Turk J Gastroenterol 2005; 16 (2): 71-74

Wilson Disease in Southern Iran

Güney İran'da Wilson hastalığı

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Background/aims: *Wilson disease is an autosomal recessive disorder of the brain, liver and cornea. It is fatal if left untreated. This descriptive study attempted to identify the demographic, clinical, and biochemical features of Wilson disease in Fars Province, Southern Iran.* ***Methods:*** *All the patients with Wilson disease who were admitted to Nemazee Hospital, Shiraz, Iran, from 1990 till 2004 were included in this cross-sectional descriptive study. This is the only hospital in Southern Iran which has pediatric and adult Gastroenterology Wards. Statistical analyses were done by t-test.* ***Results:*** *In total, 111 patients were studied (65 males, 46 females). The mean age was 11±7 years; the youngest was three years old. The most common manifestations were hepatic (83.8%), neurological (24.3%) and psychological (23.4%) signs and symptoms. The most common biochemical abnormalities were increased urinary copper (91.4%), increased prothrombin time (84.5%), increased liver enzymes (77-89%), decreased serum ceruloplasmin (75.5%), hyperbilirubinemia (67%) and anemia (62.4%). Family history was positive in 36% of the patients.* ***Conclusions:*** *In this study, sex ratio (M/F) was greater than one, similar to other studies. Age range was similar to other Asian studies, but less than observed in European and American studies. Clinical manifestations of Wilson disease in our patients were similar to the studies with similar age ranges. Biochemical abnormalities were sometimes different in our patients in comparison to previous studies, possibly due to the delay in the diagnosis in our patients.*

Key words: Epidemiology, Iran, manifestations, Wilson disease

Amaç: *Wilson hastalığı beyin, karaciğer ve korneanın otozomal ressesiv hastalığıdır. Tedavisiz ölümcüldür. Bu deskriptif çalışma, Güney İran'da Fars eyaletindeki Wilson hastalarının demografik, klinik ve biokimyasal özelliklerini tespit etmeye yöneliktir.* ***Yöntem:*** *Bu "cross-sectional" deskriptif çalışmaya 1990-2004 yılları arasında Nemazee Hastanesine (Şiraz, Iran) yatan ve Wilson hastalığı tanısı alan tüm hastalar dahil edildi. Bu hastane Güney İran'da pediatri ve adült gastroenteroloji klinikleri barındıran tek hastanedir. İstatistiki analizle t-testiyle yapıldı.* ***Bulgular:*** *Toplam 111 hasta çalışmaya alındı (65 erkek ve 46 bayan). Ortalama yaşları 11±7 yaştı ve en genç hasta 3 yaşındaydı. En sık hastalık belirtileri şöyle sıralanıyordu: Hepatik (%83.8), nörolojik (%24.3) ve psikolojik bulgular ve semptomlar (%23.4). En sık görülen biokimyasal bozukluklar artmış idrar bakırı (%91.4), düşük serum seruloplazmin (%75.5), hiperbilirubinemi (%67) ve anemiydi (%62.4). Hastaların %36'sında pozitif aile öyküsü mevcuttu.* ***Sonuç:*** *Bu çalışmada kadın/erkek oranı başka çalışmalara uygun biçimde 1'den fazlaydı. Hasta yaşı dağılımı diğer Asya çalışmalarına uygundu, fakat Amerika ve Avrupa'dan bildirilenlere göre daha düşüktü. Wilson hastalığı klinik belirtileri benzer yaş grupları içeren çalışmalarınkine uygunluk gösteriyordu. Biokimyasal değişiklikler, başka çalışmalara göre bazen farklılık gösteriyordu; bu muhtemelen hastalarımızda geç tanı konması ile ilgili olabilir.*

Anahtar kelimeler: Epidemiyoloji, İran, manifestasyon, Wilson hastalığı

INTRODUCTION

Wilson disease (WD; hepatolenticular degeneration) is an autosomal recessive disorder characterized by degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea (1). It is observed with a prevalence of approximately 1:3000 among all ethnic groups (2, 3). It is fatal if untreated; however, specific effective treatment is available. Defective mobilization of copper from lysosomes in the liver cells for excretion into bile is the basis for the multi-organ damage in the patients with WD. Manifestations of WD are variable, with a tendency to having familial pattern. Symptoms at any age are frequently nonspecific. WD should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychoactive illnesses, Fanconi syndrome, or unexplained bone disease. The clini-

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Manuscript received: 24.01.2005 **Accepted:** 03.05.2005

cal suspicion is confirmed by the study of indices of copper metabolism (1, 2). Up to now, no single test can exclude or confirm WD with 100% certainty (4). Recently, molecular genetic analysis with detection of specific mutations in the responsible gene (ATP7b gene) is evolving (3, 5).

This cross-sectional descriptive study attempted to identify the demographic, clinical and biochemical features of WD in Fars Province, Southern Iran.

MATERIALS AND METHODS

We retrospectively studied all the patients with WD admitted to Nemazee Hospital, Shiraz, Iran, between 1990 and 2004. This referral hospital is the only hospital in Southern Iran which has pediatric and adult Gastroenterology Wards. The criteria to confirm the diagnosis were based on the patients' clinical features combined with abnormal results of copper metabolism tests. Demographic, clinical and biochemical information was collected by referring to the patients' files. The collected data were kept confidential through codes. Statistical analyses were done by t-test. A*p value* less than 0.05 was considered as significant.

RESULTS

In total, 111 patients were studied during a 15-year period. There were 65 males (59%) and 46 females (41%). The difference between the two genders was not statistically significant (p=0.087). The mean age at the onset of the disease in our patients was 11±7 years. The youngest age at onset was three years and the oldest 50. Only four patients (3.6%) were younger than five years of age at the time of diagnosis. Most patients (54 patients, 48.6%) were between five to ten years of age at the time of diagnosis.

No significant difference in age at onset of the disease was noted between males (11.5±5.7 years) and females (11±7.9 years) (p=0.859). Table 1 shows the proportion of various symptoms and signs, described or detected as the presenting complaints or findings in these patients. Table 2 demonstrates the biochemical features of the patients at the time of presentation.

Hepatic manifestations were detected in 83.3% of the patients at the time of diagnosis. The most common hepatic manifestations were ascites, edema, splenomegaly and jaundice, in decreasing order. Forty patients (36%) presented with fulminant hepatic failure. Totally, 67% of the patients had hyperbilirubinemia (total bilirubin >2 mg/dl) at the time of presentation, and this was direct hyperbilirubinemia in 97%. Serum glutamic oxaloacetic transaminase (SGOT) was more than 45 u/L in 89.3% and serum glutamic pyruvic transaminase (SGPT) was more than 45 u/L in 77.5% of the patients. Albumin level was under 3 g/dl in 48.6%

Tablo 1. Presenting signs and symptoms in 111 patients with Wilson disease*

Hepatic	**83.3%**
Ascites	61.3%
Edema	52.3%
Splenomegaly	48.6%
Jaundice	30.6%
Hepatomegaly	20.7%
Bleeding (GI, nasal)	6.5%
Neurological	**24.3%**
Dystonia	15.3%
Dysarthria	12.6%
Tremor	11.7%
Gait disturbance	9.0%
Involuntary movement	1.9%
Psychological	**23.4%**
Impaired school performance	7.2%
Psychosis	7.2%
Neurosis	2.7%
Others	9.9%
Ophthalmologic	**74.7%**
K-F ring	74.7%
Cataract	2.7%
Asymptomatic	**2.7%**

*Most cases studied presented with more than one symptom, thus addition of all the percentages exceeds 100%

Tablo 2. Biochemical indices in 111 patients with Wilson disease

Liver function test	
Albumin	3.1±1 g/dl
Globulin	4±1.1 g/dl
SGOT	333±601u/L
SGPT	189±825 u/L
Direct bilirubin	7±9.9 mg/dl
Total bilirubin	11.8±14.8 mg/dl
Alkaline phosphatase	504±529 u/L
Hematological indices	
PT	27±13 seconds
PTT	67±28 seconds
Hemoglobin	10.3±2.1 g/dl
MCV	88±16 mm^3
Copper metabolism indices	
Ceruloplasmin	13.6±14.5 mg/dl
24-h urinary copper	672±639 mg
Others	
Hypokalemia (K < 3.5 mmol/L)	19.8%
Hyperkalemia (K >5 mmol/L)	1.0%
Hyponatremia (Na < 135 mmol/L)	4.7%
Hypernatremia (Na > 145 mmol/L)	10.5%
Hypoglycemia (BS < 55 mg/dl)	6.6%
Hyperglycemia (BS > 150 mg/dl)	6.6%
BUN > 20	9.2%
PH < 7.35 (acidosis)	21.8%
PH > 7.45 (alkalosis)	18.2%

of the patients and hemoglobin level was less than 11 g/dl in 62.4%. Prothrombin time (PT) was prolonged (more than 15 seconds) in 84.5% of the patients and partial thromboplastin time (PTT) was prolonged (more than 45 seconds) in 71.1%. Serum ceruloplasmin was less than 20 mg/dl in 75.5% of the patients and 24-h urinary copper was more than 100 mg in 91.4%.

Kayser-Fleischer rings were searched in all of the patients and were present in 74.7% of cases. They were present in 96% of psychologically symptomatic patients, in 89% of neurologically symptomatic patients, in 73% of hepatic patients and in none of the asymptomatic patients.

Neurological and psychological manifestations were detected in 24.3% and 23.4% of the patients at the time of diagnosis, respectively. Finally, family history was positive in 36% of the patients.

DISCUSSION

Wilson disease is uniformly fatal if left untreated. On the other hand, early diagnosis requires a high index of suspicion in various patients, namely patients with unexplained liver, neurological, psychiatric or even bone diseases, and in patients with acute hemolysis or Fanconi syndrome. In the above-mentioned cases, the clinical suspicion is confirmed by study of indices of copper metabolism.

In this study, as in the previous studies (6, 7, 8), there was a male preponderance (59% versus 41%), but the p value was more than 0.05, in contrast to the study by Saito (1987) (6).

The age range in this study was from 3 to 50 years, which is similar to the research by Saito (1987) (6). In both studies, no difference in age at the onset between male and female patients was noted. The mean age at the onset of the disease is affected by the proportion of disease patterns. Since hepatic type patients are of an earlier age at onset, comparison of mean age at the onset among various studies should be made with particular attention to this point. In this study, most patients showed hepatic signs and symptoms as their presenting manifestations and the mean age was 11±7 years. A previous study carried out in Japan (9) reported a mean age at onset of 12.2 years, which is very close to the finding in this study. In that study, 50% were hepatic type and 50% were neurological type by their definition. The mean age at onset in other countries tended to be higher than in Japanese studies. In the epidemiologic study in East Germany (10), in which 14% of the 106 cases were hepatic, the mean age at onset of all the cases was 17.2 years, and that for hepatic type was 13.7 years. In the study of European migrants to the United States (11), the mean age at onset was 23.2 years, and 22.9% were hepatic type patients. In other studies, the mean age at onset was 16.2 years in the United States (12), 12.5 years in India (13), 16.4 years in Taiwan (14) and 16.0 years in England (14). European and American patients seem to develop the disease later than Asian patients.

In this study, as in some previous studies (2, 3, 6), the most common presenting manifestations were related to liver disease; more than 83% of the patients had manifestations of liver disease (ascites, edema, splenomegaly and jaundice) at the time of diagnosis. Of course, the above-mentioned finding is based on the age range studied. For the same reason, in the report by Stremmel et al. (1991), neurological manifestations were more common in a series of adult patients (15). As can be seen, ascites and edema were more common in our patients in comparison to previous studies (6, 7). This can be due to the delay in the diagnosis and hence more liver dysfunction in our patients.

In the present study, the most common neurological manifestations were dystonia, dysarthria and tremor, also similar to previous studies (6, 15).

Kayser-Fleischer rings were present in 74.4% of our patients. They were more frequent in our patients in comparison to a previous report (16), but our neurologically symptomatic patients showed Kayser-Fleischer rings less frequently than previous reports (16, 17). This finding is also based on the age range of the patients studied (2).

Serum transaminase activities are generally abnormal in patients with WD (2). Similar findings were observed in our study as well, but hyperbilirubinemia was less common in comparison to abnormal serum transaminase activities. Coagulation indices (PT & PTT) were often disturbed in our patients, which can be interpreted as another index of delay in the diagnosis in our patients with WD. Serum ceruloplasmin was subnormal in only 75.5% of the patients. This figure is lower than that in most of the previous studies (2, 15, 18). Twenty-four hour urinary copper was elevated in most patients in this study, as in previous studies (2, 18).

Some of our patients had metabolic and/or electrolyte disturbances at the time of diagnosis; metabolic acidosis, hypokalemia and hypernatremia were the most common disturbances that should be kept in mind for more effectively managing the patients.

Finally, family history was positive in more than one-third of our patients. This finding, as previously reported, signifies the need for screening in the first-degree relatives of any patient newly diagnosed with WD (2, 3, 19). In fact, 9.3% of our patients were diagnosed by this screening, while 29% of these were totally asymptomatic.

ACKNOWLEDGEMENT

We would like to thank the Office of the Vice-Chancellor for Research of Shiraz University of Medical Sciences for financial support for this study (Grant no. 1602), and Dr N. Shokrpour for editorial assistance.

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