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Editorial

# Hoard and Accrue-Wilson's Disease

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Wilson disease emerges as a condition delineating augmented or toxic levels of copper deposition confined to hepatic or renal parenchyma, cornea and central nervous system. The condition is preponderantly engendered due to genomic mutation within ATP7B gene with absence or dysfunction of copper transporting ATPase enzyme.

Additionally designated as hepatolenticular degeneration, the disorder is associated with accumulation of copper in hepatic and renal parenchyma, central nervous system and cornea to toxic levels with configuration of Kayser-Fleischer rings. Cogent psychiatric and neurological symptoms may ensue. The condition represents with variable morphology wherein pathognomonic histological features are absent.

With significant geographic variation, the disorder depicts an autosomal recessive mode of disease inheritance with chromosomal mutations within ATP7B gene.

Wilson disease is commonly confined to hepatic and renal parenchyma, cornea or brain and expounds a disease incidence of 1:30,000 [1,2].

Copper is absorbed by intestinal cells and plasma copper is transported within hepatocytes and biliary canaliculi for biliary excretion, as moderated by ATP7B gene. Hepatic parenchyma secretes ceruloplasmin, a molecule significantly involved in copper transportation and iron haemostasis [1,2]. Wilson disease is associated with chromosomal mutations of ATP7B gene. Genetic mutations >300 mutations within ATP7B gene induces accumulation of copper within hepatocytes, basal ganglia, cornea or renal parenchyma with consequent cellular injury [2,3]. However, cogent assessment of genomic mutations may be challenging as the disorder predominantly arises within compound heterozygotes. Altered copper metabolism with decimated ceruloplasmin levels gradually induces enhanced storage of iron with iron accumulation within hepatocytes [2,3]. Wilson disease is devoid of a specific phenotype genotype concurrence. However, majority of subjects emerge as compound heterozygotes.

Wilson disease occurs due to oxidative cellular damage engendered due to copper accumulation within hepatocytes up to toxic levels [2,3].

Wilson disease depicts a variable clinical representation and may concur with conditions as acute fulminant hepatitis with hepatic failure along with or absence of haemolytic anaemia wherein Coombs test appears non reactive. Unexplained chronic hepatitis or elevated serum levels of hepatic enzymes may be encountered. Hepatic cirrhosis may ensue. Generally, hepatic symptoms preempt occurrence of neurological symptoms [3,4].

Gross, pathognomonic features appear absent wherein cogent macroscopic features are contingent to morphological features and phase of the disorder. Fulminant hepatitis with parenchymal necrosis occurring due to Wilson disease depict a small, shrunken liver. Chronic disease of extended duration with consequent cirrhosis display macroscopic features consistent with cirrhosis [3,4].

Upon microscopy, variable features are encountered contingent to clinical representation and stage of disease, designated as ~acute hepatitis demonstrates inflammation of hepatic lobules and portal tracts with infiltration of lymphocytes and plasma cells. Akin to autoimmune hepatitis, periportal hepatocytes display ballooning. Besides, acidophil bodies may be discerned. Acute cholestasis is observed [5,6]. ~fulminant hepatitis depicts massive hepatocyte necrosis with collapse of hepatic parenchyma. Copper pigment may be amalgamated within Kupffer cells or portal macrophages. Distinction from fulminant hepatitis of variable aetiology may be challenging [5,6]. ~chronic hepatitis delineates patchy, non zonal steatosis of hepatocytes along with aggregates of lipofuscin pigment. Peri-portal hepatocytes depict glycogenated nuclei and intracellular copper deposits. Mild, chronic lymphocytic and plasma cell infiltration of portal tracts is associated with discernible interface activity. Besides, acidophil bodies or peri-portal Mallory-Denk bodies (MDB) may be observed. Few instances depict hemosiderin pigment deposits and distinct Kupffer cells [5,6]. ~cirrhosis which represents as micro-nodular or macro-nodular hepatic parenchyma associated with steatosis, Hepatocytes depict anisonucleosis and ballooning. Acidophil bodies and Mallory-Denk bodies may be discerned wherein intracellular copper deposition is patchy and variable. Few lesions depict satellitosis. Fibrosis of central vein fibrosis may ensue [5,6]. Ultrastructural examination of Wilson disease remains non pathognomonic. Cells display aberrant mitochondria with heterogeneous outline and magnitude, cytoplasmic inclusions and enlarged intercristal spaces. Peroxisomes appear enlarged. Lipofuscin pigment may be enunciated [5,6].

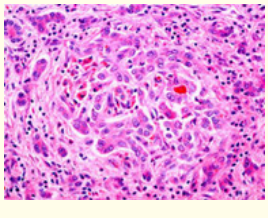

**Figure 1:** Wilson disease depicting hepatocyte necrosis, portal and peri-portal inflammation, intracellular copper deposition, acidophil bodies and nodular configuration [12].

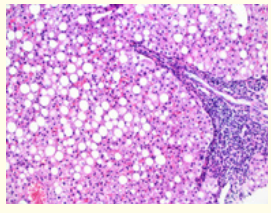

**Figure 2:** Wilson disease delineating steatosis of hepatocytes, acidophil bodies, intracellular copper, fibrosis, nodular configuration [13].

Staging modality of Barcelona clinic liver cancer (BCLC) is constituted of ~performance status ~Child-Pugh score ~tumour extent upon radiography ~tumour magnitude ~multiplicity of tumours ~vascular invasion ~regional lymph node involvement ~extrahepatic metastases [3,4].

Contingent to aforesaid parameters, hepatocellular carcinoma is categorized as ~stage 0 comprised of preliminary tumour stage or asymptomatic preliminary tumours with performance status (PS) 0, Child-Pugh A and a solitary lesion <2 centimetre magnitude. Neoplasm can be managed with singular surgical resection. Tumefaction associated with portal hypertension or hyperbilirubinemia is optimally subjected to liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation. ~stage A comprised of preliminary tumour stage or asymptomatic antecedent neoplasms with performance status (PS) 0 to 2, Child-Pugh A to C and a solitary lesion >2 centimetre diameter or antecedent multifocal disease with characteristically up to three lesions < 3 centimetre magnitude. Singular neoplasms can be subjected to surgical resection. Multiple lesions are managed with liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation. ~stage B or intermediate stage is comprised of asymptomatic multifocal disease with performance status (PS) 0, Child-Pugh A to C, multifocal disease with ≥ 1 lesion and minimally a singular lesion > 3 centimetre diameter or > 3 lesions irrespective of tumour magnitude. Neoplasm is optimally treated with transcatheter arterial chemoembolization(TACE). ~stage C or advanced

stage is constituted of symptomatic neoplasm associated with tumour invasion and/or distant metastasis with performance status (PS) 1 to 2, Child-Pugh A to C, vascular invasion and/or regional lymph node disease and/or distant metastasis. Neoplasm is managed with varieties of palliative therapy and agents as sorafenib or phase II trial agents. ~stage D or end-stage disease configures as a terminal stage and enunciates performance status (PS) >2, Child-Pugh C and appears singularly as a clinical stage. Optimally, symptomatic therapeutic options are beneficial. Tumour stage is compatible with Okuda stage III [3,4].

Wilson disease is devoid of specific or pathognomonic staining evaluation. Copper stain may be utilized to detect copper pigment permeated within hepatocytes, Kupffer cells or portal macrophages. Notwithstanding, intracellular copper may occur within diverse hepatic diseases associated with cholestasis as primary biliary cirrhosis, MDR3 deficiency, hepatic cirrhosis or primary sclerosing cholangitis [6,7]. Mallory-Denk bodies appear immune reactive CK8, CK18, p62 or ubiquitin. Besides, copper stains as orcein, Timm's silver or rubeanic acid may be beneficially employed to discern the pigment. Nevertheless, Wilson disease remains as a possibility with non reactive copper stain of hepatic parenchyma [6,7].

Wilson disease requires segregation from lesions as fatty liver disease, autoimmune hepatitis, chronic hepatitis or drug induced hepatitis. Elevated serum levels of hepatic enzymes as alanine transaminase (ALT) and aspartate transaminase (AST), encountered within adults or paediatric subjects appears indicative of Wilson disease, especially where precise disease detection may be challenging(7,8). Serum ceruloplasmin may be decimated < 50 milligrams/litre. 24 hour urinary copper appears elevated wherein symptomatic subjects expound levels > 100 µg and asymptomatic subjects display values >40 µg. Concentration of hepatic copper emerges at > 250 µg/grams (dry weight) [7,8]. Slit lamp examination of the cornea delineate Kayser-Fleischer (KF) rings wherein absence of Kayser-Fleischer rings may not indicate absence of Wilson disease. Although arising within compound heterozygotes, assessment of genomic mutations and alterations within ATP7B gene may be beneficially adopted [7,8]. Elevated serum alanine transaminase (ALT) and aspartate transaminase (AST), decimated serum alkaline phosphatase (ALP), serum ceruloplasmin levels < 50 milligrams/litre, enhanced 24 urine copper with symptomatic subjects displaying levels >100 µg and asymptomatic subjects >40, hepatic copper concentration > 250 µg/grams(dry weight) of liver may be discerned. Besides, Wilson disease enunciates discernible anti-smooth muscle or antinuclear antibodies with elevated serum gamma globulin levels, recapitulating features of autoimmune hepatitis [8,9]. Upon radiography, specific pathognomonic features appear absent. Ultrasonography depicts non specific heterogeneity of hepatic parenchyma [8,9]. Computerized tomography (CT) delineates variably hyper-dense foci or diffuse and anomalous attenuation of hepatic parenchyma. Nevertheless, diverse factors may contribute to metal deposition within the hepatic parenchyma as iron overload occurring secondary to hemochromatosis [8,9]. Characteristic factors may contribute towards non specific morphological alterations of ensuing cirrhosis as regenerative parenchymal nodules or nodularity of superficial hepatic surface [8,9]. T1 weighted magnetic resonance imaging (MRI) of Wilson disease delineates hyper-intense nodules whereas T2 weighted imaging enunciates hypo-intense nodules [10,11]. Wilson disease may be appropriately alleviated by administration of oral chelating agents as D penicillamine and trientine. Ingested zinc salts may prohibit copper absorption [10,11]. Hepatic transplantation and corrective steps of specific phenotypes may be beneficially adopted for treating accompanying cirrhosis or fulminant hepatic failure. Additional therapeutic modalities appear under experimental stage [10,11].

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12. Image 1 Courtesy: Mediniz.com

13. Image 2 Courtesy: Science direct