A clinical study of Wilson’s disease: The experience of a single Egyptian Paediatric Hepatology Unit

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A B S T R A C T

Background and study aims: Most paediatric patients with Wilson’s disease (WD) present with hepatic manifestations, but some may have neurologic or psychiatric features. Our aim was to define the clinical, biochemical features and the outcome of therapy of a group of Egyptian children diagnosed with WD.

Patients and methods: The study was carried out at the Paediatric Hepatology Unit at Cairo University Children’s Hospital, Egypt; 54 patients were diagnosed with WD from 1996 to 2009. The diagnosis was based on low serum ceruloplasmin levels, increased urinary copper concentrations before or after D-penicillamine challenge and/or the presence of Kayser–Fleischer (K–F) rings.

Results: The clinical presentation was as follows: hepatic presentation in 33 patients (61%), hepato-neurologic 3 (5.5%), neurologic 5 (9.3%) and presymptomatic 13 (24%). Increased urinary copper concentrations before or after D-penicillamine challenge was found in all patients, low serum ceruloplasmin in 97% and K–F rings in 31.5%. All patients were treated with penicillamine and zinc sulphate except one presymptomatic case who was treated with zinc sulphate only. Three patients underwent liver transplantation and eight patients died after a median duration of treatment of 6 months (1–36). The hepatic symptoms improved with treatment but the neurological symptoms remained stationary.

Conclusions: Clinical and biochemical assays remain the standard for diagnosis of WD. Penicillamine and zinc therapy can effectively treat WD with hepatic symptoms. Liver transplantation remains life saving for those with fulminant and end stage WD. Screening for presymptomatic sibs is of utmost importance.

Introduction

Wilson’s disease (WD) is an autosomal recessive disorder in which copper pathologically accumulates primarily within the liver and subsequently within the neurologic system and other tissues. The reduced biliary excretion of copper, essential for eliminating excess copper in normal individuals, is the basis for the accumulation of copper within hepatocytes of patients with WD [1]. The specific gene defect lies in the Wilson disease protein, ATP7B, a copper-transporting ATPase that is highly active in hepatocytes [2], with different gene mutations detected [3,4].

WD occurs worldwide with an average prevalence of 1 in 30,000 in the general population [5]. It can present clinically as liver disease, as a progressive neurological disorder or as psychiatric illness. In childhood, hepatic manifestations predominate with a highly variable spectrum ranging from self-limiting hepatitis to fulminant hepatic failure (FHF). Symptomatic patients usually present after 4 years of age with acute hepatitis, FHF, clinical or biochemical signs of chronic liver disease or decompensated cirrhosis [6].

There is no single diagnostic test that can exclude or confirm WD with certainty. Because at present, de novo genetic diagnosis is expensive and not universally available (and sometimes inconclusive), a combination of clinical findings and biochemical testing is usually necessary to establish the diagnosis [7].

WD was uniformly fatal until treatments were developed a half-century ago. Copper chelating agents are effective except in patients with very advanced disease and decompensated cirrhosis.
or with FHF where liver transplantation appears to be the only effective mode of treatment [8].

The aim of the present study was to define the clinical and biochemical features of children with WD presented to the Paediatric Hepatology Unit, Cairo University Paediatric Hospital, Egypt, as well as to describe the characteristics of a presymptomatic group diagnosed by screening. The outcome of the therapy will be outlined.

Patients and methods

We retrospectively reviewed the records of 54 children with WD presented to the Hepatology Unit, Cairo University Paediatric Hospital, Egypt, between 1996 and 2009. Records were reviewed after obtaining ethical committee approval with waiver of the consent. The diagnosis of WD in the probands was based on the presence of liver disease and at least two of the following criteria:

1. positive family history,
2. low serum ceruloplasmin,
3. elevated liver copper (>250 μg/g dry weight),
4. elevated baseline 24-h urinary copper excretion (>60 μg/24 h),
5. elevated 24-h urinary copper excretion following administration of two, 500-mg doses of penicillamine (>1600 μg/24 h),
6. presence of Kayser–Fleischer (KF) rings and
7. Coombs' negative haemolytic anaemia.

Because of the lack of hepatic copper quantification in liver tissue in our centre, liver copper > 250 μg/g dry weight was not among our criteria for diagnosis.

Urinary samples (basal urinary copper and after penicillamine challenge) were collected in an acid washed, plastic metal-free container. Basal 24-h urinary copper was estimated in the patients and this was followed by the penicillamine challenge test (PCT) in which patients ingested 500 mg D-penicillamine at time zero and again at 12 h while 24-h urinary copper collection progressed [9]. Normal values for basal urinary copper were < 60 μg/dl.

Serum ceruloplasmin was measured by nephelometric assay (normal: 20–60 mg/dl). Standard methods were used for liver function tests and other routine laboratory investigations. Percutaneous liver biopsy was performed in eight patients after coagulation abnormalities were corrected. Liver biopsies as a routine diagnostic tool in WD were not frequently performed because of the lack of testing for hepatic copper at our centre.

Cases diagnosed as WD were classified phenotypically according to the following classification by Ferenci et al. [10]:

Hepatic presentation (requires the exclusion of neurological symptoms at the time of diagnosis)
H1: Acute hepatic WD (acutely occurring jaundice in a previously apparently healthy subject).
H2: Chronic hepatic WD (any type of chronic liver disease, with or without symptoms).
Neurological presentation (patients in whom neurological and/or psychiatric symptoms are present at diagnosis)
N1: Associated with symptomatic liver disease.
N2: Not associated with symptomatic liver disease.
NX: Presence or absence of liver disease not investigated.
Other (O).

After the diagnosis was confirmed, siblings were screened for WD by measuring the serum ceruloplasmin level, copper in 24-h urine and KF ring in those above 8 years. The patients were classified as presymptomatic when their diagnosis was established before the onset of any symptoms, during screening of siblings of index cases.

All the patients were initially treated with penicillamine in a dose 20 mg/kg/day in two divided doses given orally on an empty stomach, zinc sulphate 25 mg three times daily for those below 50 kg weight and 50 mg three times daily for those above 50 kg weight, in addition to vitamin E and vitamin B. Chelation was considered adequate if urinary copper levels were between 200–500 μg/24 h. Patients with urinary copper levels below 200 are considered either over-chelated or non-compliant. Non-compliance is heralded by abnormalities of liver function tests. Over-chelated patients were advised to reduce their penicillamine dose. The ultimate goal of treatment was to improve the clinical condition of symptomatic patients and prevent the onset of signs and symptoms in asymptomatic patients. The outcome of therapy was assessed by regular physical examination and laboratory data (blood count, liver function tests, 24-h urinary copper) at intervals varying from 3 to 6 months, depending on the patients’ clinical condition.

During follow up, side effects of therapy were closely monitored by clinical examination for skin rashes and deterioration of neurologic condition and laboratory monitoring including urinalysis, complete blood count and renal functions.

Liver transplantation was considered in patients with FHF or end stage liver disease not responding to medical therapy.

Statistical analysis was performed using the SPSS version 11 programme (SPSS Inc., Chicago, IL). Results were expressed as median (range) and percentage and Kruskal–Wallis test was used for variable comparison.

Results

Among the 54 WD patients 31 (57.4%) were males. Forty-one (76%) were diagnosed as symptomatic index cases and 13 (24%) were presymptomatic cases diagnosed by family screening. Thirty-three of the symptomatic cases (80%) presented with predominantly hepatic symptoms and eight (20%) patients presented with predominantly neurological symptoms. The 54 patients are the offsprings of 38 couples. Fifteen couples (39.5%) were consanguineous. Twenty-six couples had one affected sib, nine couples had two sibs, and two couples had three affected sibs and one couple have four affected sibs. Two couples had more than one symptomatic child; one couple had two symptomatic children and the other had four children. Three patients were first degree cousins. Two patients had a family history of death of a sibling attributable to liver disease of unknown aetiology. Classification of the patients according to Ferenci et al. [10] is shown in Table 1. Clinical and laboratory data of patients with WD at presentation are shown in Table 2.

Data of patients presenting with liver disease [group 1] (n=33)

The median age at diagnosis was 11 years (range: 8–18). Nineteen were males (57.6%). Seven patients (21%) presented with FHF (H1). Five were males. Three died, two underwent liver transplantation and two improved with supportive measure and chelation therapy. The remaining 26 presented with symptoms and signs of chronic liver disease (H2). The presenting manifestations of the disease were as follows: jaundice in 28 (85%) patients, epistaxis in 13 (39%), abdominal pain in nine (27%), abdominal distension in 11 (33%), dark urine in 13 (39%) and ankle oedema in 10 (30%). Serum ceruloplasmin was low in 32 (97%) patients. Basal urinary copper excretion was above 100 μg/24 h in all but one patient; 24-h urinary copper after PCT was below 1000 μg/24 h in five (15%) between 1000 and 1600 μg/24 h in 12 (36.4%) and above 1600 μg/24 h in 16 (48.5%). The mean serum ceruloplasmin level of cases was 8.5 ± 1.2 mg/dl, basal urinary copper excretion...
634 ± 116.4 and 24-h urinary copper after PCT 1691 ± 148.7 μg/24 h. KF rings were detected in 11 (33%) patients. Liver biopsy was performed in six patients; chronic hepatitis with moderate fibrosis was found in three patients and micronodular cirrhosis in the other three (Fig. 1).

Two cases were previously diagnosed as autoimmune hepatitis and received immunosuppression with steroids and showed partial response to therapy. After presentation to our unit, diagnosis of WD was confirmed by low ceruloplasmin and high copper in urine.

**Data of patients presenting with neurological disease [group 2] (n=8)**

The median age at diagnosis was 12.5 years (range: 10–15). Neurological manifestations included expression-less appearance, drooling, tremors, gait disturbance, dysarthria and dystonia. Seven were males. KF rings were detected in five (62.5%). Serum ceruloplasmin was low in all patients. Basal urinary copper was above 100 mg/dl in all cases. MRI of the brain showed abnormal basal ganglia signal intensity consistent with WD in four patients. Five had normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, serum albumin and prothrombin concentration (N2) and three patients had associated liver dysfunction in the form of high transaminase levels (N1).

**Data of presymptomatic cases [group 3] (n=13)**

Screening of 41 brothers and sisters of symptomatic cases yielded 13 presymptomatic sibs (31.7%). The median age at diagnosis was 7 years [range 3–12]; eight were females. At the time of diagnosis, ALT and AST were elevated in five (38.5%), prothrombin concentration < 75% in two (15.4%), whereas alkaline phosphatase and serum albumin were normal in all. The youngest presymptomatic case with elevated transaminases was 3 years old. Serum ceruloplasmin was low in all cases. 24-h urinary copper was above 100 μg/24 h in 11 cases, above 60 μg/24 h in one and below 60 μg/24 h in another case. 24-h urinary copper after PCT was

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**Table 1**

Classification of 54 patients according to Ferenci et al. [10].

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic presentation (requires the exclusion of neurological symptoms at the time of diagnosis)</td>
<td>33</td>
<td>61.1</td>
</tr>
<tr>
<td>H1: Acute hepatic WD (acutely occurring jaundice in a previously apparently healthy subject)</td>
<td>7</td>
<td>13.0</td>
</tr>
<tr>
<td>H2: Chronic hepatic WD (any type of chronic liver disease, with or without symptoms)</td>
<td>26</td>
<td>48.1</td>
</tr>
<tr>
<td>Neurological presentation (patients in whom neurological and/or psychiatric symptoms are present at diagnosis)</td>
<td>8</td>
<td>14.8</td>
</tr>
<tr>
<td>N1: Associated with symptomatic liver disease</td>
<td>3</td>
<td>5.6</td>
</tr>
<tr>
<td>N2: Not associated with symptomatic liver disease</td>
<td>5</td>
<td>9.3</td>
</tr>
<tr>
<td>NX: Presence or absence of liver disease not investigated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other (O)</td>
<td>13</td>
<td>24.1</td>
</tr>
</tbody>
</table>

**Table 2**

Clinical and laboratory data of the 54 patients with WD at presentation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 Hepatic (n = 33)</th>
<th>Group 2 Neurologic (n = 8)</th>
<th>Group 3 presymptomatic (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, year [median (range)]</td>
<td>11 (8–18)</td>
<td>12.5 (10–15)</td>
<td>7 (3–12)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>19/14</td>
<td>7/1</td>
<td>5/8</td>
</tr>
<tr>
<td>Jaundice [n (%)]</td>
<td>28 (85)</td>
<td>1 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatomegaly [n (%)]</td>
<td>21 (63.6)</td>
<td>0</td>
<td>1(7.7)</td>
</tr>
<tr>
<td>Splenomegaly [n (%)]</td>
<td>17 (51.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding [n (%)]</td>
<td>13 (39.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ascites [n (%)]</td>
<td>8 (24)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oedema [n (%)]</td>
<td>10 (30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extrapyramidal signs [n (%)]</td>
<td>0</td>
<td>8 (100)</td>
<td>0</td>
</tr>
<tr>
<td>K–F rings [n (%)]</td>
<td>11 (33)</td>
<td>5 (62.5)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl) [median (range)]</td>
<td>2.9 (0.6–36)</td>
<td>0.75 (0.6–1.2)</td>
<td>0.65 (0.4–0.8)</td>
</tr>
<tr>
<td>AST (IU/L) [median (range)]</td>
<td>112 (41–453)</td>
<td>39 (37–102)</td>
<td>56 (11–256)</td>
</tr>
<tr>
<td>ALT (IU/L) [median (range)]</td>
<td>83 (25–341)</td>
<td>27 (17–124)</td>
<td>68.5 (13–522)</td>
</tr>
<tr>
<td>Alk. Phos. (IU/L) [median (range)]</td>
<td>228 (110–360)</td>
<td>300 (240–359)</td>
<td>238.5 (120–320)</td>
</tr>
<tr>
<td>Serum albumin (g/dl) [median (range)]</td>
<td>2.4 (1.5–4.7)</td>
<td>3.5 (2.1–4.3)</td>
<td>4.15 (3.5–4.5)</td>
</tr>
<tr>
<td>Prothrombin concentration &lt; 75% [n (%)]</td>
<td>25 (75.7)</td>
<td>1 (12.5)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Serum ceruloplasmin (mg/dl) [median (range)]</td>
<td>2.7 (1.4–33)</td>
<td>3.6 (1.6–15)</td>
<td>4.4 (2.1–13.5)</td>
</tr>
<tr>
<td>Basal urinary Cu (μg/24 h) [median (range)]</td>
<td>431 (84–2930)</td>
<td>224 (104–560)</td>
<td>199.5 (55–240)</td>
</tr>
<tr>
<td>Urinary Cu after PCT (μg/24 h) [median (range)]</td>
<td>1600 (440–3584)</td>
<td>975 (307–2068)</td>
<td>1320 (1090–2099)</td>
</tr>
<tr>
<td>Coomb's negative haemolytic anaemia [n (%)]</td>
<td>6 (18.2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk. Phos., Alkaline phosphatase; Cu, Copper; PCT, penicillamine challenge test; K–F, Kayser–Fleischer.

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![Fig. 1. Photomicrograph of a case of a 7-year-old girl with Wilson's disease showing pattern of chronic hepatitis with mild activity associated with portal fibrosis; portal–portal fibrous bridging is seen and the hepatocytes showed focal macrovesicular steatosis (Trichrome stain X200).](image-url)
between 1000 µg/24 h and 1600 µg/24 h in 12 patients and > 2000 µg/24 h in one patient. Liver biopsy was performed in two and revealed chronic hepatitis and minimal fibrosis in both cases.

Comparing the three previous groups, group 1 had a significantly higher AST (p = 0.01); total bilirubin (p = 0.001); basal and post treatment urinary copper (p = 0.001) and (p = 0.05), respectively, and significantly lower serum albumin (p = 0.001) and prothrombin concentration (p = 0.001) than the other groups.

Treatment and outcome

The median duration of chelation was 2 years (range; 1 month to 10 years). Presymptomatic cases were given penicillamine plus zinc sulphate except one case that was given zinc sulphate alone as she was 3 years old and had normal liver functions. Three patients underwent liver transplantation, two for FHF and one for end stage liver disease not responding to chelation therapy. Liver transplantation for fulminant hepatic failure was decided on the basis of the modified King’s college score Dhawan et al.[8]

Eight patients (15%) died after a median duration of treatment of 6 months (range: 1–36 months). Six were hepatic WD and two had neurologic WD.

Currently, 24 patients with hepatic WD are receiving treatment and follow up at our unit. Normalization of liver function tests occurred at a median duration of chelation therapy of 2 years (range: 1–3) in 10 patients. In the remaining patients transaminase levels decreased but are still above the upper limit of normal. Twenty-four hour urinary copper is repeated every 6 months. Four patients had values below 200 µg/24 h with normalized liver functions that indicated over-chelation and penicillamine dose was reduced. In one patient a 24-h urinary copper reached 200 µg/24 h, but with deteriorating liver functions which indicated non-compliance to therapy. The median duration for disappearance of KF rings was 2 years.

Four patients with neurological WD, without hepatic involvement, showed a stationary course and none of them experienced neurological deterioration with penicillamine and zinc therapy. Two patients with neurologic WD and hepatic involvement showed improvement in liver functions on chelation therapy but no neurologic improvement.

Side effects of therapy were closely monitored in treated cases. None developed rash or nephrotoxicity. One patient developed pancytopenia 2 years after initiation of therapy which required dose reduction.

Discussion

WD has a wide spectrum of clinical presentations, but hepatic and neurologic features are the most common, in a high variable degree of severity [11]. In the present study 80% had hepatic involvement; this prevalence is higher than the 65% prevalence reported by Medici et al. [11]. This high prevalence is explained by the age of the studied group, where hepatic manifestations predominate in childhood [6]. Also this cohort was diagnosed and followed up at a Paediatric Hepatology Unit thus it is expected that most of the patients will come for a hepatic complaint.

Some studies [12,13] reported a predominance of males, while other studies [14–16] reported female predominance. Female predominance was reported in relation to FHF [17,18]. High prevalence of acute liver failure was reported in females in the animal model of WD [19]. Sex hormones were suggested to play a role in the aetiology. In our study, at the contrary, males constituted the majority of our patients with FHF (70%). This may be explained by the fact that the majority of our patients with FHF being pre-pubertal.

Establishing the diagnosis of WD may be difficult particularly in children with liver disease. The presence of KF rings and low serum ceruloplasmin are considered sufficient to establish the diagnosis of WD [20,21]. In the present study, the combination of low ceruloplasmin and KF rings was found in only 31.5% of patients. Neither the absence of KF rings nor normal values of serum copper or ceruloplasmin can exclude WD [22–24].

Ceruloplasmin has been shown to have sensitivity and specificity of 82.4% and 94.4%, respectively [9]. In the present study, low serum ceruloplasmin was found in 97%, a figure similar to previous reports [25,26,13]. Dhawan et al. [8] reported normal serum ceruloplasmin in 20% of patients with WD. Using serum ceruloplasmin to identify patients with WD is further complicated by overlap with some heterozygotes. Approximately 20% of heterozygotes have decreased levels of serum ceruloplasmin [7].

KF rings were present in 33% in children presenting with liver disease and in 62.5% in children presenting with neurological presentation in the present study. KF rings are usually absent in children presenting with liver disease [9,27,28], but in patients with neurological presentation they may be absent in only 5% of cases [29,30]. The best diagnostic sign for WD remains the presence of KF rings, however they are not entirely specific for WD, because they can be found in infants with cholestasis [31] and children with AIH [32]. Both conditions can be distinguished from WD on clinical ground.

Another important indicator of the disease is urinary copper excretion. Recent guidelines on WD stressed that finding greater than 100 µg/24 h is typical in symptomatic patients but finding greater than 40 µg/24 h may indicate WD and requires further investigation. The urinary copper excretion after PCT was developed to confirm the diagnosis, and values greater than 1600 µg/24 h are found in patients with WD [7]. In the present study, the PCT gave low values in two presymptomatic cases. This observation may reflect the difficulty in obtaining an accurate 24-h urine collection in young children. Recent re-evaluation of the PTC in children found it valuable for the diagnosis of WD in patients with active liver disease (sensitivity 92%) but poor for excluding the diagnosis in asymptomatic siblings (sensitivity only 46%) [33]. Others have found the predictive value of the 1600 µg/24 h cut-off to be almost 100% [8–34]. Although helpful the test is cumbersome and difficult to perform in severely ill children [8].

Two of our patients had their first presentation mimicking autoimmune hepatitis and they received corticosteroid therapy with partial response. Patients with apparent autoimmune hepatitis presenting in childhood that does not readily respond to therapy, should be assessed carefully for WD because elevated serum immunoglobulins and detectable nonspecific autoantibodies may be found in both condition [35–37]. In some patients concurrent WD and autoimmune hepatitis cannot be excluded [38].

The therapeutic goal in patients with WD is to restore or maintain normal liver function by removal of toxic copper stores in the liver and other sites in the body. This can be accomplished with oral chelating agents. Penicillamine and zinc are the only drugs currently available for WD in Egypt. In the present study, liver functions normalized in 50% with improvement in the remaining patients with mainly hepatic involvement. Iorio et al. [39] were not able to identify a predictive factor for persistent hypertransaminases in patients with WD despite correct treatment and also they could not draw any conclusion regarding genotype and treatment response. Two patients in the present study presenting with FHF responded well to penicillamine. This is in accordance to Durand et al. [40] who suggested that early administration of penicillamine in patients with WD presenting with FHF may lessen the need for transplantation.

Few side effects of chelation therapy were observed in the present study. One patient had to reduce the dose of penicillamine
treatment secondary to pancytopenia. None of our patients with neurological presentation had neurologic deterioration. Merle et al. [16] reported that neurologic worsening occurred on all three treatments used for WD (penicillamine, zinc, trientine) but mainly with penicillamine where 13.8% were adversely affected. On the contrary, Pellecchia et al. [41] found that penicillamine alone or with combination with zinc was effective and safe for neurologically impaired patients. Lorio et al. [42] reported that 13% of their paediatric patients with WD had to discontinue penicillamine treatment secondary to side effects. The largest treatment experience worldwide is still with penicillamine; however, there is now more frequent consideration of trientine for primary therapy. Trientine was reported to be effective in treating WD patients with decompensated neurologic or hepatic diseases [7]. Because it is not available in Egypt, many clinicians lack the experience with its use. Since the first liver transplantation for WD performed in 1968 [43], this treatment can be considered as an effective alternative in the event of unsuccessful medical treatment or if the initial presentation (fulminant hepatitis) precludes proper evaluation of medical treatment [39]. To predict the outcome of fulminant and decompensated chronic WD patients, we used the modified King's college score for our patients [8]. In the present study, three patients underwent liver transplantation, two for FHF and one for end stage liver disease not responding to chemotherapy. In Egypt, the liver transplantation programme is, up to the present, a living donor programme. WD patients were transplanted in our unit from living related donors. The outcome of liver transplantation from heterozygote donors was reported to be equal to that from homozygote normal donors [44].

Because WD is inherited as an autosomal recessive disease, it is very important to screen the families and to investigate for parental consanguinity. In the present study, 12 couples had two or more affected sibs. Thirty-one percent of screened sibs proved to suffer from WD. Our results suggest the importance of family screening for patients with WD. Fifty percent had raised transaminases at the time of screening; the youngest was 3 years old, which agrees with the general concept of suspecting WD in children with liver disease 4 years and above. Chronic hepatitis with minimal fibrosis was already present in liver biopsies of 4- and 7-year-old presymptomatic patients. Manolaki et al. [45] reported fibrosis, inflammation and cirrhosis in 4 months, 23 months and 5 year old presymptomatic patients, respectively, suggesting that serious histological changes may develop in the early stages of the disease. For asymptomatic or presymptomatic patients treatment with penicillamine [46] or with zinc is effective in preventing disease symptoms or progression [47]. In the present study, all pre-symptomatic patients were treated with a combination of penicillamine and zinc except a 3 year old child with normal liver functions who was treated with zinc only.

In conclusion, clinical and biochemical tests, including serum ceruloplasmin levels and urinary copper excretion, and K–F rings remain the standard for diagnosis of WD. Penicillamine and zinc therapy can effectively treat WD with hepatic symptoms. Liver transplantation remains lifesaving for those with fulminant WD. Family screening is very important for early diagnosis and treatment of presymptomatic children. Presymptomatic cases can have abnormal transaminases as early as 3 years of age.

Conflicts of interest

The authors declared that there was no conflict of interest.

References


