Chapter

Histopathology of Wilson Disease

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Abstract

Wilson Disease (WD) is a genetic metabolic disease of copper metabolism. The implicated gene is ATP7B, encodes a P-type ATPase which transports copper. The resultant defective metabolism of copper results in copper accumulation in multiple tissues especially liver, eye and central nervous system. WD occurs worldwide, usually between 5 and 35 years; a wider age range is also reported. Clinical presentations are diverse and include combinations of hepatic, neurological, ophthalmic and psychiatric manifestations. Other organs or tissues may also be affected. Biochemical abnormalities such as serum ceruloplasmin and 24-h urinary copper excretion are important for the diagnosis but are not always abnormal in WD. The liver histopathology has several different patterns from mild nonspecific changes to acute fulminant hepatitis and cirrhosis. Copper histochemistry is helpful in diagnosis. Genetic testing is another diagnostic tool. It is important to diagnose WD because it is fatal when overlooked, curable when diagnosed. The diagnosis should be keep in mind at all ages in patients with hepatic disease, neurological disease, or psychiatric symptoms.

Keywords: Wilson disease, copper, liver, histopathology, histochemistry

1. Introduction

Wilson Disease (WD) is an autosomal recessive genetic metabolic disease of copper metabolism. Its incidence is vary in different geographic areas with an average incidence of 1 in 30,000 individuals worldwide. Recent studies suggest a considerably higher prevalence of 1:1500–1:3000 for WD. It is caused by mutations in the ATP7B gene encoding a copper transporting P-type ATPase required for copper excretion into the bile [1, 2]. WD is first described by the American neurologist Samuel Alexander Kinnier Wilson in 1912. There are earlier case reports mostly by neurologist in mid 1800s [3]. Kayser and Fleischer mentioned the pigmented corneal rings, in 1902 and 1903 respectively In 1911, Wilson presented his monograph describing the "progressive lenticular degeneration". Bramwell, in 1916, was the first to realize the importance of liver pathology in WD. In 1948, Cumings described the copper abnormalities in WD and in 1952, Scheinberg and Gitlin showed that the ceruloplasmin levels were low in most of WD patients. In 1956, Walshe introduced the penicillamine as a chelating agent, the first effective treatment for the condition [3, 4]. This discovery of successful chelation therapy makes WD one of the most satisfying genetic diseases to be diagnosed and treated.

Originally WD was described as a neurodegenerative disease associated with cirrhosis of the liver. Later, WD was observed in children and adolescents with acute or chronic liver disease without any neurologic symptoms [5]. Now, WD is considered a multi-systemic disorder, in which hepatic, neurological and

psychiatric symptoms are often associated with renal, endocrine, osteoarticular, corneal and myocardial disturbances, all related to abnormal copper metabolism ending with systemic accumulation of the copper [6, 7].

Ultrastructural findings of WD have also been studied. The mitochondrial changes are the most distinctive and pathogenetically significant and include heterogeneity of size and shape, increased matrix density, separation of inner from outer membranes, enlarged intercristal spaces and various types of inclusions. Importantly, ultrastructural mitochondrial changes in WD cannot be considered pathognomonic; although exceedingly rare with cholestatic liver disease, such changes are found with mtDNA depletion disorders [4, 8].

WD has considerable variation in clinical presentations, the most common ones being liver disease and neuropsychiatric disturbances [9]. There is considerable phenotypic variation in WD: Some patients present with hepatic disease during the first decade of life, some with neurological degeneration in adolescence or adult life, with or without overt liver disease. In a study by Ferenci et al., the severity of liver disease did not show correlation with the mutation status. Rather, they reported that the prevalence of cirrhosis increased with age in pediatric patients. They found that hepatic disease was more common among females, whereas neurological presentation occurred more frequently in males [10]. The wide range of disease patterns cannot be explained just by different mutations. Environmental, epigenetic, and other genetic factors are also contribute pathogenesis of WD [6, 10].

Classically low serum copper and low ceruloplasmin levels with high urinary copper content make a triad which is usually associated with WD diagnosis. But this triad may be absent or incomplete in 3% of genetically confirmed WD cases [7].

Early diagnosis of WD is important. But it is also important to make the diagnosis of WD prior to transplantation. Because organ transplant networks make special provision for acute liver failure (ALF) due to WD when considering the urgency of transplantation and the terminology relating to acute presentations of liver disease become relevant when listing a case of WD [11].

A large variability in the age of onset and in the clinical presentation of WD exists. Hepatic manifestations of WD at presentation can be extremely variable, and range from asymptomatic hepatomegaly, isolated splenomegaly, persistent or intermittent elevation of serum aminotransferases, jaundice, fatty liver or pseudo-autoimmune hepatitis, acute hepatitis, compensated or decompensated cirrhosis to acute liver failure (ALF). The varied clinical manifestations of WD due to pathological copper accumulation in different organs, even in the early course of the disease, often pose a diagnostic challenge [7].

The main therapeutic strategy is using chelating agents, particularly D-penicillamine. Liver transplantation (LT) is reserved for patients unresponsive to medical therapy or with fulminant hepatic failure. LT for neurological complications is highly controversial and generally cannot be recommended [8].

2. Pathogenesis and clinical manifestations

Copper is an essential element for cellular function. Dietary copper is absorbed in the stomach and duodenum and reaches the liver by the portal vein [1]. Intestinal uptake is regulated by the Menkes ATPase (ATP7A). The ATP7A gene is expressed in most tissues except the liver. Menkes disease, an X-linked copper deficiency disorder, results from mutations in this gene. The abnormal gene in Wilson disease is ATP7B (the Wilson ATPase) which shows 56% homology to ATP7A [8]. It is expressed mainly in the liver but its expression is not restricted to liver cells. This data suggests that ATP7B dysfunction might be responsible for the systemic

disturbances of copper trafficking in the whole human body [1, 6]. The hepatic protein ATP7B encodes a copper-transporting P-type ATPase, transporting copper into the secretory pathway for incorporation into apoceruloplasmin, forming ceruloplasmin. ATP7B moves copper into the trans-Golgi network, where ceruloplasmin peptide acquires its complement of copper, assumes its folded state and is then released into the circulation [12]. Excess is excreted eventually into the bile. Without the normal complement of copper, the peptide folds differently and has a decreased circulating half-life, leading to a low level of serum ceruloplasmin. Biliary excretion of copper is necessary for its homeostasis. When ATPB7 is defective, excess copper accumulates in the hepatocytes. Eventually the excess copper exceeds the storage capacity causing hepatocellular injury and release of copper into the circulation. Most WD patients have a low level of circulating ceruloplasmin which is a direct result of defective copper handling in hepatocytes as a result of mutation of the ATP7B gene. Free copper is extremely toxic and can produce irreversible cellular damage. The functional consequences of pathogenic ATP7B mutation are increased intracellular copper levels. This produces oxidative stress and free radical formation as well as mitochondrial dysfunction, which results in cell death in the liver, brain, kidneys, heart, eyes, and joints. As this disease damages multiple systems at one time, it poses a diagnostic challenge [2]. Over 600 gene alteration in ATP7B were recognized [6, 12]. The most common ones are single-nucleotide missense and nonsense mutations, chased by insertions/deletions, and, rarely, splice site mutations. H1069Q is the most common mutation around the world, seen in most of the WD carriers in Europe and USA, with some absence for this mutation in some countries [6]. Correlation of phenotype with specific mutations (genotype) is difficult in Wilson disease because the vast majority of affected individuals are compound heterozygotes, possessing one copy each of two different mutations. Differences in clinical features of various mutations between siblings and even identical twins suggests that other genes or environmental factors are important [6, 8]. In a study by Ferenci et al., it was suggested that the HSD17B13:TA allele may modulate the phenotype and outcome of WD by reducing the transition from copper induced hemolysis to fulminant WD. Furthermore, it is associated with milder histological changes [10]. When testing for mutations of the WD gene ATP7B becomes inexpensive and rapid, genetic testing may become the starting point for diagnostic investigation [1].

WD has a myriad of clinical presentations, hepatic, neurological, ophthalmic and psychiatric, that mimic other conditions. WD may present at any age. Although most patients present between ages 5 and 35, the age range is much wider. There are cases reported as early as 9 months and as late as the eighth decade [1, 2, 13]. So far, the oldest patient in English literature is a 77- year-old Turkish woman [14].

Approximately one half of the patients with WD present with liver disease. In the majority of cases, WD manifests its presence during childhood or teenage years in the form of liver symptoms [7]. Hepatic symptoms and presentations of WD are very variable from asymptomatic cases to cases with overt cirrhosis or with ALF. Liver disease may mimic all forms of common liver conditions. All children with an apparent diagnosis of autoimmune hepatitis should also be investigated for WD, and adults with a presumptive diagnosis of autoimmune hepatitis failing to respond rapidly and appropriately to corticosteroid therapy must be carefully evaluated for WD. In terms of the rate of progression of the disease, cirrhosis is usually diagnosed in the second decade of life, although some individuals do not develop cirrhosis, even after the fourth decade of life [15]. Hepatic manifestations usually present earlier than neurological symptoms by 5 years. The most common hepatic signs and symptoms are jaundice, hepatomegaly and abdominal pain [1]. In a subset of patients focal liver lesions may show up, showing with a wide run of imaging

highlights. The lion's share of focal liver lesions in patients with WD are benign nodules, but there are reports that have depicted malignant liver tumors or dysplastic nodules in these patients. Although rare in WD compared to other liver diseases, hepatocellular carcinoma occurs in patients of all ages. Cholangiocarcinoma may also occur in WD [8].

Neurologic manifestations include tremor, gait disturbances, choreiform movements, Parkinsonism or akinetic rigid syndrome i.e., partial parkinsonism, dysarthria, pseudobulbar palsy, rigid dystonia, seizures, migraine headaches, and insomnia. In WD cohorts, neurological presentation is associated with a significantly longer time from onset of symptoms to diagnosis than hepatic presentation, ranging from 2.5 to 6 years. In large case series, mean age at onset of neurologic problems extends from 15 to 21 a long time of age, a decade after onset of liver disease, but a number of patients have been analyzed with a starting neurologic onset earlier than age 10 [7]. Psychiatric manifestations encompass depression, neuroses, personality changes, psychosis and poor performance at school. It was reported that 30—40% of patients have psychiatric symptoms at diagnosis and 20% had seen a psychiatrist prior to their WD diagnosis [12]. WD should be ruled out in any teenager with unexplained cognitive, psychiatric, or movement disorder [13]. Neuropsychiatric signs are the predominant presentation in adults but also may be present in up to 50% of teenagers. WD should also be included in the differential diagnosis work-up of unclear neuropsychiatric syndromes in patients after age 60 years [9].

Ocular findings include the Kayser–Fleischer (KF) ring, due to copper accumulation in Desçemet's membrane, and sunflower cataracts, due to copper accumulation in the lens. They are diagnosed by slit lamp examination. In known cases of hepatic WD, the rings are present in just over half of patients. KF rings are usually absent in children with liver disease. KF rings are rarely observed in other conditions such as in patients with chronic cholestatic diseases, monoclonal gammopathies, multiple myeloma, arci senilis, and pulmonary carcinoma and are thus not specific for WD [1, 7]. Of note, KF rings are not so easy to diagnose without experience, some authors suggest that anterior segment Scheimpflug imaging (Pentacam, Oculus) could be more helpful to diagnose or confirm KF rings by ophthalmologists with little experience in patients with WD. In general it is said that when neurological symptoms are present, KF rings is present in almost all WD patients at disease diagnosis [7]. But there are reports of cases with neurological involvement without KF rings [8].

Other presentations and clinical findings are intermittent bouts of jaundice caused by haemolysis, gynaecomastia, amenorrhoea, repeated spontaneous abortion, cardiac complications including ECG abnormalities, ventricular fibrillation, cardiomyopathy, orthostatic hypotension, urolithiasis, renal tubular disease, hypoparathyroidism, pancreatitis and rhabdomyolysis [8].

3. Laboratory findings

Elucidation of some straightforward biochemical tests have been appeared to be both touchy and decently particular for WD. Two such records incorporate a proportion of alanine aminotransferase (ALT) by aspartate aminotransferase (AST), and a proportion of alkaline phosphatase (ALP) by total bilirubin (TB). An ALT/AST proportion of more than 2.2 contains a sensitivity of 94% and a specificity of 86%; the ALP/TB proportion of less than 4 encompasses a sensitivity of 94% and a specificity of 96% [4].

In Wilson disease, the 24-hour urine copper excretion is usually >100 μg (1.6 μmol) and almost always exceeds 40 μg (0.6 μmol). When penicillamine 500 mg is administered by mouth at the beginning and 12 h later during a 24-hour urine collection, copper excretion >25 μmoles (1587 μg) per 24 h is taken as diagnostic. This test has been validated only in children, and its sensitivity is not as great as originally thought [8].

Ceruloplasmin is the major carrier for copper in the blood. Testing for serum ceruloplasmin is often done when searching for the cause of unexplained liver disease. There are physiologic variations in the serum level of ceruloplasmin. It is very low in early infancy to the age of 6 months, peak at higher than adult levels in early childhood, and then decrease to the normal adult range [1]. A serum ceruloplasmin level < 200 mg/L (<20 mg/dL) has been considered consistent with WD, and diagnostic if associated with KF rings. Except WD, conditions such as marked renal or enteric protein loss, severe end stage liver disease of any etiology, neurologic diseases copper deficiency, and Menkes disease can show low ceruloplasmin levels [1, 7, 13].

Total serum copper (which incorporates non–ceruloplasmin bound copper or "free copper" and copper joined in ceruloplasmin) is ordinarily diminished in extent to the diminished serum ceruloplasmin. However, in patients with WD with extreme liver damage, serum copper may be inside the ordinary extend or uniquely hoisted within the setting of ALF due to the discharge of copper from liver tissue stores and the increase in free copper in the blood [13]. A novel approach is the direct specification of labile copper (non-Cp-bound copper), called interchangeable copper (CuEXC). It permits to calculate the "relative replaceable copper" (REC) which alludes to the proportion of CuEXC to total copper. REC was assessed as a convenient diagnostic appliance for WD with a high sensitivity and specifity allows the calculation of relative interchangeable copper (REC) that compares to the proportion between CuEXC and total serum copper. It is represented that REC is a great diagnostic biomarker with a specifity and specificity near to 100% for the determination of WD when its value is >18.5%. It allows a separation of Wilsonian liver disease from other types of liver disorders such as autoimmune, infectious. Moreover, REC can make a great aid to family screening, because it is possible to make a distinction between WD patients and heterozygous carriers or healthy subjects. The CuEXC value at diagnosis indicates of extrahepatic involvement and its seriousness [7]. But further studies are needed to evaluate its diagnostic accuracy in children with liver disease [13].

The urine copper shows to the sum of non-ceruloplasmin bound copper within the circulation. Urinary copper concentration is measured per 24 h since there's noteworthy changeability within the copper substance of spot urine collections for them to be utilized. The customary level taken as demonstrative of WD is >100 μg/24 h (>1.6 μmol/24 h) in symptomatic patients [1]. In asymptomatic children or children with mild liver disease, urinary copper values are often normal [13]. However, high urinary copper values may be seen in other sorts of liver disorders (e.g., autoimmune hepatitis, unremitting active liver disease, or cholestasis and in specific during acute liver failure of any etiology). Heterozygotes may too have borderline levels [7].

The diagnosis is not fundamentally straightforward indeed even when the disease is effectively being considered. In a patient within the age-range 5–50 years who has liver disease or characteristic neurological symptoms, finding serum caeruloplasmin underneath 5 mg/dL is profoundly compatible with WD; association too a Kayser–Fleischer (KF) ring affirms the diagnosis. In nearly one-third of patients, serum caeruloplasmin can be within normal limits. As a sole, serum caeruloplasmin

is not an adequate diagnostic test for WD. KF rings are diagnostic, but they can also be seen in patients who have persistent cholestasis of other etiology. Lack of KF rings happens in around 50% of adult patients with liver disease and hence does not run the show out WD. KF rings may not be determined even when there's neurological involvement.

4. Histopathology and histochemistry

Liver biopsy is typically performed when clinical and laboratory findings are not diagnostic or for evaluation of unexplained liver disease or abnormal liver tests. Another aim is to determine the degree of hepatic inflammation and for hepatic copper quantitation [1]. The spectrum of hepatic pathological changes occurring in WD is very broad, ranging from elementary changes typical of a toxic pathology, to inflammatory changes typical of viral or autoimmune etiology [6]. The main features are microvesicular and macrovesicular steatosis, glycogenated hepatocyte nuclei, inflammation, and variable hepatocellular anisonucleosis [16, 17].

The manifestations of liver involvement have a varied spectrum depending on the stage of the disease. In the earlier steps, hepatocyte injury may at first manifest as simple steatosis (**Figure 1**) with frequent association of glycogenated nuclei. Steatosis, Mallory-Denk bodies (MBDs), lipogranulomas and glycogenated nuclei have been represented as characteristic morphologic findings in liver biopsies with WD. This picture frequently imitates alcoholic and non-alcoholic fatty liver disease [6]. The distinction from nonalcoholic steatohepatitis (NASH) depends upon the demonstration of accumulated copper in the hepatocytes by histochemical stains. Lipofuscin accumulates in periportal areas, and some of the granules are large, irregular in shape and vacuolated. The intermediate stage of the disease shows

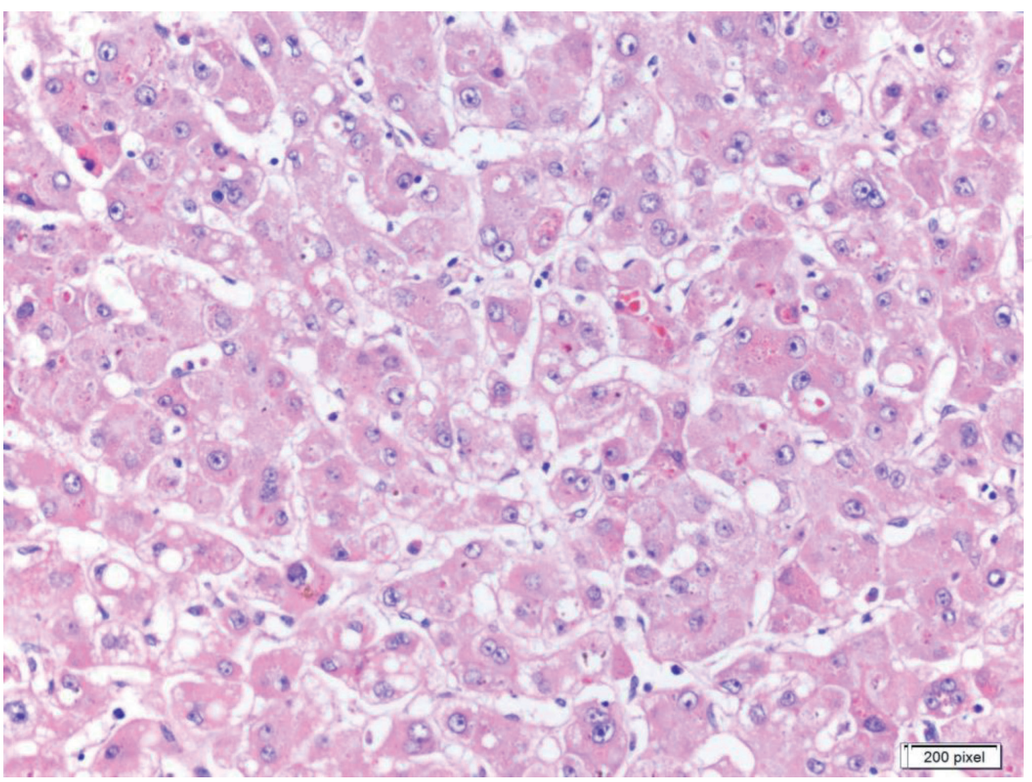

Figure 1.
Steatosis and anisonucleosis in a hepatectomy specimen (H&E).

histological features similar to those of chronic hepatitis of any etiology including viral or autoimmune hepatitis, with the arrival of the portal and periportal inflammation composed of lymphocytes and plasma cells, which results in the destruction of the limiting plate, and parenchymal necrosis followed by bridging fibrosis [4]. Because of low-titer autoantibodies (mainly antinuclear antibodies) are commonly found in patients with WD, differential diagnosis with autoimmune hepatitis (AIH) can be more complicated. Also, cases of WD and concomitant AIH have been reported [13]. More than 50% of cases may show the presence of intra-cytoplasmic eosinophilic MBDs (**Figure 2**). The literature suggests that steatosis, glycogenated nuclei and MBDs in periportal hepatocytes are features that may be used to distinguish the chronic hepatitis of WD from other more common etiologies [1]. In the cirrhotic stage which is usually macronodular but can be mixed or even micronodular, the histologic features are non-specific, and usually little or no inflammation is present. Some cases may show mild steatosis or features of steatohepatitis. Clusters of large hepatocytes with a granular eosinophilic cytoplasm (oncocytic or oxyphil cells), resulting from an increased number of mitochondria, are often seen but this is not specific for WD [8]. The distribution of copper is quite variable, with some of the cirrhotic nodules containing a lot and others containing little or none. Defining widespread copper deposits by histochemistry can help for the diagnosis. It should be noted that the distribution of copper is variable: some nodules with prominent staining, others with minimal or none (**Figure 3**). This could generate false negative impression in biopsy specimens, and it has been suggested that two liver cores may be needed for copper detection and diagnosis. Cases which present with ALF or fulminant hepatitis, the histology includes portal and parenchymal inflammatory infiltrate, associated with hepatocyte injury, swelling and necrosis. There may be massive or submassive necrosis. Copper can be demonstrated in hepatocytes and when there has been significant necrosis, in Kupffer cells and portal macrophages [1, 8]. In contrast, copper is rarely demonstrable in Kupffer cells or portal macrophages in the cirrhotic stage [8].

Excess copper storage in the hepatocytes is a relevant sign of WD, and determination of hepatic copper content in the liver biopsy, is important in the diagnosis of WD. This may be accomplished by utilizing special histochemical stains for copper

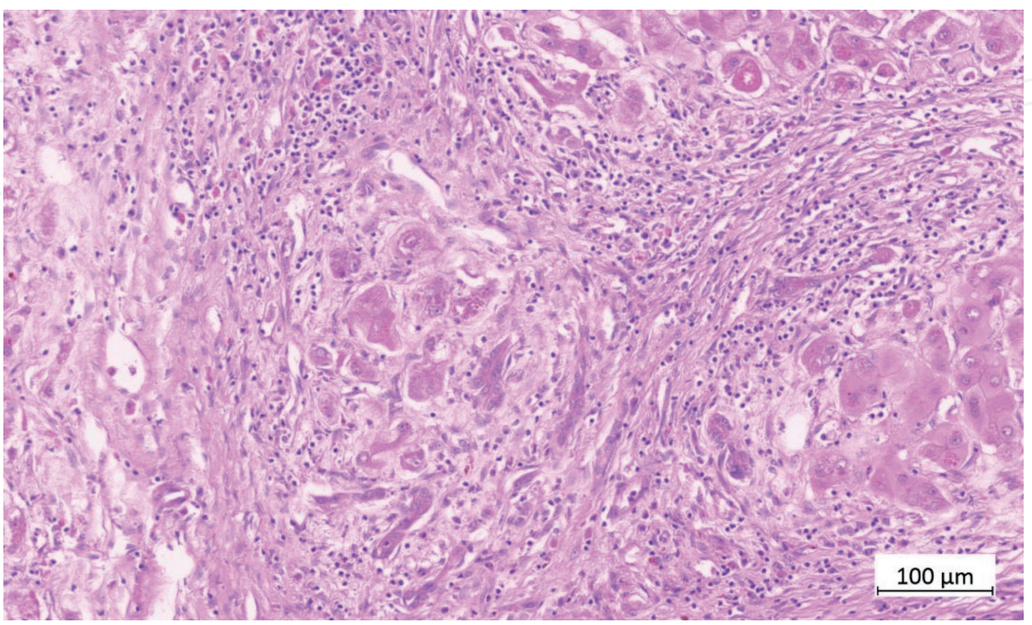

Figure 2.
Mallory-Denk bodies in a hepatectomy specimen (H&E).

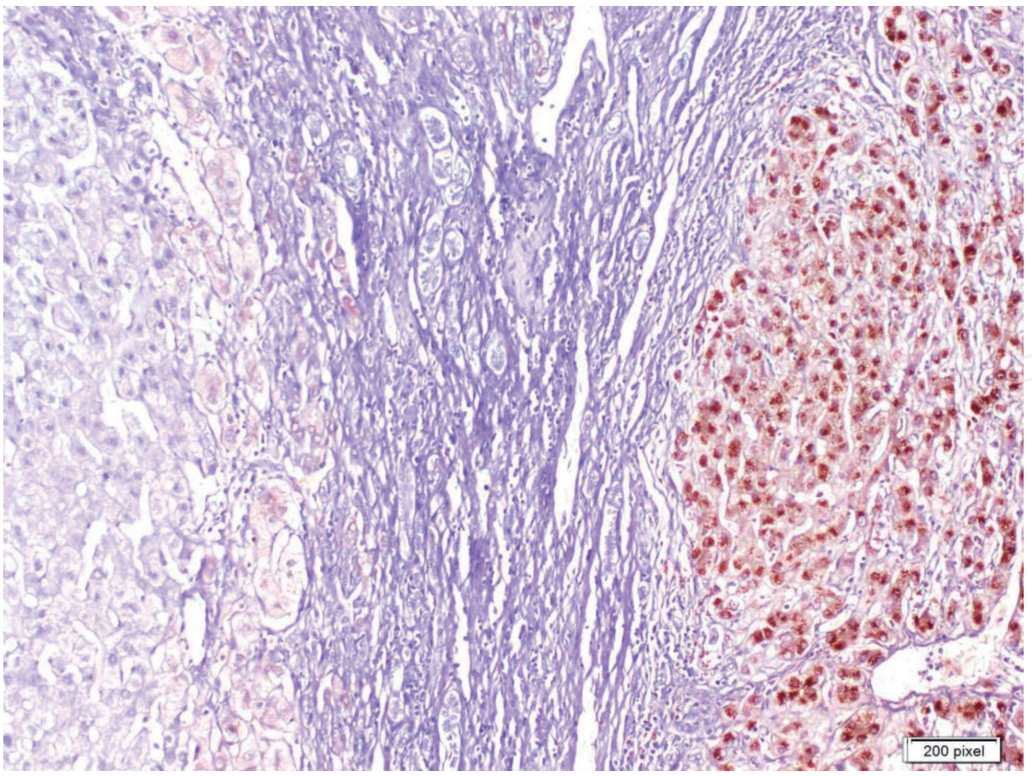

Figure 3.
Heterogenous copper accumulation in a hepatectomy specimen (Rhodanine).

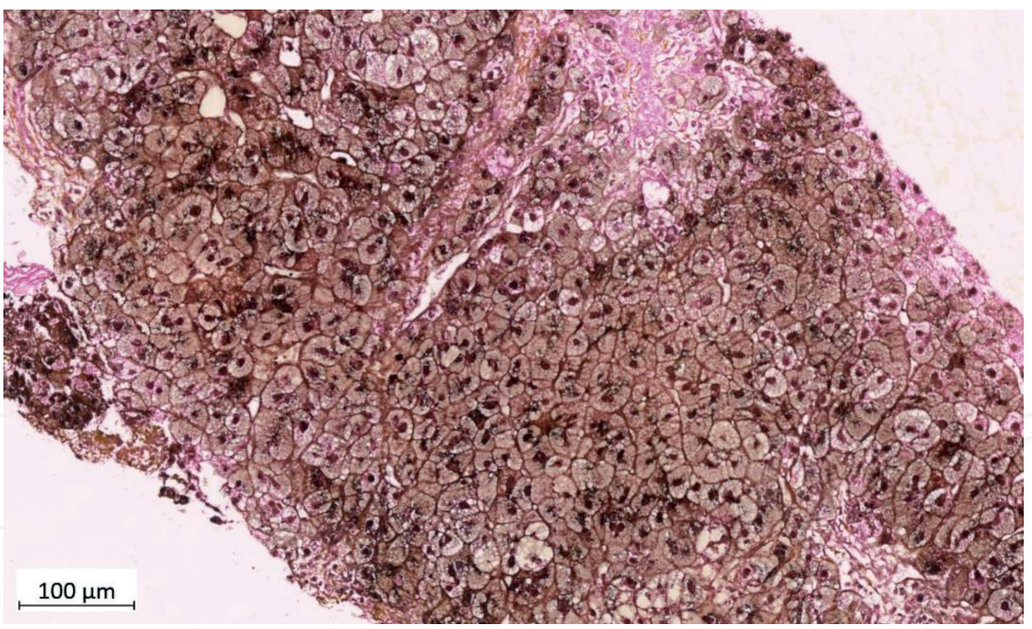

Figure 4.
Diffuse cytoplasmic staining pattern (Timm).

which are rhodanine, rubeanic acid and Timm's silver stains, and for copper related protein of which are orcein, aldehyde fuchsin and Victoria blue. None of these stains is fully sensitive nor specific. Orcein reveals the accumulation of metallothioneins, the proteins involved in excess copper sequestration. Positive staining appears as large irregular granules dark-brown in color. In the Timm's stained slides, if there is mild accumulation copper shows up small black or greenish-black granules in the intracytoplasmic perinuclear area or canalicular side of hepatocytes, and when there is heavy accumulation, the whole cytoplasm of the hepatocyte stuffed with coarse granules. With rhodanine stain copper accumulation appears as

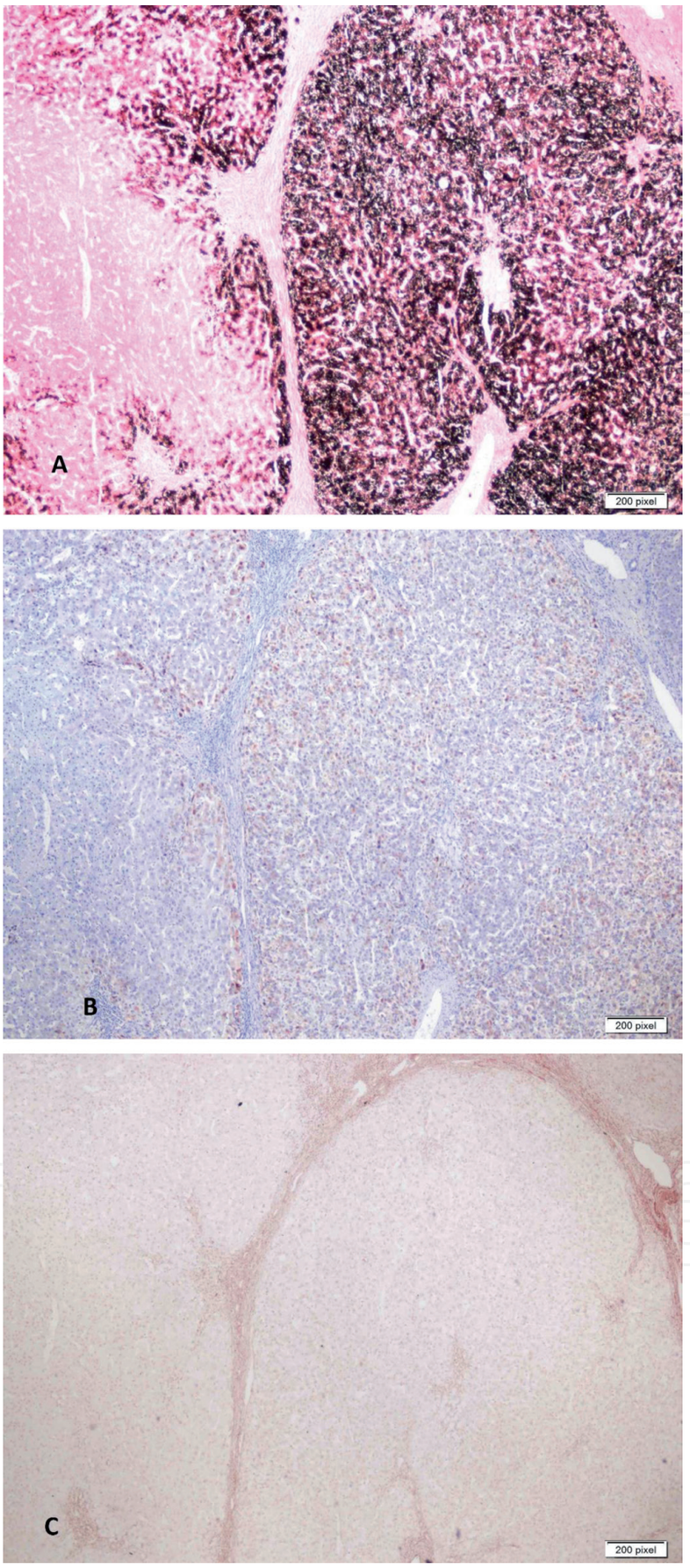

Figure 5.
Different sensitivities of copper stains in the same case (A. Timm, B. Rhodanine, C. Orcein).

small red granules [1, 6, 8]. Out of granular staining, diffuse cytoplasmic staining pattern (**Figure 4**) can be seen with copper stains, which is frequently reported in WD [18].

The most effective method is vary in different reports. In our study with transplant hepatectomies, we found that positivity rates of Timm, rhodanine and orcein are 85%, 82%, and 48% respectively (**Figure 5A-C**). We thought that pannodular (prominent diffuse staining of nodule), staining is a powerfull indicator of WD. In this context, we suggested that pannodular staining is a more convincing staining pattern for the histopathologic diagnosis of WD and against other diseases with copper accumulation [16]. In our routine practice we do Timm's stain for every liver biopsy and hepatectomy. Next to evaluating copper accumulation for diagnosis WD disease, it can help to define late stage fibrosis [18]. It should be keep in mind, copper accumulation can be seen in other diseases such as cholestatic liver diseases, alcoholic liver disease and idiopathic copper toxicosis [6]. In chronic cholestasis and non WD cirrhosis, copper staining is usually limited to periseptal areas with a patchy/focal distribution (**Figure 6**). It is suggested that that in the absence of advanced fibrosis (or WD), a positive rhodanine stain for copper argues strongly in favor of chronic biliary diseases and against other liver diseases [19]. Of note, marked hepatic copper overload mimicking WD has been described in children with MDR3 deficiency [8]. It is important to remember that negative staining for both copper and copper-associated protein does not exclude the diagnosis of WD.

In equivocal cases, measurement of liver copper content is recommended as the next step for diagnosis of WD. A 5-fold increase of hepatic copper concentration is considered as diagnostic for diagnosis of hepatic WD [5]. In a more strict definition, a copper content >250 μg/g dry weight (normal value <50 mg/g dry weight) in adult patients without cholestasis is accepted as diagnostic for WD. Probably depending on sampling error due to nonhomogeneous copper distribution in the liver, lower values are reported in up to 20% of patients with WD. The exactness of liver copper estimation is moved forward with an optimal measured biopsy sample (ideally >1 cm long, min. 0.5 cm) that ought to be put on a little piece of paper for drying,

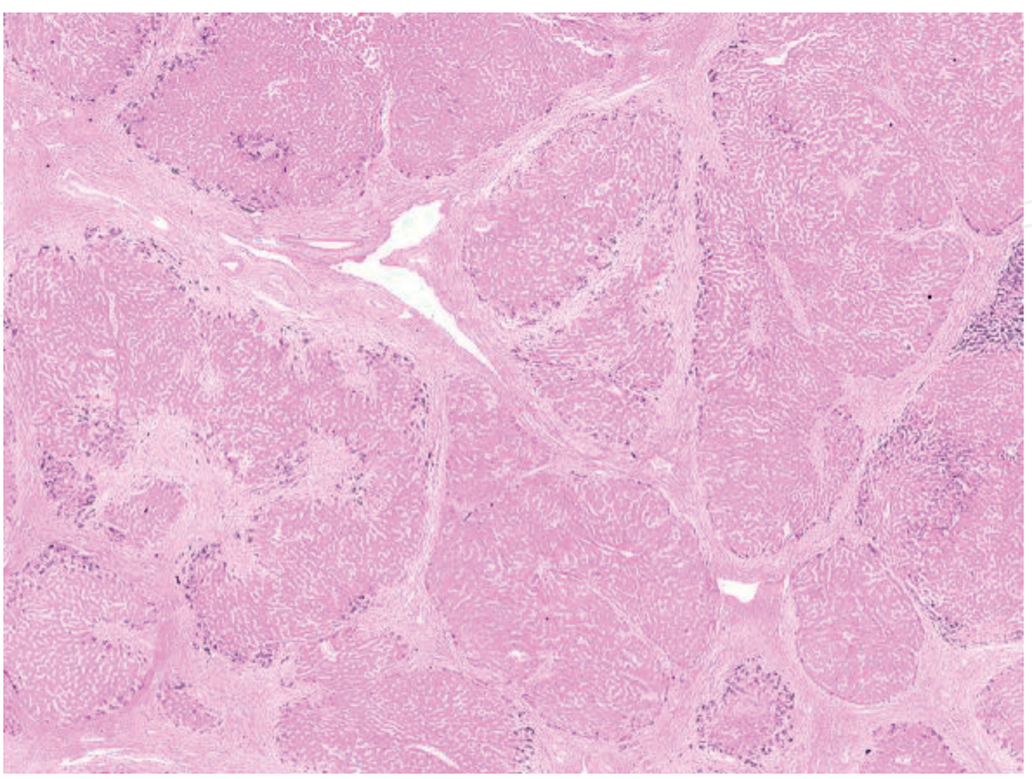

Figure 6.
Periseptal copper accumulation in a non WD cirrhosis (Timm).

and in a dry plastic copper-free holder for atomic absorption analysis on fresh tissue [13]. Hepatic copper levels in advanced stage chronic biliary diseases in adults and children often exceed 250 mg/100 g of dried liver, sometimes reaching levels higher than those observed in WD [19]. In spite of the fact that utilize of dried tissue has been proposed for tissue copper quantitation, the utilize of formalin-fixed, paraffin-embedded (FFPE) tissue is said fair as valuable. Utilizing FFPE tissue specimens evacuates the specialized troubles related to dried unfixed tissue, as well as gives the same tissue for histopathological and quantitative assessments. Since copper accumulation may well be non homogenious indeed even in most progressed cases of WD, the availability of light microscopy on the same tissue being evaluated for copper may well be a really valuable tool in mostly tending to this potential examining inclination tissue quantitation of copper is subject to [17]. Although liver copper content is a useful parameter, but a value below 250 μg/g does not exclude WD. Diagnosis requires the combination of a variety of clinical and biochemical tests [5].

5. Conclusion

WD is a curable disease, but early diagnosis is essential to stop the progression to cirrhosis or worsening of the neurological and psychiatric conditions. As a treatable disease, WD should be detected by any health professionals at any care level. If WD is not recognized and adequately treated, the progression of liver disease to cirrhosis and liver failure can be rapid or irreversible brain damage can occur. Unfortunately, even though of all advances, the diagnosis of WD shows up frequently compelling, due to the variability of its clinical manifestation and to the complexity of the microscopic findings within the liver biopsy. Liver histopathology, in reality, does not show a unique morphology, but it may appear in different patterns. From a pathologist's perspective, when evaluating the liver biopsies, WD should be included in the differential diagnosis especially in pediatric age and also cryptogenic adult cases.

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