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Clinical and Para-Clinical Features of Wilson Disease in Children in Shiraz, Southern Iran

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Abstract

Background: Wilson disease (WD) is an autosomal recessive progressive degeneration of hepatolenticular tissue that causes the increase of copper deposition in the liver and other organs, with resultant hepatic, neurologic and psychological manifestations. WD is fatal if left untreated. The aim of the current study was to evaluate the clinical and Para-clinical findings in children with WD in Shiraz, Southern Iran.**Patients and Methods:** The Medical records of all children less than 18 years of age with definite diagnosis of WD, who were admitted in Nemazee Teaching Hospital from 2001 to 2009, or were under follow up at the Pediatric Hepatology Clinic affiliated to Shiraz University of Medical Sciences, were reviewed. **Results:** Overall, 70 patients with WD (41 males, 29 females) were studied. The mean age at the onset of diagnosis was 10.3±3.2 years and the most common first presentation in our patients was hepatic (90%). The most common biochemical abnormalities were increased urinary copper content, increased liver enzymes (92.9%), and increased prothrombin time (71.4%). Wilson index was ≥11 in 44.3% of the patients.**Conclusion:** WD is a rare and fascinating disorder that often poses a diagnostic and therapeutic challenge for the physician. Maintaining a high index of suspicion is critical in diagnosing this readily treatable disease and early treatment can decrease its mortality rate.**[GMJ.2014;3(3):160-66]**

Keywords: Wilson's disease; Children; Iran; Clinical Features; Para-clinical Features

Introduction

Wilson disease (WD) or hepatolenticular degeneration is due to a genetic abnormality inherited in an autosomal recessive manner that leads to impairment of cellular copper transport [1]. The disease was first described as a syndrome by Kinnier Wilson in 1912 [2]. Its prevalence has been estimated ranging from 18 to 30 cases per million [3] and in some other studies one in 200 for heterozygote type of the disease and one in 30,000 homozygote Wilson patients [4]. The gene ATP7B is responsible for WD and is located on chromosome 13. This gene is highly expressed in the liver, placenta, and kidney and encodes a transmembrane copper-dependent P-type ATPase with synthetic and excretory tasks. It has a special major role in the transporting excess copper into the bile. The clinical manifestations of WD are predominantly hepatic, neurologic, and psychiatric complications while many patients having a combination of symptoms. Patients may

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present with a wide variety of symptoms and there is no "typical" clinical manifestation for WD [5-7]. Also, there is no unique diagnostic test for WD. The challenges in diagnosis are non-specific symptoms and the fact that WD affects many different organs. The diagnosis in individuals is usually based on suggestive symptoms, Kayser-Fleischer (KF) rings, a low ceruloplasmin concentration and high urinary copper excretion. KF ring is predominantly seen in neurological disease and its absence does not necessarily exclude the possibility of the disease. Diagnosis of WD is more difficult in patients with liver presenting feature of the disease. Molecular analysis of ATP7B gene mutations can be diagnostic but such methods are expensive and are not available in all hospitals or medical diagnostic laboratories [5, 8]. Recently Ferenci has proposed a scoring system considering clinical, biochemical, and histological features and total accumulated score indicate the possibility of the patient having WD [9].

Treatment of WD is based on chelating the copper, promotion of copper excretion from the body, or reduction of copper absorption using Zinc [10, 11]. Liver transplantation is successful in patients with liver failure that are unresponsive to medical treatment [12, 13]. However, there are serious risks associated with immunosuppressive therapy and used surgery procedure [14].The aim of this study was to evaluate the clinical and para-clinical features of WD in children younger than 18 years old in Shiraz, Southern Iran, which could be helpful for general and specialist physicians in the diagnosis of this challenging disease.

Patients and Methods

In a retrospective study, 70 children with WD aged less than 18 years old, who were admitted in Nemazee Teaching Hospital during 2001-2009 or were under follow up at Pediatric Hepatology Clinic affiliated to the Shiraz University of Medical Sciences in Shiraz, Southern Iran, were studied. The diagnosis of WD was done based on clinical signs; presence of the KF ring, family history in the first-degree relatives as well as laboratory findings such as abnormal liver function tests, low serum ceruloplasmin levels below 20 mg/dL, and 24-hour urinary copper excretion higher than 75 µg/day. Patients with liver diseases other than WD and patients with suspected diagnosis were excluded from the study.

All the demographic data such as age at diagnosis of the disease, sex, family history, clinical presentations of the disease were recorded. The laboratory and para-clinical examinations had been done in Nemazee Hospital and Motahhari Clinics with standard protocols and laboratory kits; liver enzymes (BIOTEST®, Malaysia), bilirubin (Abnova®, Australia), albumin (Abcam®), International Normalized Ratio (INR), serum ceruloplasmin (Biovision®, China) and, 24 hours urine copper (Quest Diagnostics®, India). Wilson Index was calculated as King's Score for the patients [15].The patients underwent treatment with a daily dose of 20 mg/Kg of D-penicillamine, trientine, or zinc sulfate and were recommended not to use foods containing high levels of copper. The study proposal has been approved by the Research Ethics Committee of Shiraz University of Medical Sciences.The data were analyzed and reported as mean and standard deviation. Statistical analysis of the collected data was performed by SPSS (Version 14.0) software. Data are expressed as percentages and mean± standard deviation (SD).

Results

Among 70 patient with WD, 41 (58.6%) were males and 29 (41.4%) were females with a mean age of 10.3±3.2 years (range; 3-17 year) at the onset of diagnosis.Forty six patients (65.7%) had no positive family history of WD in their first-degree relatives. Sixteen patients (22.9%) had a positive history of one involved individual in their family, 6 cases (8.6%) with two involved patients in their families and, 2 cases (2.9%) had a history of four patients in their family.In the majority of the cases (n=63; 90%) the first presentation of the disease was hepatic manifestations. The most common presenting manifestations were jaundice (n=28; 40%) and abdominal protrusion (n=11; 15.7%). Other clinical presentations are shown in table-1.Overall 20 (28.6%)

patients presented with cirrhosis, 22 (34.2%) with chronic liver disease, 11 (15.7%) with acute hepatitis, and 10 (14.3%) patients with fulminate liver failure. Neurologic manifestations were seen in 12 (17.1%) patients. The most common neurologic manifestation was abnormal gait (n=6; 8.6%). Other neurologic manifestations are shown in table-1. Psychological disorders were observed in 9 subjects (12.9%) that included sleep disorders in 4 (5.7%), mood disorders in 3 (4.3%), aggressive behaviors in 2 (2.9%), and cognitive disorders in 1 (1.4 %) patient.

Ophthalmologic examination of the patients with slit lamp showed KF ring in 43 (61.4%) individuals and sunflower cataract only in 1 (1.4%) patient. All patients with neurological manifestations had KF ring in their ophthalmologic examination.Hemolytic anemia was observed in 3 patients (4.3%) with WD and no patient had musculoskeletal involvements. In this study, 5 subjects (7.1%) were asymptomatic and only had abnormal liver enzymes or positive family history for WD and the diagnosis of WD was confirmed by laboratory tests.Increased liver enzymes were seen in 65 (92.9%) patients and prolonged prothrombin time and INR in 50 (71.4%) cases. Other laboratory data are shown in Table 2. The data regarding the serum ceruloplasmin levels was available for 40 individuals and 37 of them (92.5%) had levels lower than the normal range (20 mg/dL) and in 3/40 patients (7.5%) it was in normal range. The data on the 24 hour urinary copper excretion levels was available in 45 patients. The range of 24 hour urinary copper excretion was 42-6765 µg with a median of 937 µg. Only in one patient it was reported lower than 75 µg/day.

The data about D-penicillamine challenge test was available in 11 patients and in most of them the 24 hours urinary copper excretion had been increased noticeably.Urine analysis of the patients was normal in 26/65 (40%) individuals and there was no data for 5 (7.1%) patients. Hematuria and proteinuria was reported for 34 (52.3%) and 23 (35.4%) pa-

Table 1. The frequency of the first clinical presentations and neurological manifestations in children with Wilson's disease.

Clinical Presentations	**No of patients (%)**
Jaundice	28 (40)
Abdominal protrusion	11 (15.7)
Jaundice and Abdominal protrusion	9 (12.9)
Vomiting	5 (7.1)
Movements disorders	4 (5.7)
Weakness and Fatigue	3 (4.3)
Neurologic Manifestations	**No of patients (%)**
Abnormal gait	6 (8.6)
Dysarthria	5 (7.1)
Deterioration in school performance	4 (5.7)
Tremor	3 (4.3)
Dysphagia and drooling	2 (2.9)
Convulsion	1 (1.4)
Rigidity	1 (1.4)

Table 2. Laboratory parameters in patients with Wilson's disease.

Laboratory data	**Range**
Blood Urea Nitrogen (mg/dL)	1-88
Creatinine (mg/dL)	0.1 -15
Total Protein (g/dL)	4.7 – 10.3
Albumin (g/dL)	1.6 – 5.3
Globulin (g/dL)	1.8 – 12.3
ALT (IU/L)	5 – 845
AST (IU/L)	21 – 1100
Alkaline phosphatase (IU/L)	34 – 3770
Total bilirubin (mg/dL)	0.2 – 47
Prothrombin time (second)	12 – 55
INR	0.89 – 10
Calcium (mg/dL)	7 – 11
Phosphor (mg/dL)	2 – 10.2
Reticulocyte (%)	0.4 – 8.1
White Blood Cell (/mm^3)	1400 – 19200
Hemoglobin (mg/dL)	7 – 14.9
Platelets (/mm^3)	28000 - 800000

tients, respectively. Fourteen patients (21.5%) had pyuria.

Abdominal ultrasonography data were available for 53 individuals and among them, 34 patients (64.1%) had coarse echogenicity of the liver parenchyma that was in favor of chronic liver disease. Ten patients out of 53 (18.9%) had normal abdominal ultrasonography results and in 9 patients (16.9%) the liver size had been reduced. Hepatomegaly and decreased liver echogenicity, was observed each in 1 patient (1.9%), gall stone in 4 patients (7.5%), and kidney stone in 1 patient (1.9%). Echocardiography evaluation had been done in 29 patients and among them 23 individuals (79.3%) showed normal echocardiography signs. Three patients showed mild pericardial effusion and patent foramen oval was observed in 2 patients and one had minimal pulmonary insufficiency.

Sixty two patients were treated with a daily dose of 20 mg/Kg of D-pencillamine and in 10 patients it was changed to trientine or they only received trientine. Two patients used only zinc sulfate. In 54 and 51 patients zinc and vitamin E were used as complementary treatment, respectively. Wilson index was ≥11 in 31 patients (44.3%), which were candidates for liver transplantation. Six patients underwent liver transplantation that one of them developed liver rejection. WD led to death in 5 (7.1%) patients; in 1 patient it was 4 years after the diagnosis and in 4 patients it was few months after the diagnosis.

Discussion

In this study, the patients with WD included 58.6% boys and 41.4% girls that resemble the data of the study done by Asadi pooya *et al*. and Manolaki *et al*. They reported 59% and 56% male and 41% and 44% female, respectively [16, 17]. The mean age at diagnosis in this study was 10.3±3.2 years and the minimum age was 3 years. In Manolaki *et al*. study, the mean age was 9.3±3.6 years and minimum age was 4 months [17]. Family history for WD was positive in about one third of the patients that is comparable with the study done by Asadi pooya *et al*., in 2005 [16]. More than 90% of the patients had hepatic involvements that presented with jaundice and ascites. Other studies reported 40%-83.3% hepatic involvement in these patients [16,18,19]. This higher hepatic presentation in our study is due to the fact that we evaluated the patients from Pediatric Hepatology ward and clinic and moreover cases were less than 18 years old since WD is presented with hepatic manifestations in younger ages. In one recent study on 28 Brazilian children 12 patients were asymptomatic, 7 had signs and symptoms of hepatitis, 5 patients had abnormal liver enzyme elevation, 3 had hepatomegaly associated with neurologic manifestations, 1 of the cases had fulminant hepatitis with hemolytic anemia, and 6 patients presented with a KF ring [20].

Neurological involvements were observed in 17.1% of our patients. Studies have also reported the neurological involvements as tremor, dysarthria, and dystonia in 24.3% and 60% of cases [16, 21]. Unlike younger children, who are more likely to manifest with hepatic presentations as we seen in the present study, older patients in teen-ages and adolescence are more likely to present with neurologic signs and symptoms. The diagnosis of neurologic WD can be challenging because these patients present in a myriad of ways. Neurologic symptoms may be very mild or may be rapidly progressive leading to severe disability. KF rings are gray-green or brownish rings that are due to deposition of copper in Descemet's membrane in the cornea. KF rings are a characteristic feature of WD and are present in more than 90% of patients with neurologic symptoms and 50-60% of patients with hepatic manifestations. Overall, according to the literature, the KF ring is present in 70% of cases and in the remaining cases it may not be visible in the primary stages of evolution [22]. Ocular involvement of the disease was seen in about 62.8 % of the patients and among them 61.4 % had KF ring and only 1.4% of the patients had sunflower cataract. Sunflower cataract is another ocular manifestation of WD that present when copper deposits in the lens. All of the patients with neurological involvements had KF ring in this study. In one study done on 57 patients with WD, KF ring was observed in 38% of the patients and in

another study with a larger sample size, it was reported in 74.7% and 2.7% with cataract [16, 17].Psychiatric manifestations are more common in patients with neurologic disease than in patients with hepatic presentation. The most common psychiatric manifestations are irritability, depression, and personality changes. Other behavioral and psychiatric symptoms such as declining school performance, labile mood, impulsiveness, and inappropriate behavior are less common. Psychological involvements were seen in 12.9% of the patients in this study and in two other studies, it was reported as 23.4% and 2.4% [16, 17].

Hemolytic anemia was observed in 4.3% of the patients in the present study. In one study done in 2005, it had reported 30% hemolytic anemia [15]. The main first presentations of WD in a study on 11 Taiwanian children were abnormal liver function tests (54.5%) and hemolytic anemia (18.2%) [23]. Gall stone was seen in 7.5% of the patients. Other studies also reported considerable rates of gall stone in the patients with WD. So, it is concluded that cholelithiasis is not rare in patients with WD and young patients with WD should be monitored for cholelithiasis [24-26]. Nephrolithiasis is usually reported as case reports in patients with WD [27-29]. In our study, only one case of nephrolithiasis was observed through ultrasonography evaluation.

Serum transaminases were high in 92.9% of the patients that was the same as the study done in 2005 in this center that reported increased liver enzymes in all patients [16]. Coagulation disorders as prolonged prothrombin time and INR was seen in more than two third of the patients that was lower than that reported by Asadi pooya *et al*. [16].

Twenty four hours urine copper was more than 75 μg in 44/45 (97.8%) patients same as the study done in 2005 in this center [16]. Serum ceruloplasmin was low in 92.5% of the patients that was comparable with other studies [17, 18]. Most of the studies have shown normal blood ceruloplasmin levels in only 5% of patients [30].The most prevalent ultrasonography finding was coarse echogenicity of the liver parenchyma that was seen in 64.1% of the patients. In another study, heterogeneous echogenicity of the liver parenchyma was more prevalent [31]. The mortality was 7.1% in this study which was probably due to later diagnosis, severity of hepatic lesions and shortage of donor for early liver transplantation in Iran.

Conclusion

WD is relatively common in Iran, and necessary investigations for this disease must be conducted in all children who presented with hepatic, neurologic or psychiatric manifestations compatible with this disease.

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Conflict of Interest

None to declare

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