Wilson's Disease

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Abstract. Wilson's disease (WD), an inborn error of copper (Cu) metabolism, is now one of the leading liver diseases in children in India. The clinical presentation can be extremely varied viz., all forms of acute and chronic liver disease, minimal to severe neurological disease, psychiatric problems, bony deformities, hemolytic anemia and endocrine manifestations. A high index of suspicion is necessary along with a judicious battery of investigations for diagnosis. Hepatic copper estimation is the most reliable test but is not easily available in India. Liver biopsy may not be possible because of bleeding problems and histological features are often not diagnostic of WD. In the absence of hepatic Cu, a low ceruloplasmin, high 24 hour urinary copper and presence of KF rings aid in making the diagnosis. The mainstay of initial therapy is Cu-chelators like D-Penicillamine, and Trientine for reduction in body copper to sub-toxic levels. Subsequent maintenance therapy is necessarily lifelong with D-Penicillamine, Trientine or Zinc. Children on therapy must be monitored regularly for response, side-effects, compliance and rehabilitation. Response to therapy may be unpredictable, but acute and early presentations like fulminant hepatic failures have a poor outcome. All siblings must be screened for WD as early diagnosis and treatment result in a good outcome. The identification of the WD gene on chromosome 13 has led to the possible use of molecular genetics (haplotype and mutational analyses) in the diagnosis of WD. [Indian J Pediatr 2002; 69 (9) : 785-791]

Key words : Wilson's disease; Copper; Liver disease

Wilson's Disease (WD) is an inborn error of metabolism characterised by toxic accumulation of copper (Cu) in liver, brain, cornea and other tissues. It occurs worldwide with an estimated prevalence of 1 in 50,000 but is perhaps commoner in India. The gene frequency is 1 in 90-150. With the declining incidence of Indian Childhood Cirrhosis (ICC), WD has become one of the important causes of chronic liver disease in India. A number of aspects makes the disease especially interesting and important for pediatricians viz., (i) The clinical presentation can be extremely varied giving rise to diagnostic difficulties. (ii) WD is a treatable cause of liver damage and cirrhosis provided it is diagnosed early; and (iii) Recent advances in molecular genetics have greatly facilitated early diagnosis in asymptomatic siblings.

HISTORICAL MILESTONES4-12

"A familial nervous disease associated with cirrhosis of the liver" S.A.K. Wilson (1911)

Corneal Copper Deposits (KF rings) Kayser (1902)

Etiologic Role for Copper Postulated Fleischer (1903)

Cumings (1948)

Scheinberg & Gitlin (1952)

Walshe (1956)

Frydman et al (1985)


CLINICAL FEATURES

During the last 20 years, over a 1,000 children with chronic liver disease have been assessed at our Centre at KEM Hospital, Pune. 124 of these have been diagnosed to have Wilson's Disease. Selected clinical information of these patients with regard to type of presentation, age and outcome is summarised in Table 1. It is interesting to note that younger the age at presentation more acute were the manifestations and higher the mortality, except in asymptomatic sibs.

The age of presentation varies from 4 to 60 years, though majority present before the age of 30 years. The manifestations are more likely to be hepatic in early childhood and neurological in adolescents. Other forms of presentations are also seen. Family history is often suggestive of WD even in index cases.

Hepatic Presentation

Most patients with WD, whatever their clinical presentation (including asymptomatic siblings)
TABLE 1. Clinical Presentation and Outcome of 124 Children with WD Seen at the Pediatric Liver Unit, KEM Hospital, Pune (1980-2000)

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No.</th>
<th>Age at diagnosis (years)*</th>
<th>Duration of illness (months)*</th>
<th>Survival n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>28</td>
<td>11.5 (2.5)</td>
<td>16.5 (17.38)</td>
<td>23 (82)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>43</td>
<td>8.2 (3.4)</td>
<td>8.1 (15.45)</td>
<td>26 (61)</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>13</td>
<td>7.1 (2.6)</td>
<td>1.10 (0.40)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>11</td>
<td>5.96 (2.1)</td>
<td>0.7 (0.24)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Others (Rickets, hemolysis)</td>
<td>10</td>
<td>10.8 (3.4)</td>
<td>14.0 (19.57)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Asymptomatic sibs</td>
<td>19</td>
<td>7.3 (4.1)</td>
<td></td>
<td>15 (79)</td>
</tr>
</tbody>
</table>

*Values expressed as mean (SD)

...demonstrate some degree of liver disease. Early symptoms are often vague and non-specific such as lethargy, anorexia, abdominal pain and epistaxis. The spectrum of hepatic manifestations include all forms of chronic and acute liver disease. Chronic Liver Disease: The commonest hepatic presentation of WD is in the form of chronic hepatitis - prolonged jaundice, hepatosplenomegaly, oedema, ascites and other signs of liver cell failure. Most show evidence of portal hypertension with hypersplenism and esophageal or gastric varices. Occasionally patients present with an inactive (compensated), 'silent' liver cirrhosis. With passage of time most children also demonstrate some neurological abnormalities characteristic of WD. If specific treatment is not given, liver disease decompensates leading to rapid clinical deterioration.

Acute Hepatitis: Often, WD presents like a typical attack of 'acute viral hepatitis,' which fails to resolve or in which jaundice recurs. Presence of oedema and ascites should suggest WD especially if history suggests a sibling dying of a similar disease. Liver disease in WD may be precipitated by superadded infections like Hepatitis A, E, etc.

Fulminant Hepatic Failure: In younger patients of WD, the liver tends to fail acutely and massively leading to jaundice, hypoalbuminemia, ascites, coagulation defects, hyperammonemia and hepatic encephalopathy. Hemolysis, which is a feature of fulminant hepatic failure in WD may also occur in isolation. Prognosis is generally poor despite vigorous therapy.

Neuro-psychiatric Manifestations

Patients with WD who present with neurological disease are typically in late teens or twenties though, children as young as five or six years are also occasionally affected. The early symptoms are usually subtle, such as clumsiness, mild tremor, speech problems or difficulties in hand writing. Many are brought for deteriorating school performance. Progress of disease may be slow or rapid. Ultimately, majority show severe movement disorders, such as choreo-athetosis, dystonia, rigidity, and posture abnormalities. Dysphagia, increased drooling and difficulties in controlling movements incapacitate the patients. Intelligence is usually not affected. Occasionally WD presents to the psychiatrist with behavioral abnormalities, depression, labile moods bordering mania, or frank psychosis. Importantly, most of these patients, even those with pure neurological/psychiatric symptoms give past or concurrent history or have biochemical evidence of liver disease.

Other Presentations

A presentation of WD common in India is 'osseomuscular' with bony deformities (knock-knees) suggestive of resistant rickets. Osteomalacia, spontaneous fractures, and arthopathy are also seen. WD can occasionally present like a typical renal tubular dysfunction of the Fanconi variety. Renal calculi are also known. A well known but tricky presentation of WD is acute or recurrent Coombs negative hemolytic anemia with or without associated liver dysfunction. Gall stones too are common in WD. Other reported manifestations are cardiac involvement, skin pigmentation, ovarian dysfunction, hypoparathyroidism.

Asymptomatic Siblings

Siblings of newly diagnosed patients are often brought for screening for WD. Though asymptomatic, affected siblings frequently reveal subclinical liver disease with the presence of hepatosplenomegaly and hepatic pathology on biopsy. Some also show established KF rings at very young ages. Usually, these patients do not have neurologic or psychiatric symptoms clearly attributable to WD.

DIAGNOSIS

The key to diagnosis is a high index of suspicion, which can increase only on greater awareness of the disorder in the medical fraternity. No single test is diagnostic by itself and often a group of tests need to be done in order to diagnose WD. These tests are discussed below:

Serum Ceruloplasmin (Cp): The gene for Cp is on chromosome 3. More than 90% of the Cu circulating in serum is bound to Cp. The level of Cp in normal individuals is 20-40mg/dL, but may vary according to the laboratory. Levels in WD are usually < 20mg/dL (more commonly < 10mg/dL). Some authorities feel a Cp level > 30 mg/dL virtually rules out WD.

False Positive: Severe malnutrition, protein losing states, acute liver failure of any etiology, hypoceruloplasminia or