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Original Article

The Clinical Manifestations, Treatment Efficacy and Adverse Drug Reactions in 62 Iranian Children with Wilson Disease

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Abstract

Introduction:
The Wilson disease is an autosomal recessive disease in which the liver, central nervous system, eyes, blood and other parts of the body involved. Timely diagnosis and appropriate treatment of the disease requires awareness of the clinical presentations of this disease in children.

Materials and Methods:
This case series study included 62 patients with Wilson disease who admitted to children's Medical Center, Tehran-Iran in 2003-2012 years.

Results:
56% of patients were male. The average age of diagnosis was 9.73±2.35 years old (5-17 years) and this was higher in patients with early neurologic symptoms (P=0.85). 64.5% of the patients had the hepatic symptoms at the time of diagnosis and the most common type of hepatic involvement was cirrhosis (39.3%) and hepatitis (17.5%) respectively. 17.7% of the patients also had early neurological symptoms. A positive family history for the Wilson disease were found in 27.4% of patients. 74.2% of patients had Kayser–Fleischer rings (KF ring) and the frequency of these symptom was higher in patients with early neurological involvement. 83.9% of patients were treated successfully with D-penicillamine and in 30% of patients, adverse drug reactions were seen.

Conclusion:
Children with unknown liver disease should be evaluated for Wilson disease and the first-degree relatives of patients should be screened. D-penicillamine have important side effects, but due to the low cost and the availability is an appropriate drug to treat the Wilson disease.

Keywords: D-Penicillamine, Hepatic Involvement, KF ring, Neurologic involvement, Wilson disease.

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Introduction

Wilson's disease is a progressive hepatolenticular disease, and actually it is a genetic condition in which copper is accumulated in some tissues (1). This disease may be presented as fulminant hepatic failure (coagulopathy, coombs negative haemolitic anemia and encephalopathy) in about 5% of cases. The symptoms of chronic liver disease may be in the form of Spider angioma, portal hypertention, ascites and splenomegaly (2).

Young patients with unexplained chronic liver disease, with or without cirrhosis, should be screened for Wilson's disease (1). Chronic active hepatitis may cause liver cirrhosis, but unlike the other causes in which cirrhosis increases the risk of hepatocellular carcinoma, this risk is very low about the Wilson's disease (3). 50 % of patients have psychological and neurologic symptoms of Wilson's disease (4).

Ophthalmic findings include Kaiser-flesher (KF) ring and cataract which both are curable after pharmaceutical treatments and liver transplantation (5).

Hypoparathyroidism, tubular acidosis, cardiomyopathy, infertility and abortion are rare symptoms of Wilson's disease (6). Wilson's disease may be detected based on the occurrence of any of the foregoing symptoms or when close relatives are involved .In General, there is no a specific test for Wilson's disease.

Most of the times, a slight increase in the level of the liver enzyme, and bilirubin is seen. If the damage of hepatic cells be severe, low level of albumin and long PT would be present.

Serum ceruloplasmin concentrations of less than 200 mg/L are considered roughly equivalent with Wilson's disease and its association with KF ring confirms diagnosis (1).

The 24-hour Urinary secretion of copper more than 100 µg is suggestive for Wilson's disease (7). Because interpretation of 24-hour urine copper secretion test is difficult and the results obtained from a variety of liver diseases are overlapped, a D-penicillamine challenge test is used in children .Urinary copper secretion more than 1,600 µg /24-hour is considered as a diagnostic test in the Wilson's disease in children (7.)

The gold standard diagnostic test for Wilson's disease is liver biopsy, in which the amount of copper is over 250µg/g dried liver tissue (7).

The drugs used in the treatment of Wilson's disease include copper-binding agents, drugs enhancing the urinary excretion of copper and zinc salts.

Materials and Methods

This study was a case series study, In which all patients with Wilson's disease who admitted during the years 2003 to 2012 in the children's Medical Center, Tehran-Iran, were included. The Census sampling was performed, so it was not necessary to determine the sample size. Given that the information was extracted from the patients's records and the name and other information would remain confidential, informed consent of the parents was not necessary. Statistical analysis of the data was performed using SPSS 16 software.

Results

In this study 62 child who admitted during the years 2003 to 2012 in children's Medical Center with the Wilson's disease diagnosis were included. 35 cases (56.5%) patients were male and 27 patients (43.5%) were female. The average age of the patients at the time of diagnosis was (9.73±2.35) years(5-17 years). This average in patients with hepatic and neurologic involvement was (9.30±2.58) and (11.14±1.34) years respectively, that no significant differences was observed (P=0.085).

The main manifestation of the disease at the time of diagnosis

At the time of diagnosis, 36 patients (58%) had only hepatic involvement and 7 patients (11.3%) had only neurologic symptoms. 8 patients (12.9%) were presented with combined neurologic and hepatic symptoms: 4 patients presented with neurologic symptoms first, and then the hepatic symptoms occurred, in 3 patients hepatic involvement was occurred before neurologic symptoms, and one patient had simultaneous hepatic-neurologic involvement.

Wilson's disease were diagnosed in a patient following an accidental detection of abnormalities in the patient's liver enzymes and in 5 patients (8%) by screening because of positive family history of disease in one of the siblings. Five patients (8%) also at the time of Wilson's disease diagnosis had other symptoms KF ring were seen during ophthalmologic examination of 46 patients (74.2%).The frequency of the occurrence of this sign in patients with primary hepatic and neurologic involvement was 76.9% &81.8%, respectively.

17 patients (27.4%) had a positive family history for Wilson's disease.

The frequency of various clinical patterns of hepatic involvement in 40 patients with primary hepatic involvement was as follows:

-Hepatic cirrhosis: 22 patients (35.48%);
-Fulminant hepatic failure: 8 patients (12.9%);
-Acute hepatitis: 6 patients (9.67%);
-Chronic liver disease: 3 patients (4.83%);
-Isolated abnormal liver tests: 1 patient (1.61%).

The frequency of a variety of neurological symptoms and signs in 11 patients with primary neurologic involvement was as follows:

-Disartria and movement disorders: 4 patients (6.45%);
-Isolated movement disorders: 2 patients (3.2%);
-Seizures: 2 patients (3.2%);
-Movement disorders & migraine headaches& disartria: 1 patient (1.6%);
-Seizure and migraine headaches: 1 patient (1.6%);
-Pseudobulbar palsy: 1 patient (1.6%).

Totally, the most common symptoms in this group of patients was movement disorders (11.49%).

Finally, in one patient simultaneous primary neurologic and hepatic involvement was seen in which clinical pattern involved fulminant hepatitis, pseudobulbar palsy and tremor.

In 4 patients (6.5%), liver transplantation was performed that 2 patients died after liver transplant. During the study, 14 patients died of disease; 11 patients belonged to the (primary hepatic involvement) group; 1 patient to (primary neurologic involvement) group, and the last two patients had combined primary hepatic & neurologic involvement. The cause of death was hepatic encephalopathy in 57% of patients.

Type of drugs used to treat the patients and treatment side effects:

52 patients (83.9%) treated with D-Penicillamine, 4 patients (6.5%) initially treated with D-Penicillamine that because of the lack of recovery later changed them to trientine. In one patient, treatment with trientine began, a patient undergone liver transplantation as first treatment and for one patient treatment included ursodeoxycholic acid & zinc salts. Data about how to treat 3 patients (4.8%) was not available.

In 36 cases (73.1%) treated with D-penicillamine , no complication occurred, in 6 patients (11.5%) haematuria was seen,7 patients (13.4%) experienced bone marrow suppression and one patients(1.9%) presented with nephrotic syndrome as treatment complication. Two patients (3.8%) had skin lesions like pemphigoid.

Discussion

Wilson disease's is a progressive hepatolenticular disease, and actually it is a genetic condition in which copper is accumulated in some tissues (1).

In our study, 40 patients (64.51%) had primary hepatic involvement at the time of diagnosis, but in three of them, neurologic symptoms also presented later. The most common form of hepatic involvement was cirrhosis (36%) and fulminant hepatitis (12.9%) respectively.

In 40 years follow-upping of 36 patients with Wilson disease in Brazil, the frequency of the primary organ involvement was as follows: hepatic (38.9%), neurologic (25%) and combined hepatic-neurologic (30.6%) (12).

In a study by Tatsumity and colleagues in 2007 on 30 Japanese patient with Wilson disease, the first manifestation of the disease was hepatic (61%) and neurologic (13%), respectively (13). In another study by Asadi et al. in 2005 on 111 Iranian patients, the initial manifestation of the disease was hepatic in 83.8% and neurologic in 24.3% of patients (14). In a study by Walter Oder on 45 patients with Wilson disease in 2005, the primary involved organs were liver(60%) and nervous system(26%) ,respectively(15).

Generally, the most common primary symptoms/signs in children with Wilson disease is hepatic, our study also confirms this.

In our study, the average age of the patients at the time of diagnosis was 9.3 & 11.9 years in (primary hepatic involvement group) and (primary neurologic involvement group), respectively, in which this difference was not significant (P=0.85).

In one study by Merteu et al. in 2007, the average age of the patients at the time of diagnosis was 15.7 years in cases with primary hepatic presentations and 20.2 years in patients with primary neurologic manifestations, but there was no significant difference between two groups (16). 74.2 percent of our patients at the time of diagnosis were KF positive. This frequency was higher in patients with primary neurologic presentation (81%) than those with primary hepatic involvement (77%).

In a study conducted in Brazil on 36 patients, 55 percent of patients were KF positive that this frequency was higher in patients who have neurological involvement (77.8%) (12).

In another study in 2007 on 163 German patients, KF ring was observed in 66% of them(16).Totally, our study and other similar studies suggest that more than half of the patients were KF positive at the time of diagnosis and this sign is more common in patients with neurological involvement.

A positive family history of Wilson disease was reported in 27% of our patients. In a similar study by Asadi and his colleagues on the 111 Iranian patients, 36% of patients have a family history of the disease, which is partially similar to our patients group (14).

In our study, 83.8% of patients were treated with D-Penicillamine, but adverse drug reactions were seen in 30% of cases. In a study conducted in Brazil in , 94% of patients were treated with D-Penicillamine and in 78% of the cases, primary clinical response to therapy were seen, so this results had not significant difference when compared with our study. In a study conducted by Merteu and his colleagues, the adverse drug reactions were seen in 74% of patients treated with D-Penicillamine, which was higher than our study (16).

This difference may be due to the difference in genetic aspects, in population size, or the quality of the drugs.

Conclusion

Considering that the most common initial manifestation of the Wilson disease was hepatic in our study and the majority of other studies, this condition should be excluded in each patient with unexplained

hepatic symptoms. Family members of patients with Wilson disease should be screened for this disease. Also, in patients with unexplained Neurologic symptoms, particularly movement disorders, Wilson disease should not be neglected. Although the side effects of D-Penicillamine is more than Trientine, but also with respect to the low cost and availability of the former drug, D-Penicillamine is a good choice for the treatment of Wilson's disease.

Of course, regular complete blood count (CBC) and urine analysis (U/A) tests may be helpful in early detection of serious side effects of this drug.

Ethical considerations and limitations

This study was approved by the Ethics Committee of Tehran University of Medical Sciences. In our non-interventional study, the principle of confidentiality was considered. Some of the records in the patients files were incomplete and we had no access to some patients, but these had no significant effect on study results.

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