Clinicopathologic Findings in 35 Children with Wilson Disease

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Abstract

Background and Aim: Wilson disease is a rare autosomal recessive disorder of copper metabolism. Wilson disease is the most common metabolic cause of fulminant hepatic failure in children over the age of 3 years. The aim of this study was to find the major clinical & pathologic findings of Wilson disease in children in Tehran.

Patients and Methods: This retrospective study was carried out in the mofid children's hospital. Thirty five patients suffering from Wilson disease were studied. Ceruloplasmin level below 20mg/dl and urinary copper excretion level above 100µg/24hr were considered as the inclusion criteria.

Results: Of the patients, 20 cases were males and 15 were females with average age of 9 years. The most patients were in 8-9 and 10-11 years age group with 37% and 20%, respectively. Hepatic involvement was confirmed in 100% of patients. Jaundice was seen in 20 patients (57%), abdominal enlargement together in 20 patients (57%), and encephalopathy in 9 patients (26%). Serum copper was reduced in 100% and low-serum ceroluplasmin in 100%, increased urinary copper excretion in %97, increased AST & ALT in 100%, increased PT was in 94% patients, anemia was found in 100%, leucopenia in 14%, and thrombocytopenia was seen in 71% of patients. In this study, 37% of patients had neurological symptoms such as tremor, ataxia, difficulty in speech and delayed education. 32 patients had undergone ophthalmic examination and 62% showed KF ring in their ophtalmoscopy.

Conclusion: According to this study, hepatic and neurologic involvement is the most consistent finding in the Wilson disease. Most patients were in the age's group of 8-9 and 10-11.

Keywords: Wilson disease, liver.

(J Med J 2007; Vol. 41 (3): 153- 156)

Received	***Accepted***
April 18, 2007	*July 4, 2007*

Introduction

Wilson disease is a rare autosomal recessive inherited disorder of copper metabolism. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues.[1]

Wilson disease is the commonest metabolic cause of fulminant hepatic failure in children over the age of 3 years. [2] Its manifestations are the consequences of excessive accumulation of copper in the liver, brain, kidney, cornea, and other organs.

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The incidence of the disorder is 1/500.000-100.000 births.[3] The prevalence of this disorder is 1 in 30000 persons worldwide. Wilson's disease gene is located on the long arm of the chromosome 13. Clinical disease is rarely present before 5 years of age. Hepatic and neuropsychiatric manifestations were more common. Kayser-Fleischer (KF) ring is the common ocular finding. The diagnosis of Wilson disease is based on clinical features, KF ring, laboratory findings of copper status; including serum ceruloplasmin, serum copper, 24-hour urine copper excretion, and copper content of liver and liver histology. Approximately, 90% of all patients with Wilson disease have ceruloplasmin levels of less than 20mg/dl (reference range, 20-40mg/dl). The urinary copper excretion rate is greater than 100mg/dl (reference range, <40mg/dl) in most patients with symptomatic Wilson disease. Both the sensitivity and specificity of this test are suboptimal for use as a screening test; however, it may be useful to confirm the diagnosis and to evaluate the response to chelation therapy.[1] After the diagnosis of Wilson disease is established, initial treatment for symptomatic patients should include a chelating agents (penicillamine or trientine). Treatment of presymptomatic patients or maintenance therapy can also be accomplished with zinc. [4] This study was proposed to assess the clinical and laboratory findings of the Wilson disease in a set of pediatric patients. The patients suffering from Wilson disease must avoid highly copper content in their diets. Sheep and pork liver had the highest copper content in contrast to other food materials.[5]

Patients and Methods

All the hospital records in Mofid children hospital since 1995 to 2003 with the diagnosis of Wilson disease were reviewed. Serum ceruloplasmin level below 20mg/dl, and urinary copper excretion level above 100µg/24hr was considered the inclusion criteria.

Results

Of the patients, 20 cases were males and 15 were females with average age of 9 years. The most patients were in 8-9 and 10-11 years age group with 37% and 20%, respectively. Hepatic involvement was confirmed in 100% of patients (Table-1). Icter was seen in 20 patients (57%), abdominal enlargement together in 20 patients (57%), and encephalopathy in 9 patients (26%). Serum copper was reduced in 100% and low-serum ceroluplasmin in 100%, increased urinary copper excretion was noticed in %97, increased AST & ALT in 100%, increased PT was in 94% patients, anemia was found in 100%, leucopenia in 14%, and thrombocytopenia in 71% of patients. Liver biopsy was done for 7 patients. Of these patients, 4 patients have micro and macronodular cirrhosis, 2 patients have mild foamy degeneration, and 1 patient has chronic active hepatitis. Measurement of copper in dry liver was done for 5 patients. Two patients have 3-fold increase, two patients have 2-fold increase, and 1.5 -fold increased content was seen in one patient. In this study, 37% of patients had neurological symptoms such as tremor, ataxia, difficulty in speech and delayed education. 32 patients had undergone ophthalmic examination and 62% showed KF ring in their ophtalmoscopy.

Table 1: Clinical findings in patients with Wilson disease.

Splenomgealy	80%
Hepatomegaly	68.57%
Ascitis	65.71%
KF ring	62%
Icter	57.14%
Esophageal varices	54.28%
Neurologic manifestations	37.14%
Encephalopathy	25.71%
Spiderangioma	11.42%
Gynecomastia	8.57%

Discussion

Gow et al. [6] reported that from 30 patients with Wilson disease (m=15, f=15), 22 patients had no fulminant presentation and 8

patients had fulminant presentation. From these patients, 15 patients were in (6-17) years age group. From the 15 patients, 13 patients have liver presentation and 1 had neurologic manifestations.[6] In our study, 9 patients had fulminant presentation (m=3, f=6). Interestingly, in one series, 16 of 21 patients with fulminant Wilson disease were females.[7] This observation of a female predominance has been confirmed by others and is hypothesized to be due to the influence of sex hormones. In the series of Scheinberg and Sternlib, the initial clinical manifestations were hepatic in 42% of patients, neurologic in 34%, psychiatric in 10%, hematologic or endocrinologic in 12%, and renal in 1%. Approximately, 25% of patients had more than one organ involved. [8] Of the 50 cases reviewed by Walshe, 31 cases had hepatic and 17 had neurologic presentations. [9] In the other study that was carried out in Shiraz, the mean age of presentation was 9±2.93 (min=4, max=16). The most patients were males. The most common symptom was abdominal protrusion (84.2%). (76.3%) had jaundice, (74%) had ascitis, (95%) had an abnormal abdominal examination, (30%) had an abnormal neurological examination, and (71%) had Kaiser-Fleisher ring. [10] The above findings are similar to results of the current study (Table-2)

Table (2): The results of studies about the manifestations of Wilson disease.

	Neurologic manifestation	***Hepatic manifestation***
Walshe	*62%*	*34%*
Sheinberg et al.	*30%*	*42%*
Imanieh et al. (IRAN)	*30%*	*76%*
Current study(IRAN)	*37.4%*	*68.57%*

Conclusion

In our study, hepatic and neurologic involvement is the most dominant manifestation in the Wilson disease. Most patients were in (8-9) and (10-11) age groups. The most frequent hematologic finding is anemia. The most abdominal findings were splenomegaly and hepatomegaly, respectively. Our results were compared to other studies and there were no significant differences found between them.

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نتائج الفحوصات السريرية والمرضية لـ 35 طفلاً مصابين بداء (ويلسون)

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الملخص

الخلفية والهدف: يعد مرض (ويلسون) مرضاً نادراً يتمثل بحدوث إضطراب ذا طبيعة صبغية متنحية في أيض معدن النحاس، وهو يعد أيضاً المسبب الأيضي الأكثر شيوعاً للفشل الكبدي الخاطف عند الأطفال فوق الثلاث سنوات من العمر. كان هدف هذه الدراسة هو التوصل الى معرفة أهم الملاحظات الناتجة عن الفحوصات السريرية والمرضية للأطفال المصابين بمرض ويلسون في طهران.

المرضى وطرق البحث: تم تنفيذ هذه الدراسة الارتجاعية في مستشفى مفيد للأطفال، حيث تم دراسة 35 طفلاً مصابين بمرض (ويلسون). وكانت الأسس التي عدت معاييراً لاعتبار الأشخاص مصابين بداء ويلسون هي أن يكون مستوى (أنزيم السيرولوبلازمين) أقل من 20 مغ/ دل (ميلغرام لكل ديسي لتر) وأن يزيد مستوى إفراز النحاس في البول عن 100 ملغ / 24 ساعة.

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النتائج: كان عدد الإناث في عينة المرضى المدروسة 15 وعدد الذكور 20 والذين كان معدل أعمارهم 9 سنوات. معظم المرضى كانوا ضمن المجموعة العمرية (9-8) و (10-11) بنسبة 37% و 20% لكل منهما على التوالي. وقد لوحظ أن جميع المرضى كانوا يعانون من مشاكل كبدية بنسبة 100% ؛ لوحظ وجود اليرقان عند 20 منهم (57%) ؛ ولوحظ حدوث التوسع البطني بالإجمال عند 20 مريضاً (57%)؛ بينما وجد الاعتلال الدماغي عند 9 مرضى (26%). كما لوحظ أن نسبة النحاس المصلي قد انخفضت عند جميع المرضى (100%) بالإضافة الى نسبة (أنزيم السيرولوبلازمين) في المصل الأدنى التي أنخفضت أيضاً عند الجميع (100%)؛ ووجد ارتفاع في نسبة الإفراز النحاسي البولي عند (97%) من المرضى؛ ارتفاع نسبة (ASI) (أنزيم ناقلة أمين الاسبارتات) و (ALI) (أنزيم ناقلة أمين الألانين) عند 100% منهم؛ وارتفاع نسبة (PT) (البروثرومبين) عند 94% من المرضى. كما وجدت الأنيميا (فقر الدم) عند 100% من المرضى في العينة؛ قلة الكريات البيضاء عند 14%، ووجد حدوث نقص في الصفيحات عند 71% منهم.

بالإضافة الى أن 37% من الأطفال في هذه الدراسة كانوا يعانون من أعراض عصبية مثل: الرعشة؛ الرّنح، وصعوبات في التكلم وبطء في التعلم. غير أن 32 مريضاً من العينة كانوا قد أجروا فحوصاً عينية حيث ظهر من خلال تنظير العين لديهم أن 62% لديهم حلقة (KF) (حلقة كايزر- فلايشر) في القرنية.

الخلاصة: تبعاً لهذه الدراسة، فقد وجد أن وجود مشاكل عصبية وكبدية كان من أبرز النتائج لفحوصات مرضى (ويلسون) والتي لوحظت عند جميع المرضى. معظم المرضى كانوا في المرحلة العمرية من (9-8) ومن (11-10).

الكلمات الدالة: مرض ويلسون، الكبد.