ATP as an energy source.

ATP7B can be affected by mutations at many different sites. Over 500 different mutations in the *ATP7B* gene have been identified in patients with Wilson disease [1]. The H1069Q mutation is one of the most common mutations, with an allelic frequency of 10 to 40 percent (30 to 70 percent among patients from Central, Eastern, and Northern Europe) [22,23]. Most patients are

compound heterozygotes, carrying different mutations on each copy of chromosome 13 [21,24,25].

PATHOGENESIS

Mutations in *ATP7B* in Wilson disease impair both the incorporation of copper into apoceruloplasmin and the excretion of copper into bile, the latter reducing the major pathway of hepatic copper elimination that is responsible for the clinical manifestations and pathology of Wilson disease. (See 'Copper metabolism' above.)

Impaired incorporation of copper — The impaired incorporation of copper into apoceruloplasmin leads to it being folded differently than the holoprotein with its complement of copper. The differently-folded protein is secreted by hepatocytes but has a shorter half-life in the circulation, thereby reducing steady state circulating levels of this protein. However, low serum ceruloplasmin concentrations do not play a role in the pathogenesis of Wilson disease, though they are useful for disease diagnosis. A finding that supports the lack of an association of ceruloplasmin levels with copper metabolism or symptoms of Wilson disease is the absence of ceruloplasmin in hereditary aceruloplasminemia. This rare disease that is caused by homozygous mutation of the ceruloplasmin gene is characterized by tissue deposition of iron but not of copper [26]. (See "Bradykinetic movement disorders in children", section on 'Neurodegeneration with brain iron accumulation'.)

The impairments in copper transport due to *ATP7B* mutations result in excess copper accumulation within hepatocytes. The excess copper is initially bound to metallothionein and distributed evenly throughout the cytoplasm. With progressive copper accumulation, the capacity of metallothionein is exceeded and hepatocyte injury occurs [27]. At this stage, dense lysosomal deposits of copper-protein complexes within hepatocytes may be seen on ultrastructural analysis or on specific histochemical stains.

Hepatocyte injury from copper — The pathogenesis of hepatocyte injury from copper is incompletely understood. Both necrosis and apoptosis may be encountered. Cellular injury is mainly due to oxidative injury due to enhanced free radical production and impaired cellular reducing capacity in the form of lower levels of reduced glutathione. This observation is supported by the finding of severe mitochondrial dysfunction [28] and enhanced lipid and DNA oxidative injury, as well as inhibition of protein synthesis in the presence of excess copper in the liver. Data on the use of an experimental copper chelating agent, methanobactin, show that copper removal from mitochondria reduced the rate of copper-induced cellular injury to hepatocytes [29]. Hepatocyte apoptosis and hemolytic anemia in Wilson disease have also been

linked to copper-induced secretion of acid sphingomyelinase from leukocytes [30]. Finally, copper excess in liver cells may lead to reduced levels of an inhibitor of apoptosis (X-linked inhibitor of apoptosis), resulting in a higher susceptibility to apoptotic hepatocyte death.

Increased hepatic copper content combined with hepatocyte damage results in the release of copper into the blood, where it binds to albumin or small peptides. This leads to an elevation in free serum copper concentrations (non-ceruloplasmin bound copper), although total serum levels of copper may not be elevated because of the reduced concentration of ceruloplasmin. However, in the setting of acute liver failure due to Wilson disease, serum copper levels may be markedly elevated because hepatic injury and cell death causes massive copper release that elevates the total serum copper levels to twice the upper limit of normal.

Extrahepatic copper deposition — The increase in free serum copper presumably is the proximate cause of copper deposition and subsequent toxicity in the brain and other tissues. While urinary excretion of copper from this pool of free serum copper increases, it is not able to fully compensate for the decreased biliary excretion, and extra-hepatic tissue copper deposition increases over time, leading to damage of other organs, mainly the central nervous system.

PATHOLOGIC FINDINGS

Liver — The earliest lesions in Wilson disease are seen in the liver, the site of initial copper accumulation. Early on, there may be steatotic change within hepatocytes (macrosteatosis and also microsteatosis), often accompanied by glycogenated nuclei, and portal fibrosis (picture 1). As the disease progresses, frank hepatocellular necrosis occurs, and the histologic lesion may resemble autoimmune chronic hepatitis. There is portal inflammation and fibrosis, piecemeal necrosis with marked swelling and necrosis of periportal hepatocytes, and eventually cirrhosis (picture 2). Intrahepatic inclusions similar to Mallory bodies may be seen in periportal areas. In acute liver failure due to Wilson disease, apoptotic injury may predominate though necrotic injury may also be present [31]. In this setting, severe hepatocellular dropout occurs on the background of advanced fibrosis [32,33].

Histochemical stains for copper (that detect copper-binding protein) may demonstrate increased deposits of copper within the liver, renal tubular cells, and brain. The deposition of copper in hepatocytes is initially cytoplasmic and diffuse and may be hard to see on standard histochemical stains, but with time it becomes more detectable as concentrations of copper and copper-binding protein are increased, especially within lysosomes. Copper histochemical staining may become patchy if cirrhosis is present as concentrations differ between mature tissue and rapidly regenerating nodules [34]. With electron microscopy, striking ultrastructural

changes are noted in hepatocellular mitochondria, with dilatation of the mitochondrial cristae early in the disease [35]. Later, ultrastructural analysis reveals dense lysosomal deposits of copper-metallothionein.

Brain — Grossly, the brain most often is normal appearing, but with advancing disease may be atrophic with increased ventricular size [13]. The putamen and caudate may be brown and shrunken. In some patients with advanced disease, there may be cavitation and cyst formation in the putamen and frontal lobes, as well as spongy degeneration of the cerebral cortex and subcortical white matter (particularly in the frontal lobes). Histologic examination of affected areas in the brain demonstrates neuronal loss, pigment- and lipid-containing macrophages, and gliosis. A distinctive feature is the presence of Opalski cells in the globus pallidus.

SUMMARY AND RECOMMENDATIONS

- Wilson disease (hepatolenticular degeneration) results from a defect in hepatocellular copper transport, leading to the accumulation of copper in the liver and other tissues, including the brain. Over time, the damage from the accumulation of copper results in the hepatic, neurologic, and psychiatric manifestations of Wilson disease. (See 'Introduction' above.)

- Wilson disease is found worldwide, with an estimated prevalence of 1 case per 30,000 live births in most populations. (See 'Epidemiology' above.)

- Wilson disease is caused by a defect in the *ATP7B* gene that results in a decreased transport of copper from the liver into bile, leading to copper excess in the liver. (See 'Pathogenesis' above.)

- Excess hepatic copper leads to hepatocyte injury, in part due to enhanced free radical production and oxidative injury to cellular organelles (See 'Hepatocyte injury from copper' above.)

- Increased hepatic copper content combined with hepatocyte damage results in the release of copper into the blood. The increase in “free” serum copper (not bound by ceruloplasmin) presumably is the proximate cause of extrahepatic copper deposition and subsequent toxicity in the brain and other tissues. (See 'Extrahepatic copper deposition' above.)

- Histochemical staining may reveal copper in the liver, but its absence does not exclude Wilson disease. There are phases where copper is present but diffuse within the cytoplasm

of hepatocytes, and copper content is elevated in the liver (See 'Pathologic findings' above.)

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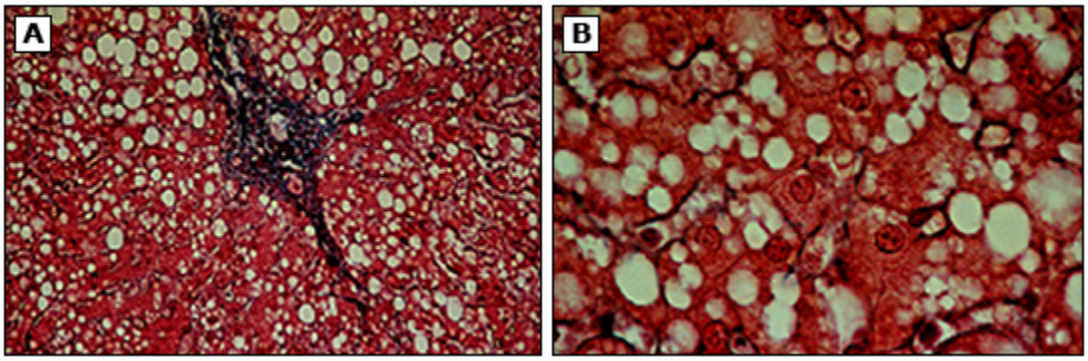
GRAPHICS

Wilson disease



Liver biopsy from a 4-year-old female patient whose 10-year-old sister presented with liver failure and cirrhosis secondary to previously unrecognized Wilson disease. Liver biopsy was performed because serum ceruloplasmin was low (4.0 mg/dL) and serum aminotransferases were repeatedly two to three times normal.

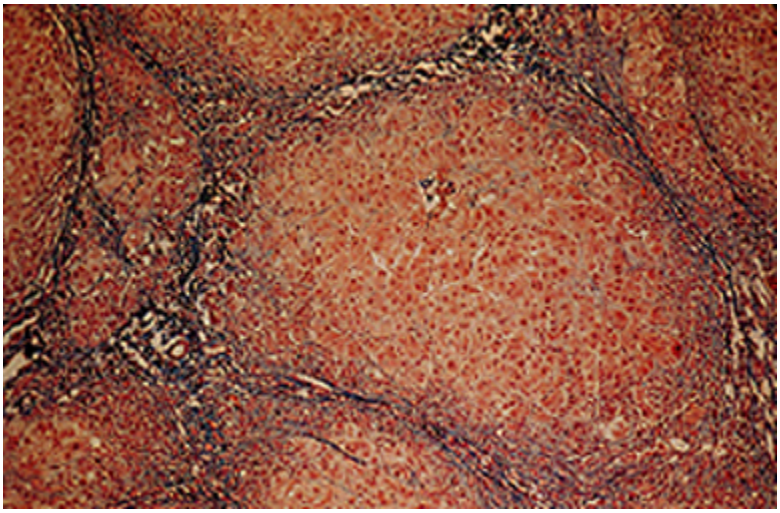
(A) Low power shows portal fibrosis, mild portal inflammation, and fatty infiltration (Masson trichrome).

(B) High power view shows fatty infiltration of hepatocytes and two glycogenated nuclei (Masson trichrome).

Courtesy of Marshall M Kaplan, MD.

Graphic 64346 Version 3.0

Wilson disease simulating autoimmune hepatitis



Liver biopsy from a patient with Wilson disease shows an island of parenchyma surrounded by thin connective tissue septa and inflammatory cells. These findings are identical to those seen in autoimmune chronic hepatitis, and this patient was treated unsuccessfully with corticosteroids before the correct diagnosis was made.

Courtesy of Marshall M Kaplan, MD.

Graphic 53643 Version 2.0

Contributor Disclosures

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