### GLOBAL CONSIDERATIONS

The *HFE* mutation is of northern European origin (Celtic or Nordic) with a heterozygous carrier rate of approximately 1 in 10 (1 in 8 in Ireland). Thus, *HFE*-associated hemochromatosis is quite rare in non-European populations, e.g., Asia. However, non-*HFE*-associated hemochromatosis resulting from mutations in other genes involved in iron metabolism (Fig. 428-1) is ubiquitous and should be considered when one encounters iron overload.

# 429 Wilson's Disease

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Wilson's disease is an autosomal recessive disorder caused by mutations in the *ATP7B* gene, which encodes a membrane-bound, copper-transporting ATPase. Clinical manifestations are caused by copper toxicity and primarily involve the liver and the brain. Because effective treatment is available, it is important to make this diagnosis early.

The frequency of Wilson's disease in most populations is about 1 in 30,000–40,000, and the frequency of carriers of *ATP7B* mutations is ~1%. Siblings of a diagnosed patient have a 1 in 4 risk of Wilson's disease, whereas children of an affected patient have about a 1 in 200 risk. Because a large number of inactivating mutations have been reported in the *ATP7B* gene, mutation screening for diagnosis is not routine, although this approach may be practical in the future. DNA haplotype analysis can be used to genotype siblings of an affected patient. A rare multisystem disorder of copper metabolism with features of both Menkes and Wilson's diseases has been reported. It is termed the MEDNIK syndrome (mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratodermia) and is caused by mutations in the *AP1S1* gene, which encodes an adaptor protein necessary for intracellular trafficking of copper pump proteins ATP7A (Menkes disease) and ATP7B (Wilson's disease).

### PATHOGENESIS

ATP7B protein deficiency impairs biliary copper excretion, resulting in positive copper balance, hepatic copper accumulation, and copper toxicity from oxidant damage. Excess hepatic copper is initially bound to metallothionein; liver damage begins as this storage capacity is exceeded, sometimes by 3 years of age. Defective copper incorporation into apoceruloplasmin leads to excess catabolism and low blood levels of ceruloplasmin. Serum copper levels are usually lower than normal because of low blood levels of ceruloplasmin, which normally binds >90% of serum copper. As the disease progresses, nonceruloplasmin serum copper ("free" copper) levels increase, resulting in copper buildup in other parts of the body (e.g., in the brain, with consequent neurologic and psychiatric disease).

### CLINICAL PRESENTATION

**Hepatic Features** Wilson's disease may present as hepatitis, cirrhosis, or hepatic decompensation. Patients typically present in the mid- to late teenage years in Western countries, although the age of presentation is quite broad and extends into the fifth decade of life. An episode of hepatitis may occur—with elevated serum aminotransferase levels, with or without jaundice—and then spontaneously regress. Hepatitis often recurs, and most of these patients eventually develop cirrhosis. Hepatic decompensation is associated with elevated serum bilirubin, reduced serum albumin and coagulation factors, ascites, peripheral edema, and hepatic encephalopathy. In severe hepatic failure, hemolytic anemia may develop because large amounts of copper derived from hepatocellular necrosis are released into the bloodstream. The association of hemolysis and liver disease makes Wilson's disease a likely diagnosis.

**Neurologic Features** The neurologic manifestations of Wilson's disease typically occur in patients in their early twenties, although the age of onset extends into the sixth decade of life. MRI and CT scans reveal damage in the basal ganglia and occasionally in the pons, medulla, thalamus, cerebellum, and subcortical areas. The three main movement disorders include dystonia, incoordination, and tremor. Dysarthria and dysphagia are common. In some patients, the clinical picture closely resembles that of Parkinson's disease. Dystonia can involve any part of the body and eventually leads to grotesque positions of the limbs, neck, and trunk. Autonomic disturbances may include orthostatic hypotension and sweating abnormalities as well as bowel, bladder, and sexual dysfunction. Memory loss, migraine-type headaches, and seizures may occur. Patients have difficulty focusing on tasks, but cognition usually is not grossly impaired. Sensory abnormalities and muscular weakness are not features of the disease.

**Psychiatric Features** Half of patients with neurologic disease have a history of behavioral disturbances with onset in the 5 years before diagnosis. The features are diverse and may include loss of emotional control (temper tantrums, crying bouts), depression, hyperactivity, or loss of sexual inhibition.

**Other Manifestations** Some female patients have repeated spontaneous abortions, and most become amenorrheic prior to diagnosis. Cholelithiasis and nephrolithiasis occur with increased frequency. Some patients have osteoarthritis, particularly of the knee. Microscopic hematuria is common, and levels of urinary excretion of phosphates, amino acids, glucose, or urates may increase; however, a full-blown Fanconi syndrome is rare. Sunflower cataracts and Kayser-Fleischer rings (copper deposits in the outer rim of the cornea) may be seen. Electrocardiographic and other cardiac abnormalities have been reported but are not common.

### DIAGNOSIS

Diagnostic tests for Wilson's disease are listed in Table 429-1. Serum ceruloplasmin levels should not be used for definitive diagnosis, because they are normal in up to 10% of affected patients and are reduced in 20% of carriers. Kayser-Fleischer rings (Fig. 429-1) can be definitively diagnosed only by an ophthalmologist using a slit lamp. They are present in >99% of patients with neurologic/psychiatric forms of the disease and have been described very rarely in the absence of Wilson's disease. Kayser-Fleischer rings are present in only ~30–50% of patients diagnosed in the hepatic or presymptomatic state; thus, the absence of rings does not exclude the diagnosis.

Urine copper measurement is an important diagnostic tool, but urine must be collected carefully to avoid contamination. Symptomatic patients invariably have urine copper levels >1.6 μmol (>100 μg) per 24 h. Heterozygotes have values <1.3 μmol (<80 μg) per 24 h. About half of presymptomatic patients who are ultimately affected have diagnostically elevated urine copper values, but the other half have levels that are in an intermediate range between 0.9 and 1.6 μmol (60–100 μg) per 24 h. Because heterozygotes may have values up to 1.3 μmol (80 μg) per 24 h, patients in this range may require a liver biopsy for definitive diagnosis.

The gold standard for diagnosis remains liver biopsy with quantitative copper assays. Affected patients have values >3.1 μmol/g (>200 μg/g [dry weight] of liver). Copper stains are not reliable. False-positive results can occur with long-standing obstructive liver disease, which can elevate hepatic and urine copper concentrations and rarely causes Kayser-Fleischer rings.

## TREATMENT WILSON'S DISEASE

Recommended anticopper treatments are listed in Table 429-2. Penicillamine was previously the primary anticopper treatment but now plays only a minor role because of its toxicity and because it often worsens existing neurologic disease if used as initial therapy. If penicillamine is given, it should always be accompanied by pyridoxine (25 mg/d). Trientine is a less toxic chelator and is supplanting penicillamine when a chelator is indicated.