RESEARCH ARTICLE

NEUROLOGICAL AND OTHER MANIFESTATIONS OF WILSON DISEASE; 1998-2005

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Abstract

Objective

Wilson disease (WD) is an inherited copper metabolism dysfunction disease characterized by cirrhosis and CNS findings. Wilson disease is important because it is fatal if not recognized and treated. Our Goal of study is to investigate the clinical signs and symptoms, lab results and other relevant matters in our patients in order to obtain a better understanding of this potentially lethal disease in our country.

Materials & Methods

We have evaluated 21 cases of children with Wilson disease who were referred to Loghman and Imam Hussein Hospital between years 1998-2005. The mean age of our patients was 9 years.

Results

The presenting symptom was ascites and extremity edema in 6(28.5%) patients, behavioral changes or neurological signs in 5 (24%) simultaneous Ascites and icter in 9(43%) patients and in one patient the presenting manifestation was hemolytic anemia(4.8%). One of our patients died because of fulminant hepatitis in the course of admission(4.8%).

Conclusion

we showed in this study that Wilson disease can be presented by a manifold symptoms in children and adolescence .Having a good concept of these symptoms and high clinical suspicious are required to diagnose this potentially lethal disease at the proper time in order to decrease the potential adverse effects of the disease especially the neuropsychiatric damages significantly.

Key Words: Wilson Disease , Kayser-Fleischer ring , ceruloplasmin

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Introduction

Wilson disease (WD) is an inherited copper metabolism dysfunction disease characterized by cirrhosis and Central Nervous System (CNS) findings. An American neurologist, Samuel Alexander Kinnier Wilson, first described Wilson disease in 1912 (1). Wilson identified seven patients with a new familial disorder presenting with progressive degeneration of the lenticular nuclei and liver cirrhosis at autopsy. Although Wilson hypothesized the presence of a toxin affecting the liver and the brain, the role of copper in disease pathogenesis was not recognized for another 35 years (2).

The condition is characterized by excessive deposition of copper in the liver, brain,

and other tissues. The major physiologic aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver (3). The genetic defect, localized to chromosome arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver(4).

Patients with Wilson disease usually present with liver disease during the first decade of life or with neuropsychiatric illness during the third decade. The diagnosis is confirmed by measurement of serum ceruloplasmin, urinary copper excretion, and hepatic copper content, as well as the detection of Kayser-Fleischer rings (5). Although it is extremely rare in clinical practice, Wilson disease is important because it is fatal if not recognized and treated. Some have speculated that Wilson disease goes undiagnosed in one half of patients with the disease. Often, the diagnosis is not made until adulthood despite manifestations of the disease in childhood.

In this study we have evaluated 21 cases of children 7-12 years old with Wilson disease who referred to Loghman and Imam Hussein Hospital between years 1998-2005. Our Goal of study is to investigate the clinical signs and symptoms, lab results and other relevant matters in our patients in order to obtain a better understanding of this potentially lethal disease in our country.

Patients and Methods

Our study consists of 21 patient who were diagnosed as Wilson in Loghman and Imam Hussein Hospital during an eight year period (1998-2005).Our inclusion criteria for diagnosis of Wilson disease were a combination of clinical manifestations consisting of liver involvement, neurological signs and symptoms especially extrapyramidal symptoms,behavioral changes and Kayser-Fleischer rings diagnosed by experienced corneal specialist and laboratory results consisting of Serum ceruloplasmin levels lower than 20 mg/dl, low total serum copper level and increased urinary copper excretion (>100 mcg/d).Liver biopsy was performed on 19 patients to confirm the diagnosis and to assess the amount of hepatic damage. It is necessary to announce that patients with high probability of Wilson disease in whom initial Lab data refused to confirm the diagnosis and the measurement of hepatic copper was not available, were excluded from the study. All patients' demographic, clinical, imaging and lab data were charted and analyzed using SPSS 14. It is necessary to announce that the patient's confidentiality was completely respected in our study.

Results

Our study included 21 patients diagnosed by Wilson disease who came to us between years 1998-2005.The mean age of our patients was 9 years (figure-1).The sex distribution were 13 boys and 8 girls.

The presenting symptom in 6 patients was ascites and extremity edema. Behavioural changes and neurological signs, hemolytic anemis and simultaneous ascites and icter were other presenting symptoms in our patients (table-1).

On admission 12 cases had Kayser-Fleischer rings confirmed by corneal specialist. Hepatosplenmegaly and Fulminant hepatitis were other reported manifestations on admission (table-2). Liver Biopsy was performed on 19 patients.All of them had histopathological changes compatible with liver cirrhosis mostly micronodular. 2 patients refused to do liver biopsy.All but 3 patients didn't report any adverse effect of penicillamine therapy during the course of admission. Malaise and worsening of the neurological symptoms were the adverse effects in these patients. 42.8% of our patients had neuropsychiatric symptoms. In 23.8% of cases it was the presenting manifestation of the disease (table -3).All of our cases with neuropsychiatric symptoms had Kayser-Fleischer rings.

The laboratory evaluation of the patients included CBC, Billirubin, liver function tests, PT, PTT, Serum Ceruloplasmin and copper, Urinary copper, HbsAg and liver Biopsy (table-4). Among 18 patients with high serum billirubin, 8 had serum billirubin less than 4 mg/dl. Of 4 patients with abnormal PT one died of fulminant hepatitis in the course of hospitalization.

Serum ceruloplasmin level (normal, 20-60 mcg/dl), copper level (normal, 80-160 mcg/dl) and urinary excretion of copper (normal, 10-80 mcg/24 h) of our patients are reported in table-5. 62 % of 8 patients) with normal urinary excretion had high urinary copper (>100) on repeated collection after oral challenge with D-penicillamine 500 mg. High hepatic Copper content

(>250 µg/g dry weight) was the confirmatory test in 4 patients for whom we had high clinical suspicion for Wilson disease but the other Lab tests refused to confirm the diagnosis of Wilson disease.

One patient was diagnosed with childhood rickets 1 year before admission that could be due to the metabolic effect of the disease on skeletal system.

Discussion

Wilson disease (WD) is an inherited copper metabolism dysfunction disease characterized by cirrhosis and CNS findings. Although it is extremely rare in clinical practice, Wilson disease is important because it is fatal if not recognized and treated. Some have speculated that Wilson disease goes undiagnosed in one half of patients with the disease. Often, the diagnosis is not made until adulthood despite manifestations of the disease in childhood. It is very important for the pediatrician to be familiar with the presenting symptoms of Wilson disease in order to make an appropriate clinical decision at early stages of the disease.We tried to give a better understanding of this disease in our study in children. This can be helpful for the patients in order to hinder the consequent damages of the disease especially to CNS by early treatment.

The mean age of our patients were 9 years. Non of our patient was younger than six years old. Many studies have shown that children younger than 5 years rarely present with symptoms of Wilson disease(6). Our age group of patients is in accordance with the study conducted by Imanzadeh et al in our country that showed the most patients were in 8-9 and 10-11 years age group with 37% and 20%, respectively(7). In study by imanieh in shiraz,there were 4 years old children(8). The sex distribution were 61.9 % (13) boys and 32.1% (8 cases) girls ($p<0.005$).This is in contrast to other studies results that show the equal prevalence of this disease between two sex groups.We could not find a reason for this discrepancy, and in the other study in IRAN boys were predominant(7,13). The fulminant presentation of Wilson disease is more common in females than in males (4:1).Our only patient with fulminate liver damage who died in hospital admission was female(9).

Hepatic dysfunction is the most common initial manifestation in childhood, with patients in this category presenting at an average age of 10-13 years, a decade or more sooner than those presenting with neurologic symptoms (10). The presenting symptom in 28.5 % of our patients was ascites and extremity edema. 43% of our patients had simultaneous Ascites and icter at the time of presentation. Almost all of our patients had a degree of hepatic involvement in History,physical examination or initial basic laboratory tests. It is confirmed by the fact that of 19 Liver biopsies that were performed all showed histopathological changes compatible with liver cirrhosis mostly micronodular. This is compatible with Davies et al study that showed Liver disease ranges from mild elevation of the serum transaminases in asymptomatic individuals to chronic active hepatitis and cirrhosis. In certain circumstances, the initial presentation may be that of acute liver failure accompanied by the sudden release of excess copper into the bloodstream with resultant hemolytic anemia (11). Davies et al showed that irrespective of the initial symptoms, almost all patients will have some evidence of cirrhosis on liver biopsy, reflecting the response to years of hepatic copper accumulation before clinical symptoms. Such biopsies may reveal micronodular cirrhosis with evidence of copper deposition in a variable distribution throughout the liver lobules. Eventually, this histology progresses to that of chronic hepatitis with nodular regeneration (12).

In one of our patients the presenting manifestation was hemolytic anemia.It was reported in Schilsky et al study on liver transplantation in Wilson disease that in certain circumstances, the initial presentation may be that of acute liver failure accompanied by the sudden release of excess copper into the bloodstream with resultant hemolytic anemia. This process of rapid hepatic degeneration in a previously well-appearing individual suggests the presence of a viral illness or external factor that has triggered injury in a copper-loaded liver (13).

In our study which was performed on children age group only in 24 percent of the patients were the neuropsychiatric symptoms the obvious presenting manifestation of the disease.On detail physical and clinical examination 42.8 % of patients had neuropsychiatric symptoms that is reported in detail in table-3. This is relatively in accordance with the study conducted by Oder W. They concluded that neurologic symptoms may occur at initial presentation in 60% of patients, usually in the

third or fourth decade of life, however in children the presentation of neurological symptoms are much less common and may be seen in 25-30% of the cases (14). However our results are lower than the results of the study of Imanzadeh et al that revealed neuropsychiatric abnormalities in 37% of patients (7). All of our cases with neuropsychiatric symptoms had Kayser-Fleischer rings,we had a group of best ophthalmogist with latest equipments..Because these symptoms arise from copper deposition in the central nervous system, awareness of Wilson's disease as a possible cause can lead to early diagnosis and treatment with a rapid overall improvement. These underlying structural changes and the copper deposition can be detected by magnetic resonance imaging at an early stage in symptomatic patients and may be observed to decrease with chelation therapy (15). 42.8 % of our patients had psychiatric symptoms. These symtoms, defined in Dening et al study on psychiatric manifestations of Wilson disease, revealed that psychiatric illness may occur alone or in combination with other symptoms in the course of the disease and includes abnormal behavior, personality changes, depression, and cognitive impairment indicative of schizophrenia(16).

Laboratory evaluation to confirm the diagnosis of Wilson's disease is warranted in anyone with isolated elevation of serum transaminases, chronic hepatitis of undetermined cause, Kayser-Fleischer rings, basal ganglia symptoms, or unexplained psychiatric illness, including sudden behavioral changes. In our study Low serum ceruloplasmin level of <20 mg/dl (normal, 20-60 mcg/dl) was detected in all patients and 20 out of 21 patients had low copper level (normal, 80-160 mcg/dl).This is in contrast to the study of Steindl et al who discussed Ceruloplasmin as an acute phase protein; thus this value will be in the normal range in 5% of patients due to infection or inflammation (17,18). Another inexpensive screening test is measurement of urinary copper concentration. Martins da Costa C et al study concluded that in pediatric cases of WD—in particular those of the hepatic variety—a provocative test for urinary copper excretion using the chelating agent D-penicillamine has been undertaken, with high levels of sensitivity reported(19). This was confirmed by our study. While in 61.9 % of patients urinary excretion of copper was high >100 mcg/24 hours (normal, 10-80 mcg/24 h) on the initial test, 62.5 % of 8 patients with normal urinary excretion had high urinary copper (>100) on repeated collection samples after oral challenge with D-penicillamine 500 mg.

One patient was diagnosed with childhood rickets 1 year before admission that could be due to the metabolic effect of the disease on skeletal system.

Therapy with penicillamine is initiated as a test oral dose that if tolerated is then given four times daily. In our study 14.2 % of patients reported adverse effect of penicillamine therapy during the course of admission. Malaise and rash were the side effects in two patients. One patient experienced deterioration of neurological symptoms after treatment with D-penicillamine that made us stop the drug and change the therapy to zinc salt. This is lower than 20-30% exacerbation of neurological symptoms that was reported by Brewer et al in their study.Brewer et al study revealed that in 20-30% of cases, an exacerbation of the neurological symptoms occurs over a period of 2 weeks to 12 months (commonly after 6 weeks). This occurrence is caused by the rapid mobilization of liver copper in the circulation, and can sometimes be permanent (20). The lower rate showed in our study can be due to a failure in precise follow-up or it can be caused by different age groups of the patients in two studies (children vs adults).

In our study low Hemoglubin was seen in 33.3 % (7)of patients. 4 patients had Iron deficiency anemia that was treated appropriately.Coombs-negative hemolytic anemia was the reason in 3.Our results are a confirmation to Schilsky et al study that proved acute release of copper into the circulation can damage red blood cells, thereby inducing hemolysis. They saw this phenomenon in 10-15 % of patients with Wilson disease in the course of disease (21).

In conclusion, we showed in this study that Wilson disease can be presented by a manifold symptoms in children and adolescence.Having a good concept of these symptoms and high clinical suspicious are required to diagnose this potentially lethal disease at the proper time in order to decrease the potential adverse effects of the disease especially the neuropsychiatric damages significantly.

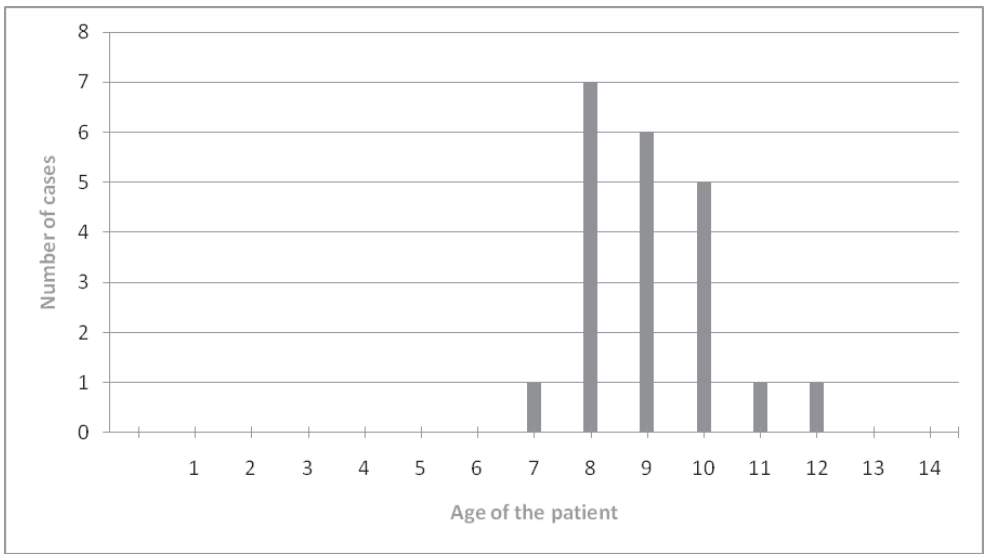

Figure1: Age distribution of our patients

Table1. Presenting symptoms of Wilson in our patients (n=21)

Presenting Symptom	Number	Percent
Ascites And Extremity Edema	6	28.5 %
Behavioral Changes Or Neurological Signs	5	24%
Hemolytic Anemia	1	4.8%
Simultaneous Ascites And Icter	9	43%
Total	21	100%

Table 2. Physical Examination of patients on admission

Gastrointestinal Manifestaitons	Number	Percent
Only Splenomegaly	1	5%
Only Hepatomegaly	2	9.5 %
Hepatosplenomegaly	18	85 %
Fulminant Hepatitis	1	4.8%
Total patients with abnormality	21	100%

Table 3. Neuropsychiatric manifestations of Wilson disease on admission

Neuropsychiatric manifestations	Number	Percent
As presenting symptom	5	24%
Behavioral Changes incuding irritability and poor concentration	6	28.5 %
Extrapyramidal signs including poor hand-writing	5	24%
Dysdiadochokinesia	3	14%
Total patients with neuropsychiatric manifestation	9	43%

Table 4. Lab results in our patients, showing abnormal finding

Evaluation/Results	Number	Percent
Low Hemoglubin due to Iron deficiency	4	19 %
Coombs-Negative hemolytic anemia	3	14 %
High serum billirubin	18	86 %
Elevated Aminotransferases	12	57 %
Abnormal PT	4	19 %

Table 5. Serum & Urinary copper profile of patients in our study

Parameter	Number	Percent
Low Serum Ceruloplasmin	15	71.5 %
Low Serum Copper	17	81 %
High urinary copper excretion	13	62 %

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