

Wilson's Disease among Children at King Hussein Medical Center

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ABSTRACT

Objectives: To describe the demographic characteristics and clinical presentation of 37 patients with Wilson's disease followed up at the Pediatric Gastroenterology Clinic.

Methods: A specially designed data collection form was used to collect the relevant data; Medical history and a thorough clinical examination for patients who were diagnosed with Wilson's disease during the period between February 2000 and October 2010 at King Hussein Medical Center, Amman, Jordan was done. Laboratory investigations include ceruloplasmin level, liver enzymes, albumin, prothrombin time, partial thromboplastin time, international normalized ratio, complete blood count, urine analysis, abdominal ultrasound and liver biopsy. Simple descriptive statistics (frequency and percentage) were used to describe the study variables.

Results: A total of 37 patients diagnosed as Wilson's disease with age ranges between two and 13.5 years were included in this descriptive review. Out of 37 patients, 19 (51%) were males and 18 (49%) were females. Patients with affected siblings were 29 (78%). Central nervous system involvement was found among 9 (24.3%) patients. The commonest presenting symptoms were jaundice (n=16, 43%), abdominal distension (n=13, 35%), fatigue and delayed school performance (n=12, 32.4%). The most common clinical findings were hepatomegaly (n=26, 70%), jaundice (n=16, 43%), splenomegaly (n=14, 37.8%), Kayser-Fleischer ring (n=11, 29.7%), and lower limb edema (n=11, 29.7%) respectively. Low ceruloplasmin level was found in 34 (92%) patients, high liver enzymes in 23 (62%) patients, hemolytic anemia in 13 (35%) patients successively. Twenty-four hour urine collection average copper post D-penicillamine challenging test was above 230µg/dl. The most common ultrasound findings were hepatomegaly, abnormal echogenicity, splenomegaly and ascitis. Liver biopsies commonly showed liver fibrosis, however fatty liver changes, hepatosteatosis and liver cirrhosis were the least common finding.

Conclusion: Family screening is needed once a child in the family is diagnosed. Full investigations to rule out Wilson's disease should be performed in any patient with unexplained elevation of liver enzymes, hepatomegaly, hemolytic anemia, jaundice or neurological/behavioral disturbances.

Key words: Jaundice, Hepatomegaly, Splenomegaly, Kayser-Fleischer ring, Wilson's disease

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Introduction

Wilson's disease is a disorder of copper

metabolism characterized by degenerative changes in the liver, brain, cornea and kidney. It is an autosomal recessive disease (chromosome

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13 q gene: copper binding p-type ATPase, ATP 7B).^(1,2) It is not a common disease worldwide, its incidence is 1/100,000-1/500,000 live births according to American studies.⁽³⁾ Although a Greek and an Indian study showed a higher incidence of the disease (1 in 30,000) with an average age of hepatic symptoms being 10-14 years.^(1,4) Wilson's disease has a wide spectrum of clinical manifestations, although some patients may be entirely asymptomatic with delayed diagnosis.⁽⁴⁾ This study was conducted to determine the demographic characteristics and clinical presentation of 37 patients with Wilson's disease, followed up at the Pediatric Gastroenterology Clinic.

Methods

This is a descriptive retrospective review of the medical records for all patients who were clinically confirmed and laboratory diagnosed cases with Wilson's disease at King Hussein Medical Center during the period between February 2000 and October 2010, in the Pediatric Gastroenterology Clinic. We enrolled 37 patients in our study, aged 2-13.5 years, reviewed and followed up at the Pediatric Gastroenterology Clinic, focusing at symptoms on first presentation, family history, clinical examination, laboratory data, radiological findings and liver biopsy. A full detailed history was taken for each patient and a complete clinical examination was performed. Laboratory investigations included ceruloplasmin level, liver function tests, albumin, partial thromboplastin time (PTT), International Normalized Ratio (INR), prothrombin time (PT), complete blood count (CBC) with blood film and reticulocytes, and urine analysis. Abdominal Ultrasound was performed for all our patients and finally, liver biopsy was performed for a group of patients only and was not done for the others because of significant coagulopathy or family refusal of liver biopsy. Ferenci's diagnostic score of Wilson's disease was used (8th international conference of Wilson's disease and Menkes disease, Leipzig/Germany in April 2001).⁽⁵⁾ A specially designed data collection form was used to collect the relevant data.

Results

The male to female ratio was almost 1:1 (51%

and 49% respectively). Family history was positive in 29 (78%) patients, CNS involvement in 9 (24.3%) patients. The commonest presenting symptoms were jaundice (n=16, 40%), abdominal distension (n=13, 35%), fatigue and delayed school performance (n=12, 32.4%) (Fig. 1). The most common clinical findings were hepatomegaly (n=26, 70%), jaundice (n=16, 43%), splenomegaly (n=14, 37.8%), Kayser-Fleischer ring (n=11, 29.7%), and lower limb edema (n=11, 29.7%) respectively (Fig. 2). Low ceruloplasmin level was found in 34 (92%) patients, high liver enzymes in 23 (62%) patients, hemolytic anemia 13 (35%) patients successively. Ceruloplasmin level was never low in 100% of cases in international studies.^(1,6,8) Concerning 24 hour urine collection: copper post D-penicillamine challenging was above 230 micrograms/24hr. Ultrasonography was performed in all our patients, 64% of which had abnormal findings of which the commonest finding was hepatomegaly (50%), abnormal echogenicity of the liver (26%) followed by splenomegaly (20%) and ascitis (13%). Finally, liver biopsy was performed in 15 (40%) patients and showed liver fibrosis in 54%, fatty liver in 45%, hepatosteatosis in 18% and liver cirrhosis in 18%.

Discussion

We noticed a high percentage of affected relatives due to consanguinities especially in Al-Tafeelah and Al-Mafraq district areas. The ceruloplasmin level was low in 92% of patients compared to 88% in a Brazilian study,⁽⁶⁾ and 93% in Nazer *et al.* study.⁽⁷⁾ In several patients, liver biopsy may be needed to assess the extent and severity of liver disease. Neurological features may be the presenting manifestation of Wilson's disease even in the absence of clinical evidence of hepatic involvement.⁽⁴⁾ We compared our finding with Nazer *et al.*'s study results which was conducted at King's College Hospital/London. They found that the commonest symptoms of presentation of Wilson's disease were lethargy and anorexia (70%), jaundice (56%), and abdominal pain(48%).⁽⁸⁾ Patients below five years of age were diagnosed during family screening(affected siblings) and they were asymptomatic. In a recent study from Karachi/Pakistan,⁽⁹⁾ viral causes were

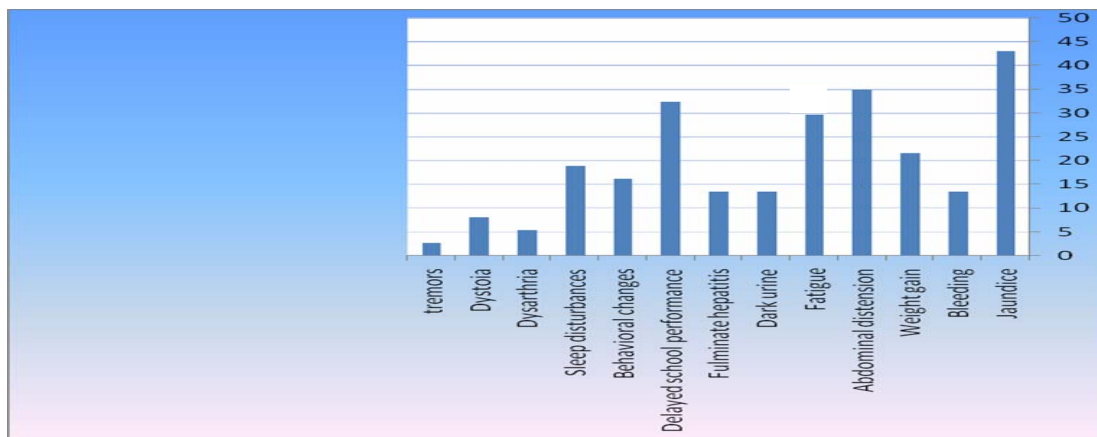


Fig. 1: Symptoms at presentation(in percentage) among the study group

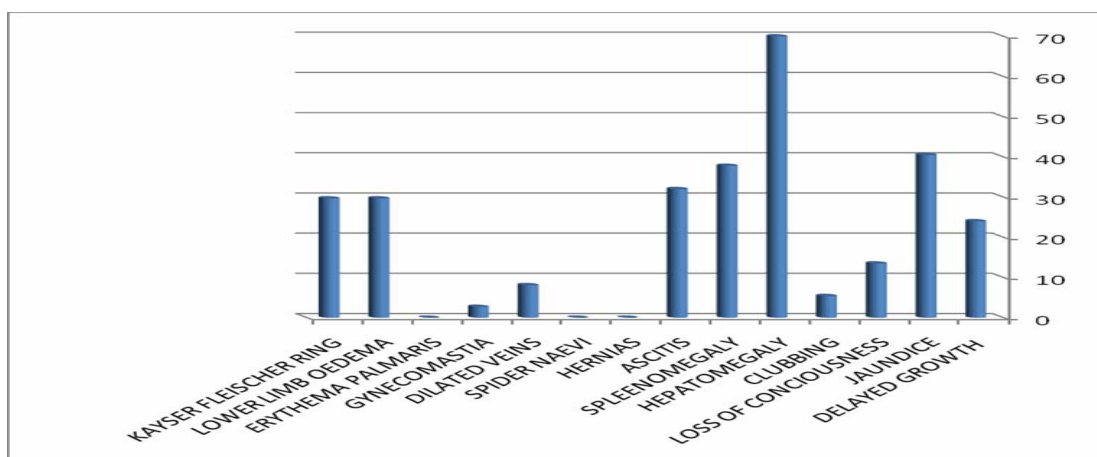


Fig. 2: Signs at presentation (in percentage) among the study group

found to be the most common factor for fulminant hepatic failure in children (37 patients out 50) which makes 74% of the total, 56% of them had hepatitis A virus, and 18% had hepatitis B virus. The remaining 26% of the total (13 patients) were negative for acute serology of hepatotropic viruses, of which 8% had Wilson's disease, 2% with autoimmune hepatitis and finally the etiology could not be established in 16% of cases. In our study, 9 patients (24.3%) were found to have CNS involvement, which was significantly less than the international numbers. This could be partly explained by the presence of different methods to identify the CNS involvement. In our practice, we do not perform MRI as a routine test. Kayser-Fleischer ring has been found in 11 patients (29.7%), compared with 41% in a Brazilian study,⁽⁴⁾ 38% in a Greek study⁽¹⁾ at Athens University and in 32% in an Indian study.⁽¹⁰⁾ Some striking findings were found in our study concerning microscopic haematuria found in 14 patients (37%) and albuminuria in 6 patients (16%). The Wilson's

disease gene is expressed in kidney tissue,⁽¹¹⁾ and patients may resemble those with Fanconi syndrome, urolithiasis, also haematuria and proteinuria can occur before treatment as part of the disease process and after therapy as adverse reaction to D-penicillamine therapy.⁽¹²⁾ Cases presented with negative direct Coomb's test, haemolytic anemia in our study constituted 35% (13 patients), compared to 15 % in Rahil Shah study in 2009.⁽¹³⁾ The copper in tissue assay can produce false negative results in children since it is dependent on sample size, length of time during which the metal has been accumulating and a fact that it may be irregularly distributed.⁽⁴⁾ In international studies, histopathological findings of hepatic involvement may vary from steatosis to end stage liver cirrhosis. In Nazer *et al.*'s study,⁽⁸⁾ the majority of their patients who underwent liver biopsy, were found to have micronodular cirrhosis, followed by chronic active hepatitis with moderate piece-meal necrosis.⁽⁸⁾ In our study, the most common histopathologic finding was liver fibrosis

followed by fatty liver (fatty liver can very rarely present in nodular pattern.⁽¹⁴⁾ In a Greek study,⁽¹⁾ fibrosis was found in a 4 months old infant, and inflammation was found in a 23 months old child, suggesting that serious histological changes may develop during the early stages of the disease.

Conclusion

The commonest clinical presentations of Wilson's disease in Jordan were Jaundice and hepatomegaly. Family screening is important once you diagnose Wilson's disease. Full investigations to rule out Wilson's disease should be performed in any patient with unexplained high liver enzymes, hepatomegaly, haemolytic anemia or neurological/behavioral disturbances. Finally, haemolytic anemia, microscopic haematuria were strikingly higher in our patients than that found in international studies.

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