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■ ■ROLE OF HFE MUTATIONS IN OTHER

LIVER DISEASES

There is considerable interest in the role of HFE mutations and hepatic iron in several other liver diseases. Several studies have shown an increased prevalence of HFE mutations in PCT patients. Iron accentuates the inherited enzyme deficiency in PCT and clinical manifestations of PCT. The situation in metabolic dysfunction– associated steatohepatitis is less clear, but some studies have shown an increased prevalence of HFE mutations. Available evidence does not support a role for phlebotomy therapy unless there is a proven increase in hepatic iron stores. HFE mutations are not increased in frequency in alcoholic liver disease. However, alcohol does reduce hepcidin expression, which accounts for increased iron absorption and hepatic iron sometimes seen in alcoholic liver disease. Hemochromatosis in a heavy drinker can be distinguished from alcoholic liver disease by the presence of the C282Y mutation. PART 12 Endocrinology and Metabolism End-stage liver disease may also be associated with iron overload of the degree seen in hemochromatosis. The mechanism is uncertain, although studies have shown reduced hepcidin and intestinal iron transporter expression. Hemolysis also plays a role. HFE mutations are uncommon. ■ ■GLOBAL CONSIDERATIONS The HFE mutation is of northern European origin (Celtic or Nordic) with a heterozygous carrier rate of ~1 in 10 (1 in 8 in Ireland). Thus, HFEassociated 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. 426-1) is ubiquitous and should be considered when one encounters iron overload. African iron overload occurs primarily in sub-Saharan Africa and was previously thought to be due to the consumption of an iron-rich fermented maize beverage. However, recent evidence suggests that it is primarily the result of a non-HFE-related genetic trait that is exacer bated by dietary iron loading. A similar form of iron overload has been described in African Americans. Acknowledgment The authors extend their gratitude to the late Professor Lawrie W. Powell and recognize his outstanding contributions to previous versions of this chapter. ■ ■FURTHER READING Adams PC et al: Haemochromatosis. Lancet 401:1811, 2023. Anderson GJ, Bardou-Jacquet E: Revisiting hemochromatosis: Genetic vs. phenotypic manifestations. Ann Transl Med 9:731, 2021. Girelli D et al: Hemochromatosis classification: Update and recom mendations by the BIOIRON Society. Blood 139:3018, 2022. Olynyk JK, Ramm GA: Hemochromatosis. N Engl J Med 387:2159, 2022. Powell LW et al: Haemochromatosis. Lancet 388:706, 2016. Stephen G. Kaler

Wilson’s Disease Wilson’s disease is an autosomal recessive inherited disorder of cop per transport that primarily impacts the liver and brain. This reflects the critical need for homeostatic

mechanisms to properly utilize this trace metal, both systemically and in the central nervous system. Since the initial detailed clinical description in 1912, Wilson's disease has emerged as arguably one of the best-characterized and most effectively managed human inborn errors of metabolism. The condition results

from variants in ATP7B, a highly evolutionarily conserved P-type ion-motive ATPase that normally mediates copper removal from the liver via biliary excretion and prevents brain copper accumulation. Prompt diagnosis in the presymptomatic or early symptomatic phase of the illness and lifelong treatment are needed to prevent premature mortality in affected individuals. HISTORY OF WILSON'S DISEASE Wilson's disease (hepatolenticular degeneration) was first described in 1912 by neurologist S.A.K. Wilson, who recognized the heritable aspect of the condition. In 1948, the pathologist J.N. Cumings pro posed an etiologic connection with copper overload. Several years later, a metal chelator developed to counteract an arsenic-based chem ical warfare agent (lewisite) was used to successfully treat advanced Wilson's disease. In 1956, copper chelation by d-penicillamine was introduced and found preferable to anti-lewisite with respect to route of administration and side effect profile. In the early 1970s, an alternative copper chelator, triethylene tetramine, became the second U.S. Food and Drug Administration (FDA)–approved treatment for Wilson's disease. Also in the early 1970s, the first liver transplants were performed for Wilson's disease, with resultant correction of both hepatic failure and crippling neurologic impairments in patients unresponsive to medical therapies. The treatment potential of zinc salts to reduce gastrointestinal copper absorption in Wilson's dis ease was recognized in the early 1960s, eventually leading to FDA approval for this indication. Tetrathiomolybdate, which forms a tripartite complex with copper and albumin, and a bacterial peptide, methanobactin, which traverses mitochondrial membranes, are more recently proposed copper chelators with potential for treatment of Wilson's disease. In 1993, the gene for Wilson's disease was identified and found to encode a copper-transporting ATPase, ATP7B, expressed primarily in liver and kidney. In addition to providing a molecular basis for diagnosis and genotype-phenotype correlations, the finding presents current opportunities for viral gene therapy that could impact future management of this illness. PHENOTYPES ■ ■CLINICAL Presenting clinical features of Wilson's disease include nonspecific liver disease, neurologic abnormalities, psychiatric illness, hemolytic anemia, renal tubular Fanconi syndrome, and various skeletal abnor malities. Age influences the specific presentation in Wilson's disease. Nearly all individuals who present with liver disease are <30 years of age, whereas those presenting with neurologic or psychiatric signs may range in age from the first to the fifth decade. This reflects the sequence of events in the pathogenesis of the illness. However, regard less of clinical presentation, some degree of liver disease is invariably present. Hepatic Presentation With hepatic presentations, signs and symptoms include jaundice, hepatomegaly, edema, or ascites. Viral hepatitis and cirrhosis are often initial diagnostic considerations in individuals who, in fact, have Wilson's disease. Neurologic Presentation In patients with neurologic presenta tions, abnormalities include distinctive speech difficulties (dysar thria), dystonia, rigidity, tremor (e.g., wing-beating) or choreiform movements, abnormal gait, and uncoordinated handwriting. Wilson's disease can properly be classified as a movement disorder. The neu rologic signs and symptoms reflect the predilection for basal ganglia (e.g., caudate, putamen) involvement in the brains of affected persons. Wilson's disease may be mistakenly diagnosed as Parkinson disease or other movement disorders. Psychiatric Presentation In psychiatric presentations, changes in personality (irritability, anger, poor self-control) or school perfor mance, depression, and anxiety are common symptoms. Typically, patients presenting in

this fashion are in their late teens or early

FIGURE 427-1 Kayser-Fleischer ring in Wilson’s disease, representing copper deposition in Descemet membrane of the cornea. (Image courtesy of Tjaard U. Hoogenraad MD, PhD, Department of Neurology, University Medical Centre Utrecht, Utrecht, The Netherlands.) twenties, a period during which substance abuse is also a diagnostic consideration. Wilson’s disease should be formally excluded in all teen agers and young adults with new-onset psychiatric signs. Ocular Manifestations The eye is a primary site of copper deposition in Wilson’s disease, producing a pathognomonic sign, the Kayser-Fleischer ring (Fig. 427-1), a golden to greenish-brown band in the peripheral cornea. This important diagnostic sign first appears as a superior crescent, then develops inferiorly, and ultimately becomes circumferential. Slit-lamp or optical coherent tomography examina tions are required to detect rings in their early stage of formation. Copper can also accumulate in the lens and produce “sunflower” cata racts. Approximately 95% of Wilson’s disease patients with neurologic signs manifest the Kayser-Fleischer ring compared to two-thirds of those with hepatic presentations. Copper chelation therapy causes fad ing and eventual disappearance of corneal copper. Other Clinical Manifestations Secondary endocrine effects of Wilson-associated liver disease may include delayed puberty or amen orrhea. Renal tubular dysfunction in Wilson’s disease leads to abnormal losses of amino acids, electrolytes, calcium, phosphorus, and glucose. Presumably, this effect is related to renal copper toxicity; high copper levels have been noted previously in the kidneys of patients with Wilson’s disease. Treatment with copper chelation often improves the renal disturbances. There also can be skeletal effects of Wilson’s disease, including osteoporosis and rickets, which may be attributable to renal losses of calcium and phosphorus. Osteoarthritis, primarily affecting the knees and wrists, may involve excess copper deposition in the bone and cartilage. Hemolytic anemia due to the direct toxic effects of copper on red blood cell membranes is usually associated with release of massive quantities of hepatic copper into the circulation, a phenomenon that can be sudden and catastrophic. ■ ■BIOCHEMICAL Laboratory findings that support the diagnosis of Wilson’s disease include low levels of serum copper and serum ceruloplasmin, elevated hepatic transaminase levels, aminoaciduria, and hemolytic anemia. Incorporation of radiolabeled 64Cu into serum ceruloplasmin, mea sured as the appearance of copper in the serum after an oral load, is a highly specific diagnostic test; patients with Wilson’s disease incorpo rate very little 64Cu into ceruloplasmin. Increased urinary excretion of copper (>100 µg/24 h) is an easily per formed and important diagnostic test for Wilson’s disease. Acid-washed (copper-free) collection containers should be used. The penicillamine

challenge is a variation using serial urine copper measurements in which 500 mg of penicillamine are administered orally after collecting a baseline 24-h urine. The penicillamine dose is repeated after 12 h, the midpoint of the second 24-h urine collection. A several-fold increase in copper excretion in the second collection suggests the diagnosis.

Although invasive, percutaneous needle liver biopsy for mea surement of hepatic copper remains a gold standard technique for biochemical diagnosis of Wilson’s disease. Hepatic copper values

> “ 200 µg per gram of dry weight (normal 20–50 µg) are characteristic of Wilson’s disease. Inductively coupled plasma mass spectrometry and atomic absorption

spectrometry are preferred quantitative meth ods; histochemical staining for copper in liver biopsy specimens is considered less reliable. Wilson’s Disease CHAPTER 427 ■ ■MOLECULAR Wilson’s disease is caused by loss-of-function variants in ATP7B. Despite similar genomic structures, large deletions are much less common in ATP7B than in ATP7A, the closely related X-linked gene responsible for Menkes disease. Several ATP7B missense variants are common (H1069Q, M645R, and R778L), with various allelic frequen cies reflecting geographic, racial, and/or ethnic differences. Major ATP7B databases list >650 pathogenic or likely pathogenic variants. Population-based and genomic-based estimates of prevalence range from 1 in 7000 to 1 in 30,000, with genome-based ascertainments sup porting the higher prevalence. This disparity may reflect incomplete penetrance, although there is little doubt that some affected individuals unfortunately escape medical attention. Advances in the application of whole genome sequencing (and/or measurement of ATP7B peptides) from newborn dried blood spots may transform presymptomatic diag nostic screening for Wilson disease in the future. DIAGNOSIS Currently, a formal diagnosis of Wilson’s disease relies on a combina tion of clinical, biochemical, and molecular features (Table 427-1). A scoring system (Leipzig) that weights and collates various signs and symptoms was produced by an international expert group in 2001 and remains a valuable guide to diagnosis that is endorsed by the European Association for the Study of the Liver (EASL). TABLE 427-1 Main Diagnostic Features of Wilson’s Disease CLINICAL SIGNS AND SYMPTOMS BIOCHEMICAL FINDINGS MOLECULAR FINDINGS Hepatic: Jaundice Anorexia Vomiting Ascites and/or edema Splenomegaly Neurologic: Dysarthria Facial grimace (risus sardonicus) Drooling Dysphagia Dysgraphia Dystonia Tremor (“wing-beating”) Ataxia Seizures (rare) Ocular: Kayser-Fleischer ring Sunflower cataract (rare) Psychiatric: Decline in school performance Personality change Mood disorder Schizophrenia Low serum copper Low serum ceruloplasmin Increased urinary copper excretion Elevated liver enzymes Hypoalbuminemia Increased liver copper Fatty liver Cirrhotic liver Hemolytic anemia Renal Fanconi syndrome Variants in ATP7B on both chromosomes Variants or polymorphisms in other genes (e.g., CAT, SOD2, MTHFR) may influence clinical expression of Wilson’s disease in some individuals

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