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Wilsons Disease. Diagnostic Difficulties and Role of Liver Biopsy

Dr. Meenakshi Balasubramanian	Additional Professor, Department of Pathology, T.N.Medical College, Mumbai Central, Mumbai 400008
Dr. Shilpa Lad	Assistant Professor, Department of Pathology, Nair Hospital, Mumbai Central, Mumbai
Dr. Radha Ghildiyal	Professor, Department of Pediatrics, Nair Hospital, Mumbai Central, Mumbai
Dr. Vikas Kavishwar	Additional Professor, Department of Pathology, Nair Hospital, Mumbai Central, Mumbai

ABSTRACT

Wilson disease is a rare, inherited autosomal recessive disease of copper metabolism. It may be more common where consanguinity is prevalent. It occurs due to dysfunction of a copper transporting p-type ATPase that has a crucial role in copper excretion in bile. The gene that encodes this ATPase, is located on chromosome 13q14.3. This leads to copper accumulation in liver, brain, cornea and kidney. The most frequent clinical presentation of WD is liver involvement.

Wilson disease in children poses diagnostic challenges, as many other conditions can present similarly. Even at biopsy, definitive diagnosis may be difficult. We attempted to study the role of liver biopsy in Wilson disease, assess close differential diagnosis, and take note of the limitations of liver biopsy in diagnosing liver biopsy. Nine out of ninety five liver biopsies done over a 5 year period, and diagnosed as Wilsons disease were selected, based on the clinical presentation, investigative findings and biopsy features. Liver biopsy helped in identifying cirrhosis, assessing compliance and response to treatment. Close differential diagnoses were viral hepatitis and auto immune liver disease. While ballooning of hepatocytes and nuclear glycogenation were consistently found, not all cases showed classical features of Wilson disease, making biochemical investigations as important as the clinical opinion and biopsy findings, all three forming a diagnostic triad.

KEYWORDS : Wilson disease, liver biopsy, urinary copper

INTRODUCTION

Wilson disease is a rare, inherited autosomal recessive disease of copper metabolism. It may be more common where consanguinity is prevalent1. It occurs due to dysfunction of a copper transporting p-type ATPase that has a crucial role in copper excretion in bile. The gene that encodes this ATPase, is located on chromosome 13q14. 32This leads to copper accumulation in liver, brain, cornea and kidney. The most frequent clinical presentation of WD is liver involvement2

Wilsons disease (WD), also known as hepatolenticular degeneration was first described by Kinnear Wilson in 1912.3

The incidence of Wilsons disease in India is on the rise.4 Diagnosis of Wilson disease poses many challenges, as there are many other conditions that behave as close mimics4. Early diagnosis is very important as it defines prognosis. Definitive diagnosis requires the help of ancillary investigations4.

We aimed to study the role of liver biopsy in WD, assess the close differential diagnoses that may occur with similar presentation, to identify consistently present histological features and to note the limitations of liver biopsy towards diagnosis of WD.

MATERIALS AND METHOD

9/95 paediatric liver biopsies done over a 5 year period in a tertiary care centre were selected for the study, based on clinical features of patient, biopsy features, serological and biochemical features, serum ceruloplasmin levels and 24 hour urinary copper levels. Penicillamine challenge test and liver dry copper weight levels were available in some cases.

The clinical features considered were age of the child (>4 years), presence of hepatomegaly, hepatitis, liver cell failure and presence of Keyser Fleischer ring seen on slit lamp examination.

Liver biopsy sections stained by H&E, reticulin & orcein stains were reviewed. Biopsy features considered were micro or macro vesicular fatty change, glycogenated nuclei, interface hepatitis, cholestasis, Mallory's hyaline, cirrhosis and submassive necrosis.

Investigations that were considered were LFTs, serum ceruloplasmin levels(N≥20mg/dl), 24 hours urinary copper levels(N≤40mcg) and liver dry copper weight(N<50mcg/g).

This was a retrospective study and all details were obtained from the records. Institutional ethics approval was taken prior to commencement of the study.

RESULTS

Our 9 patients ranged in age between 6 and 12 years. 3 presented with features of cirrhosis, 4 with features of acute hepatitis with interface inflammation, one patient with neurological symptoms and one was a child, a known case of WD diagnosed earlier, on treatment, biopsy done to evaluate response to treatment. None of our cases presented with haematological or renal manifestations.

The 3 cases that presented with cirrhosis were a 12 y/F, who presented with hepatomegaly and neuropsychiatric symptoms, a 6y/F and an 8y/M, both of whom presented with features of decompensated liver disease.(Figure 1,2,3). .

All 3 cases had macro-vesicular fatty change, glycogenated nuclei, intra hepatocytic and canalicular cholestasis and Mallory's hyaline. Interface hepatitis was present in the younger children. All the three patients had elevated 24 hour urinary Cu, reduced serum Ceruloplasmin levels, therefore leading to diagnosis of WD. The older child also showed clinical and LFT improvement after a penicillamine challenge test, while both the younger children succumbed to liver cell failure. Of the four cases that presented with markedly elevated serum transaminases, icterus and fever, suggestive of acute hepatitis, liver biopsy showed hepatocytic ballooning and cholestasis, peri portal widening with moderate to dense inflammation, predominantly mon-

onuclear, with interface hepatitis. (Figure 4,5) At morphology diagnosis given was acute hepatitis with activity, possibilities of viral induced hepatitis/auto-immune liver disease/WD. Viral markers, IgM HAV, HBV, HCV, HIV and serologic markers for autoimmune liver disease, SMA/ANA(type 1) and LKM1(type 2) were negative in 3 cases, but in one case, in a 7 y/F, IgM HAV and ASMA were positive. This patient also had abundant necrosis and inflammation. In all four cases, the 24 hour urinary Cu was found raised, more than 250mcg/g of dry liver, along with normal to reduced serum ceruloplasmin, confirming diagnosis of WD. Three of the four patients improved on D penicillamine, while one patient (the child who had abundant necrosis), died following a major bout of hematemesis.

One child, 11y/M presented with scholastic backwardness and involuntary movements since 6 months. There was a mild alteration in the LFTs. Slit lamp examination revealed presence of KF rings at the limbus. A liver biopsy done showed hepatocytic ballooning and nuclear glycogenation. Serum ceruloplasmin was normal but liver dry copper weight was remarkably increased over the normal level. Patient was diagnosed as Wilson disease. Patient improved on treatment with D penicillamine.

The ninth case was of an asymptomatic 6y/F, with history of 2 older siblings, one male and one female, having been diagnosed as liver cell failure and who had expired while on treatment with D penicillamine. The H&E stained section revealed no abnormality, the orcein stain for Cu associated protein was negative. Serum ceruloplasmin was reduced, with increased 24 hour urinary excretion of copper. The patient was put on D penicillamine treatment and was on follow up.

DISCUSSION

In literature Wilson disease has a range of clinical manifestations, from an asymptomatic state to fulminant hepatic failure, chronic liver disease with or without cirrhosis, neurologic, and psychiatric manifestations. 5 Patients with cirrhosis, neurological manifestations, and Kayser-Fleischer rings are easily diagnosed as having WD because they resemble the original clinical description. The patient presenting with liver disease, who is at least 5 years old but under 40 years old, with a decreased serum ceruloplasmin and detectable Kayser-Fleischer rings, has been generally regarded as having classic WD.3 However, about half of the patients presenting with liver disease do not possess two of these three criteria and pose a challenge in trying to establish the diagnosis6. Moreover, as with other liver diseases, patients may come to medical attention when their clinical disease is comparatively mild7.

Wilson disease needs to be considered in the differential diagnosis of any unexplained chronic liver disease in any child around adolescence, and even younger child, but usually not under the age of 4. The condition may also manifest as acute hepatitis8. Hepatic dysfunction is the presenting feature in more than half of patients. The 3 major patterns of hepatic involvement are as follows: (1) chronic active hepatitis, (2) cirrhosis, and (3) fulminant hepatic failure. The most common initial presentation is cirrhosis9. Three of our cases presented with cirrhosis.

At least 50% of patients with Wilson disease have neurologic or psychiatric symptoms and may have cirrhosis9. Large series of patients with WD show that Kayser-Fleischer rings are present in only 44%-62% of patients with mainly hepatic disease at the time of diagnosis1. In children presenting with liver disease, Kayser-Fleischer rings are usually absent10. Only one patient in this study had a KF ring, and he presented with scholastic backwardness and involuntary movements. Liver biopsy revealed presence of hepatitis.

The earliest changes on light microscopy include nuclear glycogenation of peri portal hepatocytes and moderate fatty infiltration8. Both these features were seen almost in all our cases. Although elevated hepatic copper levels exist in patients with Wilson disease, histochemical staining of liver biopsy for copper or Cu associated protein is of little diagnostic value8. Early in the disease, copper distribution is primarily cytoplasmic and is not readily apparent with orcein stain or even rhodamine or rubeanic acid staining11, 12. There is further progression to cirrhosis, with or without chronic active hepatitis, bile ductular proliferation, and variable septal mononuclear cell infiltration. Hepatocytes at the periphery of the nodules frequently contain Mallory hyaline8.

One a 7 y/F child presented with features of hepatitis and IgM HAV and ASMA were positive. This patient also had abundant necrosis and inflammation. The initial opinion on liver biopsy was auto-immune liver disease or infective hepatitis. The 24 hour urinary Cu was found raised, more than 250mcg/g of dry liver, along with normal to reduced serum ceruloplasmin, confirming diagnosis of WD. It is possible that this patient had a super-infection with Hepatitis A. In literature there are reports of Hepatitis A super infection in cases of Wilson disease that have not been diagnosed, nor have severe symptoms, but have worsened and become decompensated13. Low ASMA titres have been found in patients with viral infections such as Infectious mononucleosis, EBV infection, chronic hepatitis C infection, rheumatic heart disease, primary biliary cirrhosis or neoplastic process14. Therefore, despite the presence of viral or autoimmune markers, clinical evaluation and biochemical tests for WD can help arrive at correct diagnosis.

SUMMARY AND CONCLUSIONS

Liver biopsy helped in differentiating between patients with cirrhosis and those without. This knowledge helped in estimating the prognosis. Other than that biopsy helped in assessing response/compliance to treatment.

Close differential diagnosis in young children with severe inflammation and/or cirrhosis would be viral hepatitis and autoimmune liver disease.

We also conclude that ballooning of hepatocytes and glycogenation of nuclei, both early changes in WD, were consistently present in almost all the cases we studied and should be looked for in all pediatric liver biopsies.

While classic morphology may be seen in some cases, not all features may be seen, thus making clinical examination and opinion, liver biopsy and biochemical tests as the three limbs of an effective tripod. With any ambiguity in results, a liver dry copper weight estimation of >250mcg/g will clinch the diagnosis, and, if this is not raised, genetic testing for the presence of mutation in the ATP7B gene would be confirmatory for the diagnosis of Wilsons disease.

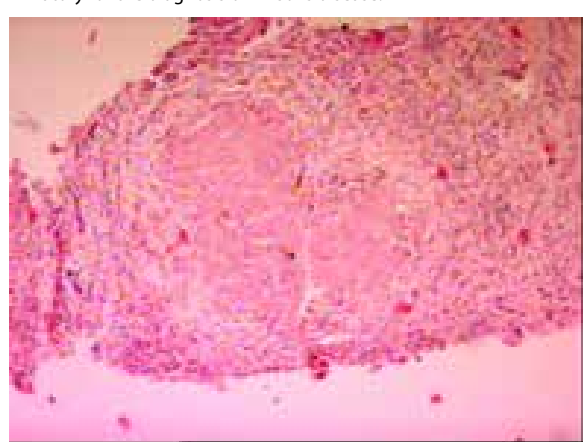

Figure 1

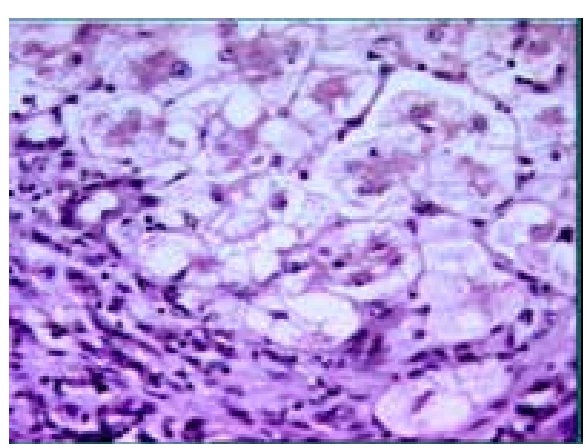

Figure 2

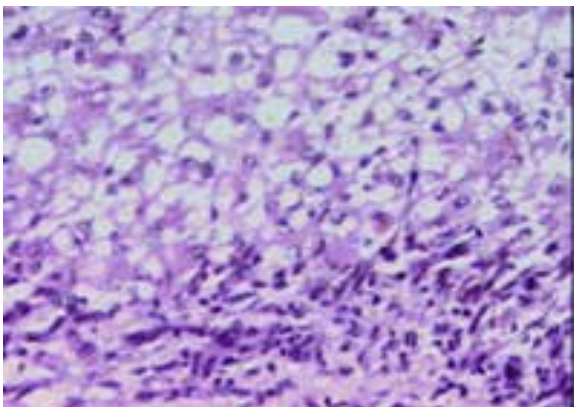

Figure 3

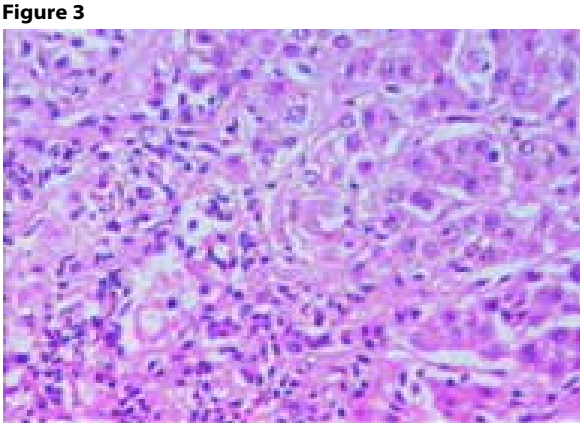

Figure 4

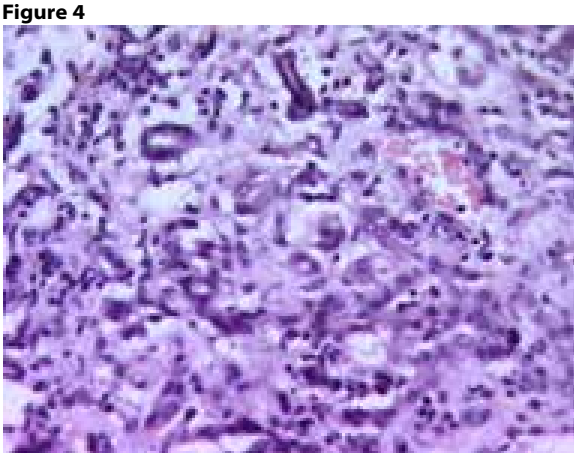

Figure 5

LEGENDS

1. Scanner view of liver biopsy showing cirrhotic nodule with dense inflammation along fibrous septa(H&Ex40X)
2. Ballooning of hepatocytes, intra hepatic cholestasis, interface inflammation, bile duct proliferation(H&Ex400X)
3. Macro-vesicular fatty change and interface hepatitis(H&Ex100X)
4. Marked peri portal widening, moderate to dense mononuclear inflammation(H&Ex100X)
5. Peri portal biliary duct proliferation, dense lymphocytic infiltration and bile duct destruction(H&Ex100X)

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