ORIGINAL ARTICLE

Wilson's Disease - A Review of Cases at University Hospital, Kuala Lumpur

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Summary

The clinical course of 18 patients with Wilson's disease is reported. There were 13 males and five females of whom one is Malay. The prevalence of Wilson's disease in Malaysia is probably the same as elsewhere. Being a genetic syndrome, the genetic carrier rate for Wilson's disease is probably lower amongst the Malays. At diagnosis, the clinical signs were predominantly hepatic in 10 patients, neurological in five patients with three asymptomatic cases. All patients were commenced on penicillamine but poor compliance was observed in many patients.

Two patients defaulted follow-up and seven patients died. Out of the nine surviving patients, only four are well with no clinical symptoms.

Key words: Wilson's disease, Prevalence, Clinical features, Treatment.

Introduction

Wilson's disease, a copper loading condition, has a broad spectrum of clinical features which include hepatic, neurologic, psychiatric, hematologic and renal dysfunction. Untreated Wilson's disease leads to gradual copper accumulation in tissues, especially of the liver and brain, due to impaired biliary excretion of copper[1]. The key to successful outcome is early detection of the disease and institution of treatment.

The present study reports our cumulative experience gained over a period of 10 years with patients affected by Wilson's disease.

Patients and Methods

During a ten year period, from 1981 to 1991, 18 patients were proven to have Wilson's disease at University Hospital, Kuala Lumpur. The diagnosis of Wilson's disease was based on characteristic clinical features, biochemical findings of low or absent serum caeruloplasmin (< 20 mg/ 100 ml), decreased serum copper (< 80 ug/dl), elevation of urinary copper excretion (>100ug/24 hours) and the detection of Kayser-Fleischer rings.

The diagnosis is further confirmed by histological evidence of increased copper accumulation in the liver biopsy specimen. Absolute histological confirmation by the quantitative measurement of copper per gram of liver tissue was not available in the University Hospital.

Clinical Observations

The 18 patients consisted of 13 males and five females. Age at the time of diagnosis ranged from 11 to 23 years with a mean of 15.5 years. The ethnic background of the patients were 10 Chinese, seven Indians and only one Malay patient.

In three patients, there were no clinical symptoms when the diagnosis was made. These three patients were diagnosed as part of the family screening of patients with Wilson's disease. Two of the patients had "silent" cirrhosis on liver biopsy. The third patient was diagnosed on the basis of abnormal serum caeruloplasmin, urine copper and a liver biopsy showing copper accumulation.

Ten patients presented with hepatic dysfunction: jaundice was the initial manifestation in seven patients, all of whom had evidence of portal hypertension. Hepatomegaly was seen in all patients. Fulminant hepatitis occured in one patient who had a concomittant history of excessive alcohol intake. The other patient had mild ankle oedema due to hypoalbuminaemia.

Five patients had predominant neurological disease at presentation. The average age of these five patients was 16.4 (11-20) years which did not differ very much from the average age of the eight patients with hepatic disease of 16 (11-23) years. The most common clinical signs were tremor, chorea, dysarthria and ataxic gait. Hypomania preceded the overt neurological involvement in one patient.

One patient presented to another hospital with Coomb's negative hemolytic anaemia as the first manifestation of Wilson's disease. The diagnosis of Wilson's disease was only established two years later when persistent elevation of serum transaminases were noted: this patient had pre-existing chronic active hepatitis. Kayser-Fleischer rings occured in every patient with clinical symptoms and one patient who was asymptomatic.

Amongst our patients with Wilson's disease, seven families have more than one family member affected by Wilson's disease, including the Malay patient (whose two sisters were diagnosed and treated at another hospital). There were consanguinous marriages in five out of the seven families.

After diagnosis, all patients were treated with penicillamine. Compliance with therapy was poor in nine patients. In only one patient was the drug discontinued because of the development of Stevens Johnson's syndrome. No alternative therapy was given to this patient as he died shortly after penicillamine was stopped from hepatic failure and bleeding esophageal varices.

Two patients were lost to follow-up: both patients had severe Parkinsonian features at the time of diagnosis and were last seen at this hospital nine and 10 years ago. Seven patients had succumbed to this disease. The mean duration of illness from time of diagnosis to death was four years (range three months - six years). Except for one patient, all patients who died presented with liver disease. Out of nine who are alive, five have troublesome neurological involvement. Only four patients have remained well including two who have been asymptomatic throughout.

Discussion

Wilson's disease, an autosomal recessive inherited disorder of copper metabolism, is common in Caucasians with an estimated prevalence of 1 in 30,000[2]. The prevalence for Wilson's disease in Malaysia based on comparison with amyotrophic lateral sclerosis[3] can be estimated to be 1 in 50,000.

The primary genetic abnormality has been localized to chromosome 13[4] whereas the associated defect responsible for the low caeruloplasmin is located on chromosome 3[5].

It is of interest to note that the patients were predominantly of Chinese and Indian descent. The only Malay patient had two sisters affected by Wilson's disease probably as a result of consanguinous marriage of the parents. The presence of the gene for Wilson's disease is probably low amongst the Malay race as Malays accounted for only 5.5 per cent of the cases in this series although they form 40 per cent of the admissions to this hospital.

There are different modes of presentation of Wilson's disease. The age at which clinical symptoms develop is also very variable. In general, hepatic dysfunction clinically manifest in the pediatric age group and neurological disease usually present in older children, adolescents or young adults. This trend, however, was not seen in our small series of patients because of the late presentation and diagnosis of the hepatic manifestations.

Fulminant hepatic failure is an uncommon but well established presentation of Wilson's disease and is associated with a uniformly fatal outcome[6-8]. One patient had a fulminant course of hepatitis, partly due to alcohol abuse. Typically, Wilsonian fulminant hepatic failure occurs in association with acute intravascular hemolysis, which was not observed in this patient[9, 10].

Kayser-Fleischer rings, a brown or greenish-brown ring, is due to deposition of copper in the Descemet's membrane in the cornea. Kayser-Fleischer rings may be present in other conditions like primary biliary cirrhosis and other long-standing cholestatic and noncholestatic hepatic diseases[11, 12]. On the other hand, Kayser-Fleischer rings may not be detected in younger patients with only hepatic involvement by Wilson's disease[13].

It is sometimes difficult to arrive at the diagnosis of Wilson's disease due to the protean clinical manifestations of the disease. Often, there is a delay in establishing the diagnosis when Wilson's disease is not considered in the differential diagnosis of young patients with atypical neurological, hepatic, or hematologic disorders like hemolytic anaemia, thrombocytopaenia or pancytopaenia. Ideally, patients should be diagnosed at the asymptomatic stage. This is made possible by screening the family of patients with Wilson's disease which should extend beyond the patient's siblings.

The laboratory tests routinely used for the diagnosis of Wilson's disease are serum caeruloplasmin and urinary copper excretion. Low serum caeruloplasmin (less than 20 mg/dl) is found in 95 per cent of patients with Wilson's disease[14]. Decreased serum caeruloplasmin can occur in patients with low serum protein such as in the nephrotic syndrome, protein losing enteropathy and severe hepatitis[15].

Total serum copper is usually low in patients with Wilson's disease. A more reliable indicator of disease is elevated serum free or noncaeruloplasmin-bound copper. Serum free copper, determined by calculating the difference between total serum copper and caeruloplasmin-bound copper has been shown to be useful in assessing effectiveness of therapy[16].

The diagnosis was relatively easy to make in the 16 patients with Kayser-Fleischer rings. The two patients without Kayser-Fleischer rings had family histories of Wilson's disease and exhibited copper studies characteristic of Wilson's disease. All but four patients, were diagnosed late in the course of the disease.

As dietary restriction of copper contributes little to the control of the disease, drug therapy remains the principal mode of treatment and is required lifelong. Penicillamine, despite the numerous side effects observed, is the therapeutic gold standard.

Alternative agents include trientine, zinc and tetrathiomolybdate. Trientine, short for triethylene tetramine is another copper chelating drug. Elemental zinc, in the form of either zinc sulphate or acetate, acts in the gastrointestinal tract to inhibit copper absorption. Tetrathiomolybdate is an agent that appears to block the absorption of copper. All three agents have been shown to be effective in causing copper depletion[17-19].

Patients with endstage liver disease or fulminant hepatic failure are candidates for hepatic transplantation. Successful liver transplantation has resulted in normalization of copper metabolism but it is not known whether this effect would be sustained.

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