Wilson's Disease and Copper Metabolism—A Review

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Introduction

Wilson's disease may be defined as an inborn error of copper metabolism inherited as a recessive trait, characterised by disturbances in the absorption, circulation, excretion and deposition of abnormal and toxic amounts of the metal in various tissues including the brain. The chain of the above abnormal events may be traced to the basic defect of hypercopperamia.

Clinical Features

The Central Nervous System

The literature abounds in clinical reports of Wilson's disease, commencing of course with the classical description by Wilson. A fine tremor, a slight indistinctness of speech, or a mere slowing of voluntary movements in general are often the first neurologic features. After a variable period, usually months, one of these symptoms becomes continuous and progressive, most frequently the tremor. Hypertonia of muscles, though not an early manifestation, steadily advances and rigidity supervenes as the disease becomes established. As Wilson himself described it, the established clinical picture is characteristic, with the mouth held open in a stereotyped smile or with a vacant or furtive look. We have also reported these clinical features.

Kasrsky-Fleischer (K-F) ring

The K-F ring in the cornea is the single most pathognomonic sign of Wilson's disease. It was first described in 1902 by KASRsky in a patient with "multiple sclerosis"; a decade later strong evidence was produced by Fleischer that the granules were due to a deposition of copper. It has a smoky appearance on direct illumination but a granular appearance on slit-lamp microscopy.

Liver

The essential basis of the disease is a progressive subacute hepatitis leading to a covertly nodular cirrhosis of the liver. More commonly, symptoms of liver damage are entirely absent, though cirrhosis is invariably present to some degree. A history of one or two episodes of jaundice is not infrequent; overt ascites and edema are rare. A smooth, firm, enlarged and at times tender liver can be palpated in most cases. Prominent signs of hepatic insufficiency are frequent in children and young patients and carry a poor prognosis.

Kidney

The renal lesion in Wilson's disease is diffuse and affects many aspects of renal function. Although reduction of renal plasma flow and decrease in glomerular filtration rate have been reported in Wilson's disease, the more frequent and prominent signs of renal involvement appear to be based on a defective renal tubular reabsorption.

Metabolic Aspects and Pathogenesis

The pathogenetic chain of events which characterises the main metabolic disorder in Wilson's disease appears to be (1) greatly increased absorption of copper from the intestine and/or failure of excretion from the liver into the bile; (2) ceruloplasmin is markedly reduced; (3) marked increase of non-ceruloplasminbound circulating copper; (4) its increased deposition in tissues such as brain, cornea, liver and kidney; and (5) increased excretion of copper in urine.

Ceruloplasmin, an alpha-2 globulin, which binds nearly 98% of the serum copper in man, has been found reduced in cases of Wilson's disease. It acts as an oxidase and this activity is manifested with paraphenylenediamine as the substrate. Its concentration can be very low, but it is still at zero level. Although there are stray reports of normal serum ceruloplasmin levels in Wilson's disease, our study which extended for over 20 years showed a remarkable and constant reduction in the copper oxidase activity in patients. Moreover, parents and siblings of the patients occupied an intermediate position between the patients and the controls (laboratory staff) and the differences in activity between the three groups were significant.

Although ceruloplasmin binds copper more avidly than any other blood protein, metabolically the most active fraction of serum copper appears to be that bound to albumin. In normal subjects, 90% of serum copper gets attached to globulin within minutes of ingestion and only 10% is dissociable or "free". In patients with Wilson's disease, due to diminished amount of ceruloplasmin, the copper apparently remains loosely bound to albumin. This moiety is often referred to as "direct reacting copper", because it reacts with diethylthiocarbamate. Ceruloplasmin, i.e. globulin-bound copper, does not give this reaction. We feel that this test is reliable in Wilson's disease where considerably elevated levels of this "free" copper are observed. As with copper oxidase, the mean value of direct reacting copper in our normal subjects was higher than that reported by others. However, when calculated as a percentage of the total serum copper, the figure of 6.9±7.4% was similar to that reported by others. Considering that a large concentration of dissociable circulating copper is responsible for the deposition of copper in vital and vulnerable tissues, it appears essential to undertake an estimation of this fraction.

Observations of Uzman and Denny-Brown of increased aminoniciduria in this disease has led to
the suggestion that there may be a production of abnormal proteins with unusual affinity for copper which are incompletely metabolised, with resultant formation and excretion of excess amino acids. No increase in the circulating blood amino acids was observed in Wilson's disease in contrast to the high levels encountered in liver disease, especially hepatic cirrhosis or neoplasia, studied earlier by us. Aminoaciduria, phosphataturia, calciumuria and even glycosuria in patients with Wilson's disease are believed to be a result of renal tubular damage due to copper deposition. Thus a renal tubular reabsorption defect prevails and is particularly marked in the "cerebral-muscular type" of the disease where the picture resembles that in the Toni-Fanconi syndrome. Nearly a third of our patients manifested unusual features such as stunted growth, bony deformities, radiological evidence of rickets, and generalised muscular weakness, usually of the proximal type.5,7

The other major pathogenetic hypothesis is the formation in liver and other tissues of abnormal proteins with an unusual avidity for copper, which makes copper unavailable for ceruloplasmin, with consequent reduction in its synthesis. Furthermore, the abnormal protein metabolism was believed to lead to the formation and excretion of excess oligopeptides and amino acids. Porter's elegant work14 ruled out the occurrence of abnormal proteins in either liver or brain, demonstrating rather an excessive binding of copper to normal proteins.

Histopathological Findings
The gross changes in the brain are generally confined to the corpus striatum, which may appear shrunken. Microscopic alterations occur in the basal ganglia, the anterior-superior portions of the cerebral cortex and the cerebellum. The putamen, the caudate, the globus pallidus and the nucleus subthalamicus also show some loss of neurones and the characteristic proliferative astrocytes. The reactive astrocytes do not form glial fibres. More extensive areas may show diffuse loss and chronic neuronal changes, with diffuse reaction of Alzheimer type II glii. Histochemical preparations stained for copper by rubineic acid show that the metallic granules were more frequent in glial cells than in nerve cells.

As Wilson originally described it, the gross appearance of the liver is indistinguishable from that of postneonatal cirrhosis. Grossly the liver is shrunken, firm and very nodular. On microscopic examination, replacement fibrosis of degenerated lobules, increase of intercellular reticulin, and occasional regenerating nodules are observed. In the less affected areas the liver cell nuclei appear enlarged and pale, and the Bouer-Feulgen stain reveals accumulation of glycogen in the nuclei and in the cytoplasm. The clustered proliferation of bile ductules within the replaced fibrous tissue creates an impression of "ghost" lobules.13 Accumulation of copper within the parenchymal cells appears to be the most interesting and specific change.

Indian Childhood Cirrhosis vis-à-vis Wilson's Disease
Indian childhood cirrhosis (ICC) is characterised by an insidious onset, a slow clinical course, hepatosplenomegaly, with Mallory's hyaline bodies in the vacuolated liver cells, jaundice, ascites as a late feature, and an invariably fatal outcome. Histochemical procedures show that copper and copper associated protein (CAP) accumulate from an early stage of the disease and are useful diagnostic criteria.6 Copper and CAP have also been found in moderate amounts in a large proportion of siblings of patients with ICC.10 In Wilson's disease, histochemical demonstration of copper and copper associated protein in the hepatocytes is difficult, except in the late stages of the disease when cirrhosis is well advanced. Further, whereas serum ceruloplasmin is decreased in Wilson's disease, its concentrations are normal in ICC.15

Although the morphological changes have been fairly documented there is paucity of data on the electron microscopic features of the disease.15,20 While on light microscopy glycogen-like vacuolation of the hepatocytes is the conspicuous feature, at electron microscopy, Mallory's hyaline with its fine fibrillar structure was found to be a well recognised feature of intermediate and even early stages of ICC.20

In ICC, therefore, the exact mechanism of hepatotoxic effects of copper remains as yet undetermined and abnormalities in copper metabolism are considered to have a direct effect on hepatic structure and function. Copper absorbed from the intestine is normally transported in the blood as an albumin complex; liver cells separate the copper from this complex, and metabolise it with a low molecular weight protein. If more copper reaches the liver than can be readily converted into ceruloplasmin or excreted in the bile, the excess is stored in the lysosomes of hepatocytes. It is possible therefore that in ICC, there may be an inherent genetic constitution of delayed maturation of hepatocyte function with respect to copper metabolism, which causes accumulation of the copper in the hepatocytes following a physiological overload or due to as yet undetermined environmental factors.16

Treatment of Wilson's Disease
Treatment by diets designed to favour liver function has not had any lasting effect on the neurologic symptoms. BAL (British anti-Lewisite or Dimercaptopropionel) releases various metals, including copper, from the body and was used in Wilson's disease to remove excess copper from the tissues by chelation action, and to prevent further damage to the organs. The occurrence of local and systemic toxic reactions seems to have limited the use of BAL.

A more effective decomplexing agent, penicillamine (ββ-dimethyl-cysteine), when given orally, mobilises copper in normal individuals and in patients with Wilson's disease with equal facility.21 A single test-dose of 600 mg can bring about as much as a 50 fold increase in urinary copper excretion in six hours. Administration of penicillamine with labelled copper has confirmed similar and effective mobilization of copper from untreated patients as well as from those treated for years with penicillamine. Mild maculopapular erythematous rash, low fever, urticaria, arthralgia or
lymphadenopathy may occur occasionally as allergic reactions, especially early in treatment. Walsh et al. recently reported 20 patients with Wilson's disease in whom severe penicillamine intolerance developed. These patients in whom the stage of illness ranged from the preasymptomatic through severe neurological or hepatic disease to the "decoppered" post-asymptomatic stage, have been successfully managed with the orally active chelating agent trientine ditrihydrochloride (Trient). Trien was thus found to be a safe and highly effective treatment for reversing symptoms and maintaining patients previously successfully decoppered with penicillamine.

Recently the efficacy of zinc therapy has been demonstrated. Zinc therapy induced a negative or neutral copper balance in all five patients with Wilson's disease who were receiving no therapy other than zinc. Zinc increases the rate of faecal excretion of copper in patients with Wilson's disease. Oral ingestion of zinc induces the synthesis of a protein, metallothionein, in intestinal cells. This protein contains 35% cysteine, and has a higher affinity for copper than for zinc. After metallothionein synthesis is induced by zinc ingestion, copper absorption is blocked and a significant amount is excreted into the gastrointestinal tract. Thus the blocking effect caused by zinc therapy results in a high rate of faecal excretion of copper. However, it may be premature to convert patients to zinc therapy if they tolerate penicillamine well.

Finally, as Carruthers et al. rightly said "resources are limited in medicine, indeed, and those resources that society can be persuaded to devote to Wilson's disease would be far better spent in seeking out patients whose Wilson's disease is undiagnosed than in finding new suprise agents".

References