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Wilson's disease: Etiology, diagnosis, and treatment

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Genetics of Wilson's disease

Wilson's disease (WD) is an inherited autosomal recessive disorder of copper balance. Kinnier Wilson in his original description recognized that it was a familial disease but did not consider it hereditary.[1] A genetic origin was proposed by Hall in 1928, and an autosomal recessive inheritance was reported in 1953.[2] By 1993, the specific chromosome and gene were localized.[3] The offending gene, named ATP7B, is located on chromosome 13q14.3.[4] The product of ATP7B is a cation-transporting P-type ATPase.[4] This group of ATPases is involved in transporting metals into and out of cells by using energy stored in ATP.[5] ATP7B is primarily located in the trans-Golgi Network (TGN) and in cytoplasmic vesicles.[4] The structure of ATP7B is complex. It includes six copper-binding domains, a transduction domain involved in the transduction of the energy of ATP hydrolysis to cation transport, a cation channel and phosphorylation domain, a nucleotide-binding domain, and eight hydrophobic transmembrane sequences.[5] Once copper has been bound, both secondary and tertiary structural changes take place, inducing phosphorylation. In the TGN, ATP7B mediates the incorporation of copper molecules into apoceruloplasmin to form ceruloplasmin. Ceruloplasmin, which is subsequently secreted from hepatocytes into the plasma, carries 90% of copper in plasma and is a source of copper for peripheral organs.[4] The function of ATP7B is quite different in the cytoplasmic vesicles of hepatocytes. It acts to sequester excess copper and the vesicles are in turn excreted into bile.[6] This is the major pathway of elimination of excess copper. When taking the function of ATP7B under consideration, one can begin to understand the laboratory values that are characteristic of WD (low ceruloplasmin and excess copper). Excessive intracellular copper leads to mitochondrial injury. This results in oxidative damage to hepatocytes and spillage of copper into blood, leading to further downstream events, including damage to the brain, kidney, and red blood cells.[7]

Though WD is thought to be an autosomal recessive disease, most individuals are compound heterozygotes, carrying different mutations on each allele encoding the WD gene.[8] Over 500 distinct disease-causing mutations have been found, with some only in single families and others accounting for larger numbers of cases.[5] Mutations generally result in loss of function. The most common mutation seen in the European population involves H1069Q in which histidine is replaced by glutamine in a highly conserved motif close to the ATP-binding region.[9] Another common mutation seen predominantly in Asian populations is the R778L mutation.[4] An

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intriguing aspect of WD is that individuals with the same genotype, e.g., monozygotic twins, can present with different phenotypes.[7] Therefore, other genetic or environmental factors could influence the expression of the genotype, including dietary copper intake and the individual's intrinsic capacity to handle copper overload.[4]

Awareness of the manifestations and treatment of WD is important both to primary care physicians and specialists in gastroenterology, neurology, psychiatry, and pediatrics. Wilson's disease can cause severe disability and can be fatal if left untreated. With the protean and multisystem manifestations, it is easy to overlook the diagnosis. However, when diagnosed early, treatment options are available that can prevent or reverse many manifestations of WD and restore life expectancy to near normal.[10]

Pathology of Wilson's disease

The earliest lesions in WD are seen in the liver, the site of initial copper accumulation. The changes are nonspecific and include both macrosteatotic and microsteatotic changes within hepatocytes, often accompanied by cytoplasmic inclusions within nuclei.[11] During the intermediate stage, lobular necrosis and periportal inflammation, swelling, and necrosis create a picture that may resemble autoimmune chronic hepatitis. Mallory bodies may be evident on biopsy. As WD progresses further, cirrhosis can develop. It may be of the micronodular type or a mixed macronodular–micronodular histological pattern.[11] Central pontine myelinolysis (CPM) is often seen in WD. CPM may occur in the absence of specific etiological factors, such as electrolyte disturbances, and is much more common with the neurological form of WD.[12]

Ultrastructural abnormalities visualized with electron microscopy include large vacuoles, enlargement and separation of the mitochondrial inner and outer membranes, widening of the intercristal spaces, and increases in the density and granularity of the matrix. These findings on EM can be pathognomonic of WD if cholestasis is not present.[11] Immunohistochemical stains for copper may demonstrate deposits of copper within the liver, renal tubular cells, and brain.[11]

On MRI and gross examination, the brain often is atrophic with white matter changes (hyperintense on T2 and hypointense on T1). Usually, the putamen, globus pallidus, caudate, thalamus, midbrain, pons, and cerebellum are most affected by copper overload. Histologically, there is in increase in the number of astrocytes within the gray matter. There are also signs of spongiform degeneration in more advanced cases with swollen glia and liquefaction. Opalski cells, which are thought to originate from degenerating astrocytes, are distinctive for WD. They are large cells with a fine granular cytoplasm and abnormal nuclei.[11,12]

Approach to diagnosis

A high degree of suspicion is the key to early diagnosis (Table 1). Neurological symptoms in the form of tremor, dystonia, or parkinsonism and unexplained jaundice or abnormal liver

Table 1
Diagnostic considerations in Wilson's disease.

WD should be considered in individuals with abnormal liver function of unclear etiology or movement disorders with early-onset or atypical presentations
Assessment includes clinical evaluation, liver function tests, complete blood count, serum ceruloplasmin, and 24 h urinary copper excretion
Liver biopsy to estimate liver copper content is the best biochemical evidence of WD
Kayser–Fleischer rings should be sought by slit-lamp examination if not evident to clinical inspection
First-degree relatives should be screened for WD
When possible, genetic diagnosis should be used, especially in patients with indeterminate clinical and biochemical findings