Original Article

A narrative retrospective study of a sample of Iraqi children with Wilson disease

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ABSTRACT

Background: Wilson's disease or hepatolenticular degeneration is a treatable inherited metabolic disease in which copper accumulates in tissues, These are mainly liver and brain . Wilson's disease can be very effectively treated if diagnosed in the proper time, with early appropriate anti copper treatment. **Patients and Methods:** This retrospective study was carried out in the pediatric clinic of the gastroenterology center and the Children Welfare Teaching Hospital /medical city complex, during the period from January 2007 till September 2011. Thirty patients with Wilson disease were studied. Clinical presentations ,laboratory findings ,mode of treatment ,and follow up .**Results:** The mean age for these thirty patients at time of diagnosis was 8.6years ,with age of presentation ranging from 3-15 years .Fifteen of them were above 10 years of age(50%),13 of them were between 5-10 years (43%),and just 2 were below 5 years(7%).Males were 19(63%),females were 11(37%). Hepatic presentation was confirmed in 23 cases out of 30(76.6) ,and 4 patients out of the 30(13.3%) had neurological symptoms while 3(10 %)had both hepatic and neurological(mixed) . Abnormal 24 hours urinary copper excretion was checked in 27(90%), 16 patients(53.3%)showed positive Kayser Fleisher rings, all of them were above 8 years of age, family history was positive in 9 cases (30%). Penicillamine was quite effective treatment , zinc was used alone or in combination with penicillamine **Conclusion:** According to this study, in Wilson disease hepatic insult is the most common presentation in children below 8 years, whereas the neurological manifestations are uncommon in children below 8 years. WD is quite possible in children presenting with acuteor chronic liver disease after excluding other possible causes specially in cases with positive family history.

Keywords: Wilson disease children

Introduction:

Wilson disease (hepatolenticular degeneration) is an autosomal recessive defect(1) in cellular copper transport, with a prevalence of approximately 1 case in 30,000 live births in most populations. An impairment in copper excretion leads to the accumulation of copper in the liver, cornea ,brain, blood... Over time the liver is progressively damaged and eventually becomes cirrhotic.copper accumulation on corneas leads to the Kayser Fleischer Rings ,brain affection leads to different neuropsychological problems.

WD was first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration," a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis(2). In 1993, the abnormal gene in WD was identified(3) ,this gene, ATP7B, encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper within hepatocytes.

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Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease (4,5) with or without neurological manifestations was straight forward if clinical symptoms and signs were associated with elevated level of copper in a 24 hour urine collected sample , KFR on ophthalmological examination, low serum ceruloplasmin level and increased urinary copper excretion. However in patients with hepatic manifestations alone, KF rings are often absent and serum ceruloplasmin may be normal (6).

This study was to spotlight on a group of Iraqi children with WD and evaluate the major clinical , pathologic findings, tools of diagnosis and modes of treatment of WD.

Patient And Methods:

:This retrospective study was conducted on 30 patients with WD, cases were collected from the pediatric clinic department of the gastroenterology center and Children Welfare Teaching Hospital, during the period January 2007 till September 2011. The medical records of all the patients with established diagnosis of WD in the hepatology section, were reviewed ,detailed follow-up data on the course of the disease had been collected. Criteria for the diagnosis of WD was by, measurement of serum ceruloplasmin levels, and determination of 24-hour urinary copper excretion with or without penicillamine challenge, slit lamp examination for KF rings. Abdominal Ultrasonography to asses liver size and texture and splenic size , colored. patients with history of heamatamesis and or melena ,or those with cirrhotic liver on ultrasonic abdominal exam., were subjected to OGD and Doppler study to asses them for signs of portal hypertension. basic workup of chronic liver disease was done to most of patients including viral screen and auto immune markers evaluation, to exclude other causes of chronic liver diseases . Liver biopsy was not performed to any patient(no facility was available to measure copper in dried liver tissue). After establishing the diagnosis, siblings and first-degree relatives were to be screened for WD and actual steps were taken to screen the affected families. Genetic analysis is not available in Iraq.

Results:

Out of the thirty patients, 19 cases (63%) were males and 11 (37%) were females, the age range of the studied group was (3- 15) years with average age of 8.6± 2.46 Regarding the age distribution of the studied sample of patients, cases were divided into 3 age groups .**I**n table 2, WD was , significantly, more prevalent among those who were aged (11-15) years, they were 15 cases out of 30 (50%), rather than among younger age groups. Table 3 shows Mode of presentation and clinical findings of WD in this study: Among the 30 cases ,Hepatic presentation was the most frequent presentation , they were 23 cases (76.6%) , the neurological presentation mode was found in 4 cases (13.3%) , and only 3 cases (10%) presented with mixed presentation(hepatic and neurological). 16 cases (53.3%) were KF ring positive, all of them were above 8 years of age. Number of hepatic presentation cases with positive KFR were 9 patients only, all of them were above 8 years of age. the neurological features were mainly ,speech difficulties , dysphonia, dysartheria, tremors, abnormal choreoathetotic movements Hepatic injury was expressed in different ways; among the 23 cases with pure hepatic findings, jaundice was the most frequent feature ,22 patients out of the 23(95.6%) hepatomegaly with or without splenomegaly was present in 86.9%(2o patients out of 23), on the other hand 2 young female cases (6.6%) presented with jaundice and coomb's negative acute hemolytic anemia. the clinical and lab. findings had been summarized in table (5and 6)respectively.Tools of Diagnosis: It had been found that 24 hrs urine Cu++ was significantly high in 27 patients who were investigated(90%) , while 3 patients were missed to follow and the test was not done ,but the diagnosis in those patients was already settled (presence of the neurological signs and symptoms with the positive KFR)(1). Low Level of Serum creuloplasmin was found in 17 patients out of the 27(62.9%) ,Low serum copper was found in 15 patients out of 27(55.55%).It had been concluded that the 24 hrs urine Cu+ + was the highly sensitive and highly specific diagnostic test with a sensitivity (95%) and specificity of (98%)and the predictive positive value was (90%) as compared to other tests , sensitivity to Serum ceruloplasmin was (62%) and specificity was(70%) , while sensitivity of serum copper was (56%) and specificity (50%) . Neurologic manifestations were mostly seen above 10 years Table (8)shows Family history among studied cases Out of the 30 studied patient, positive family history was present in 9 cases (30%). There was a highly significant correlation between family history and WD.

Outcome of patients:

*Two patients died in hospital ,with hepatic encephalopathy and end stage liver disease.

*Two females patient had hemolytic anemia and passed into fulminant hepatic failure, both survived and kept on penicillamine therapy but lost during follow up.

*Complications of pencillamine was noticed in one female patient who started to show generalized myopathy ,after 3 months period of treatment.
*For the remaining 24 patient out of 30 ,3 patients developed end stage liver disease, and now they are candidates for liver transplantation.
*21 patients out of 24 ,are not fully compliant to treatment and follow up.*screening was done to three families only. Two families were negative ,and the third one is waiting for the result of screening.

Discussion:

Knowing that Wilson disease remains difficult to be diagnosed straight away, We must rely on a constellation of clinical features and laboratory tests rather than on a single one (7). In this study the diagnosis of WD was mainly decided upon the exclusion of other causes of liver insult specially, viruses and immunological causes. In addition to the other criteria of diagnosis ,this criteria involved the low serum ceruloplasmin, raised urinary copper excretion before and after the penicillamine challenge test and the presence of KF rings(8) . The upper age limit for WD in this study was 15 years .In this study the mean age of presentation was (8.6 years),which is similar to Auday's study (9) (in Iraq), in his study the mean age of presentation was (8.5 years), but in comparison to Bushra's study(in Iraq) (10) & F Durand's study (11) , there was no age limit ,in those 2 studies adults were included in the studies. The incidence of male: female in this study was 1.7 :1, this result almost matches with Bushra's study (10) (a male to female ratio 0f 1.5:1) , In Auday's study(9)(a male :female ratio 2:1) and in Farid's Imanzadeh et al study in Iran(12) (a male :female ratio 1.3:1).It is evident in most of the studies mentioned ,that there is a male predominance in WD.

Most of our cases presented with hepatic problems because those cases were referred to our hepatology unit as acute or chronic liver diseases. In this study the mode of hepatic presentation constituted (76.6%) (23 out of the whole 30 cases), which is n early similar to Auday's study (9) 17 case out of 24(70.83%) ,because the taken age groups were near similar in both studies ,and also near similar to Bushra's study(10) 23 cases 0ut of 33(69.69%).

The neurological presenting problems in this study was quite evident in older age group of patients (>8 years),which is nearly similar to Auday's study (9) ,because the studied age groups were near similar in both studies.

The mixed presenting mode (hepatic and neurological) constituted 3 cases (10%), which is nearly similar to Bushra's study(10),the mixed type constituted 4cases(12.12%),while Auday's study(9) was not included in this comparison ,because the mixed type in that study was the combination of the hepatic and hemolytic elements.The presence of KF ring in this study was 53.3% (16 out 0f 30 cases) while in Bushra's study(10),82%(14 out of 17cases) , Farid's Imanzadeh et al study(12) was 91.4 (32 patient out of 35) and Durands study it positive in 100% (11) ,this difference in results is mostly due to the older age groups enrolled in those studies. In this study other hepatic manifestations , especially those of portal hypertension ,e.g. esophageal varices constituted 7(23%) patients ,3 of them with liver cirrhosis ,passed into uncompensated hepatic function ,they are now candidates for liver transplant. Another 4 cirrhotic patients ,have so far compensated liver function. Which makes the total cirrhotic patients only 7(23%). In this study ,the increase in urinary copper excretion was positive in most of cases ,test was done to 27 out of 30 cases(90%) ,while 3 patients were missed to follow up and the test was not performed to them , this result nearly similar to Bushra's study(10), in which(11 out of 13 patients), showed positive results(84.6%),and in Farid's Imanzadeh et al study(12) (97%). S.ceruloplasmin in this study was low in 17 out of 27 patients(62.9%) which agrees with Bushra's study(10) in which it was (66.6%) , and Gow et al study(13) ,the low S. ceruloplasmin level was in most of the cases (75%). Two patients with WD in this study were positive for hepatitis viruses(A,C), co morbidity of WD with viral hepatitis can change the course of the disease into rapidly progressive liver disease ,leading to acute liver failure (14) fortunately both patients survived .

Relation between age & mode of presentation in this study agrees with Auday's study (9) & Bushra's study(10) .

The positive family history in this study was relatively high 30%(9 patients out of 30) , which is similar to Bushra's study(10) 33%(11 out 33 patients),this high family incidence in our studied groups most probably due to the high incidence of consanguineous marriages in our society.

All of Wilson's patients in this study were treated with pencillamine with or without zinc supplementations. one female developed generalized weakness and muscle pains with raised CPK, expressing the myopathic side effect of penicillamine therapy ,it was replaced by zinc supplementation, she improved soon after. while in Brewer GJ et al study(15) ,30 patient were successfully treated with zinc ,which is considered the drug of choice. Penicillamine is usually started to all our patients with diagnosis of WD with or without Zn ,at least for few months to assist rapid CU++ excretion, then Zn therapy continues.

lamp examinations was done 3-6 months after regular penicillamine therapy in 4 patients , KF ring disappeared completely in 3 of them ,and was faintly present in just one , but we can hardly rely on its disappearance as a prognostic value ,KF rings will gradually disappear with effective medical treatment or following liver transplant,

though the rate of disappearance does not correlate with resolution of clinical symptoms(16,17) .The reappearance of either of these ophthalmologic findings(KR rings and sunflower cataracts) in a medically treated patient in whom these had previously disappeared suggests noncompliance with therapy

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Table1.Characteristics of patients with WD by sex

Variable	Characteristic		
Sex	Male	N (%)	19 (63%)
	Female	N (%)	11 (37%)
Age	Mean ± SD		8.6 ± 2.46 years
	Range		3 – 15 year

Table2.Distribution of age of diagnosis of WD

Age group (year)	No. of patients	%
= 5	2	7%
6 - 10	13	43%
11 - 15	15	50%
Total	30	100%

Table (3) Modes of presentation of WD in this study

Presentation	No. Of patient	Percent
Hepatic	23	76.6%
Neurological	4	13.3%
Mixed(hepatic+ Neurological)	3	10%
KF ring	16	53.3%

Table(4) Mode of presentations in the 23 patients with pure hepatic features

Clinical finding	Frequency	%
Jaundice	22	95.6%
Hepatomegaly and or splenomegaly	20	86.9%
Ascitis	17	73.9%
Esophageal varices	7	30.4%
Encephalopathy	5	21.7%
Liver cirrhosis	5	21.7%
Hemolytic anemia	2	8.6%
Spiderangioma	1	4.3%
Gynecomastia	1	4.3%
Plural effusion	1	4.3%
Gall Bladder mass	1	4.3%

Table(5):laboratory investigations results in the 23 patients with hepatic presentations

Lab..results	**Number**	**%**
Elevated liver enzymes	19	82.6%
Prolonged PT	16	69.5%
Hepatitis A virus	1	4.3%
Hepatitis B virus	1	4.3%
Positive immune markers,ANA,lowC3,C4	3	13%
Shrunk liver on U\S exam.	3	13 %
Abnormal OGD finding	6	27%

Table (6) :Investigation for diagnosis(*N*=27)

Screening test	NO.of +ve value	Percent
24hr urine CU++	27	**100%**
S. ceruloplasmin	17	62.9%
S.CU++	15	55.55%

Table(7) :Relation between age and modes of presentation

Age (year)	Hepatic presentation n(%)	Neurological presentation n(%)	Mixed Presentation	Total
0 - 5	2(8.6%)	0	0	2
>5-10	12(52.2%)	0	1(33.3%)	13
>11-15	9(39%)	4(100%)	2(66.7%)	15
Total	23(100%)	4(100%)	3(100%)	30

***T*able (7) shows that younger age groups present with hepatic manifestations**

Table (8).Family history among studied cases

Family history	Number	%
Positive	9	30%
Negative	21	70%
Total	30	100%

Conclusion and recommendations:

1. Hepatic insult is the most common presenting symptom of WD in children below 8 years of age, while neurologic involvement is uncommon before 8 years of age.
2. WD in children should may be obscure and requires extensive investigation to establish the diagnosis(the 24 hour collected urine CU++ estimation with or without challenge is the most reliable investigation, and the most frequently used tool for diagnosis and screening for WD).
3. We should emphasize on that effective treatments are available that will prevent or reverse many manifestations of this disorder.
4. Screening tests for the first degree relatives of patients with WD are mandatory and strongly recommended
5. Genetic study of WD is now accessible in most countries ,highly needed specially for relatives of patients with WD.

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