

Wilson's Disease in Children (Clinical Presentations & Diagnostic Difficulties)

(Three years experience in Children Welfare Teaching Hospital- Baghdad)

Sawsan I.I. Al-Azzawi*, Dheia Hassan Al-Baldawi*, Auday Yasin Abbas**

ABSTRACT:

BACKGROUND:

Wilson's disease (WD) is rare but curable hereditary metabolic disease presents in childhood in different ways which make the diagnosis difficult and delayed.

OBJECTIVE:

To evaluate all cases of WD, modes of presentations, available diagnostic methods, treatment and follow up in a sample of Iraqi children.

PATIENTS AND METHODS:

Clinical presentations and management of 24 patients with WD were studied after the exclusion of other chronic liver diseases by thorough investigation. Low ceruloplasmin level and high copper excretion in urine pre and post challenge with penicillamine, in addition to the presence of Kayser Fleischer rings were the main stay of the diagnosis. The diversity of the results with the response to treatment and side effects of drugs used were registered over 3 years period in the GIT & Hepatology unit and consultation clinic at the Children Welfare Teaching Hospital, Medical city, Baghdad in the period from the 1st of May 2003 till the 1st of May 2006.

RESULTS:

From the twenty four patients with WD included in the study, we had 17 patients (70.8%) with hepatic manifestations (4 with acute hepatitis, 3 with fulminant hepatic failure and 10 as chronic liver diseases). Only two patients (8.3%) had neurological symptoms. One patient had hepatic manifestation + evidence of hemolysis (4.1%) and 4 (16.7%) asymptomatic siblings. The mean age of presentation was less in hepatic than the neurologic presentation (7.5 and 9.2 years respectively). The time interval between the symptoms and the diagnosis was more in the neurological than hepatic cases (95 vs. 42 days). Low ceruloplasmin found in 70.1% & Kayser-Fleischer ring present in 47.1% of hepatic cases and in all neurological cases. Family history was positive in 3 patients of the index cases. On follow up after treatment one child had bone marrow depression and two patients had thrombocytopenia. One patient died (4.2%) with fulminant hepatic failure, ascites and encephalopathy.

CONCLUSION:

Acute hepatitis, chronic liver affection, fulminant hepatic encephalopathy acute hemolytic anemia may be the presentation of Wilson disease in children. They also may exhibit a neurological manifestation as tremor and ataxia. At least two of the three diagnostic criterion plus index of suspicion, family history of affected sibling or death in the family of a jaundiced child raises the possibility of WD after exclusion of other chronic liver diseases by investigations.

KEY WORDS: wilson disease, jaundice, encephalopathy, children.

INTRODUCTION:

Wilson's disease (WD) is an autosomal recessive disorder characterized by decreased biliary copper excretion and reduced incorporation into

ceruloplasmin leading to excessive copper accumulation in many organs predominantly the liver, brain and cornea with prevalence in most population of 1 in 30000⁽¹⁾. In the 1993 the WD gene was identified and its structure elucidated^(2,3). Approximately 100 individual mutations have been identified in patients with WD, a phenomenon which may in part explain the clinical heterogeneity of the disease. Due to the number of individual

*Department of pediatrics, Baghdad Medical College, University of Baghdad.

**Children Welfare Teaching Hospital, Medical City, Baghdad.

mutation a diagnosis based on DNA studies and identification of mutations is not practicable for most laboratories so that clinician still have to rely on standard clinical and laboratory criteria⁽⁴⁾.

Establishing the diagnosis of WD is usually straight forward if the major clinical and laboratory features are present: typical hepatic and neurological symptoms and signs, Kayser Fleischer (KF) ring, low serum ceruloplasmin concentrations, and increased urinary copper excretion. However in patients who present with liver disease alone, KF rings are often absent and serum ceruloplasmin may be normal⁽⁵⁾.

Diagnosis has an added difficulty in fulminant hepatic failure as serum ceruloplasmin may be low and urinary copper excretion high in patients who do not have WD⁽⁶⁾. Asymptomatic siblings of patients with WD, in whom the diagnosis needs to be confirmed or ruled out, can, also present diagnostic uncertainties⁽⁷⁾.

The aim of this study was to evaluate all cases of Wilson disease seen over 3 years, modes of presentation, available diagnostic methods and response to treatment with its side effects.

PATIENTS AND METHODS:

All patients with acute liver diseases and those with stigmata of chronic liver problem and all who presented with fulminant hepatic encephalopathy were evaluated thoroughly in the GIT & Hepatology unit in the Children Welfare Teaching Hospital during 3 years period. The ages ranged from 3-15 years.

Full history of the clinical presentations and duration of appearances with family history of any liver problem were taken. Excluding any history of drug intake and previous history of blood transfusions, the patients were fully examined for jaundice, organomegaly, ascites, peripheral edema, state of consciousness, neurological manifestation as tremor or abnormal movements and any clinical signs of chronicity. Thorough extensive investigations (as liver function tests, PT, PTT, CBP, serum immunoglobulin, immune markers as ASMA, ANF, ALKM, C3, C4, alpha-one antitrypsin level, serum iron and iron binding capacity with serum Ferritin level, hemoglobin electrophoresis, bone marrow study, coomb's test, viral screen include HAV IgM antibody, HBS antigen, HCV antibody, U/S of the abdomen, Doppler study for the portal vein, slit lamp examination for the KF rings). The diagnostic screen for Wilson disease was done to all patients and considered positive if the ceruloplasmin was less than 20 mg/dl and the increase in 24 hours

urine copper after penicillamine challenge (500 mg given orally at the beginning of urine collection and 500 mg 12 hours afterward) to four folds levels of the normal or above (normal level in our lab was less than 40 microgm/24h), and the presence of KF rings by slit lamp examination⁽⁸⁾. For the positive cases of Wilson disease, the siblings in all families had the same diagnostic screening tests. No facilities were available for measuring hepatic copper content in our country or genetic study so we rely solely in the diagnosis of WD on clinical presentation and biochemical screening and the favorable clinical response after treatment with Penicillamine, Zinc and Pyridoxine. The improvement in the biochemical and hematological values gave an additional criterion for the diagnosis.

Follow up of all our patients done in the clinic and all the progress and the side effect of the drugs used were registered.

RESULTS:

Twenty four patients with WD were studied, table (1) shows that the commonest age group presented was between 5-10 years (54.1%) mostly male patients. The mean age of presentation was 8.5 years and the male to female ratio was 2.4:1. The youngest age of presentation was male 3 years of age with hepatic manifestations.

Table (2) indicates the modes of presentation which was mostly hepatic in 17 cases (70.8) and only 2 (8.2%) neurological cases as the referral was to our Hepatology unit.

The most common clinical presentation in the hepatic cases were jaundice in 14 patients (93.2%), hepatomegaly in 13 patients (86.5%), Seven (46.9%) had ascites & leg edema. and 2(11.7%) had bleeding varices out of nine (59.8%) with portal hypertension.

There was only one case (4.2%) presented with coomb's negative hemolytic anemia and hepatic manifestation. Three of our four asymptomatic siblings were brothers of one of the patients.

Three patients (12.3%) presented with fulminant hepatic failure, 2 with encephalopathy (13.3%) and one child 9 years old presented with bilateral parotid swelling and jaundice to start with and went into hepatic failure in less than three days.

Acute hepatitis features were evident in 4 patients (16.6%), 2 of them had HAV IgM+ve.

Two neurological cases admitted to the unit, both had family history of WD in siblings. One girl presented with coarse tremor & ataxic gait her brother was WD and a boy 8 years old presented with deteriorated school performance and slurred

speech, his sister died 4 years before with fulminant hepatic failure.

Table (3) shows that the mean age of presentation of the hepatic cases were less than the neurological and the asymptomatic cases (7.5ys vs. 9.2ys).

The delay in the diagnosis since the first symptom was evident in the neurological cases (95 days) in contrast to hepatic cases of (42 days) as seen in table (4).

Table (5) indicated the results of the diagnostic criterion which we used, low ceruloplasmin found in 12 hepatic cases (70.6%) and in all other patients in the study, while KF ring was positive in 8 patients (47.1%) of hepatic presentation and in the two neurological cases (100%) and in the hemolytic case. The 4 folds increase in the 24 hours urine copper was seen in all cases except the hemolytic case where there was 2 folds rise only but he had KF ring +ve.

Table (6) is showing the mean biochemical and hematological value in the hepatic cases, there is low hemoglobin value & total serum bilirubin (TSB) mostly in the younger age group (3-5 years). Also ALT & AST were higher in the same age group while prothrombin partial thromboplastin time was higher in the older age group.

The Alkaline phosphatase / TSB ratio in the fulminant hepatic cases was (3.1) while in other hepatic cases were (4.5).

The AST / ALT ratio was 1.7 in the fulminant cases and in the other hepatic cases was (1.3).

DISCUSSION:

Wilson disease remains potentially difficult to diagnose. We must rely on a constellation of clinical features and laboratory tests rather than on a single one (4). The age limit in this study was 15 years and the mean age of presentation was (8.5 years), it was low comparing to the other studies (9,10,11) probably because these studies include adolescent till 18 years.

No patient presented below 3 years of age in this study, although the disease was reported in a 4 months old baby in a study done by Manolaki et al (11).

The male: female ratio was 2.4:1 which is the reverse to Bernuau, et al (9).

The delay in the diagnosis since the first symptom appears prolonged in the neurological cases (9.2 yrs vs. 7.5 yrs for hepatic cases) as the symptoms mimic many neurological diseases but because they have positive family history of WD in their siblings, the diagnosis was easier.

Jaundice was the most common symptom and hepatomegaly was the most common clinical

finding in this study 93.2%, 86.5% respectively. In a study done by Manolaki et al jaundice was found in only 24.6% and hepatomegaly in 77% (11). This probably because families brought their children to hospitals because of the yellowish discoloration which is a frightening symptom in our community. Seven cases (46.9%) with ascites and leg edema was the presentation of the chronic cases in this study as in other study but he collects (12.3%) cases with acute coomb's negative hemolytic anemia while in this study one case was found with the same presentation (11). Acute hemolysis with symptoms of fulminant hepatic failure were the initial presentation of WD in many other studies (12,13,14).

A number of studies have demonstrated that the acquisition of Hepatitis A or B in patient with chronic liver disease is associated with high rates of morbidity and mortality and could precipitate an attack of fulminant hepatitis on an already diseased liver (8). Two cases proved to have HAV IgM+ve, at the same time their Wilson screen was positive and KF rings present in both cases.

In asymptomatic siblings, the delay in the diagnosis is usual unless there is an index case in the family.

Different neurological manifestation misled the physician about the correct diagnosis unless there is a history of the disease in the family or a death of one of the family members; this explains the late presentation in table (3) and also the longer interval between the symptoms and the diagnosis in table (4). The relative short interval of the diagnosis in the mixed hepato-hematological case is attributed to the alarming pallor which the patient had with hepatomegaly.

Although the low ceruloplasmin and the presence of KF ring considered to be sufficient to diagnose WD (1,15), this combination is not always present as KF ring was present in 47.1% of cases in this study and low ceruloplasmin in 70.6% cases only. Likewise in the study done by Steindl et al. 44% and 60% respectively (16). But in Manolaki et al. study 50% of their cases had KF ring and 56% had low ceruloplasmin (11).

KF ring reported in asymptomatic sibling in one study (17) but not found in the present study.

Urinary copper excretion is important indication of WD although it may be abnormal in other hepatic diseases and normal in some cases of WD (5,10,18). But the penicillamine challenge had an important impact in the diagnosis of WD in this study. It was positive in all cases with hepatic manifestation 17(100%) but not in the case with hemolytic anemia, while in the study done by

Manolaki et al, it contributes to diagnosis in (56.5%) only⁽¹¹⁾.

The mean level of alkaline phosphatase (ALP) in all hepatic cases was 19u/l which is relatively low and provides a clue to the diagnosis of WD as mentioned by some authors, coomb's negative hemolytic anemia with low alkaline phosphatase level in a chronic liver diseases is suggestive of Wilson disease^(8,14,19).

To facilitate a prompt diagnosis of WD in the setting of fulminant hepatic failure, two screening indexes (ALP/TSB< than 2.0) and (AST/ALT) >4.0) were proposed by Berman et al⁽²⁰⁾ in 1991. But there specificity for WD compared to the urinary copper excretion test was shown to be unsatisfactory in a later study done by Sallie et al, in 1992⁽²¹⁾.

Two of the hepatic cases in this study were fulminant hepatitis and ALP/TSB ratio was 3.1 and AST/ALT ratio was 1.7 which fails to indicate the diagnosis which agrees to that recorded by Sallie et al⁽²¹⁾.

Mean prothrombin time at admission for hepatic cases was 22 sec., mean hemoglobin concentration 9.1 g/d, and the mean serum bilirubin 6.2 mg/dl, which was close to the results recorded by Durand et al⁽⁹⁾.

All children were treated with a combination of chelating agents including Penicillamine, Zinc sulfate, Pyridoxine usually added because one of

the side effects of Penicillamine is pyridoxine deficiency and supportive vitamins also given. One patient (4.2%) died during admission with fulminant hepatic failure.

Siblings with elevated liver enzymes were treated with the same treatment as the patient. A recent study done by Mizouchi suggested that zinc monotherapy should be started from time of diagnosis for young pediatric patients with asymptomatic Wilson's disease⁽²²⁾.

The side effects of the drugs were registered during follow up of cases which revealed bone marrow depression in one patient after one month of treatment and low platelet count in 2 cases. All other cases improved through the period of follow up. A study done by Karla et al. found 18/25 improved and the others had different complications like dysarthria, renal tubular acidosis, prolonged persistence of KF rings and osteopenia⁽¹⁷⁾.

The variability's seen between the clinical features and screening tests explain the difficulties of the diagnosis but the family history and the index of suspicion should be taken in consideration in any hepatic or neurological presentations. Detecting a curable disease at an early stage and family screening of all index cases is imperative to avoid future dangerous sequelae.

Table no1: Showing the age & gender distribution of the study group.

Age group	Patient no. 24		Percent %
	Male	Female	
3-5ys	2	2	16.6
5-10ys	10	3	54.1
10-15ys	5	2	29.3
Total	17	7	100

Table no 2: The mode of presentation of Wilson disease in this study.

Mode of presentations	Numbers	Percent %
Hepatic manifestation :		
1. Acute hepatitis	4	16.6
2. Fulminant hepatic failure	3	12.3
3. Chronic liver disease	10	42
Neurological manifestations	2	8.3
Mixed (hepatic & hemolysis)	1	4.2
Asymptomatic siblings	4	16.6
Total	24	100

Table no 3: The mean age of onset in relation to the type of presentations.

Types of presentations	Mean age of onset (yrs)	S.D
Hepatic (17)	7.5	2.59
Neurological (2)	9.2	1.25
Mixed (hepatic & hemolysis) (1)	9	-
Asymptomatic siblings (4)	10.8	4.76

Table no. 4: The time interval between the first symptom and the diagnosis.

Type of presentations	Time interval (days)	Mean (days)	S.D
Hepatic	5-60	42	17.74
Neurological	7-180	95	86.5
Mixed	14	14	-

Table no 5: The results of the diagnostic criterion in different types of presentation.

Type of presentation no. (%)	Low ceruloplasmin no. (5)	KF ring no. (%)	Increase 24 urine copper after challenge no. (%)
Hepatic no. 17 (100%)	12 (70.6)	8 (47.1)	17 (100)
Neurological no.2 (100%)	2 (100)	2 (100)	2 (100)
Mixed no. 1 (100%)	1 (100)	1 (100)	Only two folds increase
Asymptomatic no. 4 (100%)	4 (100)	Negative	4 (100)

Table no 6: The mean biochemical & hematological values in the hepatic cases.

Mean age / yrs (range / yrs)	S.D	Hepatic cases no.	Mean Hb mg/dl	Mean TSB mg/dl	Mean ALT U/L	Mean AST U/L	Mean ALP U/L	Mean PT sec.	Mean PTT sec.
4.5 (3-5)	0.816	3	8.3	10.5	83	95	18.5	15	40
7.9 (5-10)	1.499	11	9.7	5.6	62	99.4	15	25	48
11.5 (10-12)	0.5	3	9.2	2	45	50	24.8	27	46
Mean / total	1.29	17	9.1	6.2	65	83	19	22	45

CONCLUSION:

Acute hepatitis, chronic liver affection, fulminant hepatic encephalopathy acute hemolytic anemia may be the presentation of Wilson disease in children. They also may exhibit a neurological manifestation as tremor and ataxia. At least two of the three diagnostic criterion plus index of suspicion, family history of affected sibling or death in the family of a jaundiced child raises the possibility of WD after exclusion of other chronic liver diseases by investigations.

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