Wilson disease: 30-year data on epidemiology, clinical presentation, treatment modalities and disease outcomes from two tertiary Greek centers

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Objective: Wilson disease is a rare genetic disorder of copper metabolism with a wide range of clinical presentations. The aim of this study is to describe the 30-year clinical experience in the management of Wilson disease patients followed at two Greek referral centers.

Methods: A retrospective chart review was performed to identify past and present Wilson disease patients diagnosed during the last 30 years.

Results: Sixty-three patients were included. The median age of diagnosis was 19 (3–59) years, while nine (14%) patients were older than 40 years old. Clinical presentation included asymptomatic liver disease (57.1%), neurological disease (20.6%), overt liver disease (12.7%), acute liver failure (6.3%) and other (3.2%). Kayser–Fleischer rings were detected in 27/62 with a higher frequency in neurologic patients ($P < 0.001$). Ceruloplasmin values were low in 55/63 with significantly lower values in patients with neurological disease ($P = 0.048$) and in cirrhotic patients ($P = 0.017$). Increased 24-hour urine copper was measured in 59/63 patients. D-penicillamine was administered in 56/63 patients (88.8%), followed by trientine (6/63, 9.5%), while one patient needed liver transplantation at baseline. At least one treatment switch was performed in 18 patients. By the end of follow-up, all non-cirrhotic patients (25/25) were stable, 3/23 (13%) cirrhotic developed decompensated liver disease, two developed HCC, three received a liver transplant and two died. Five out of 13 neurologic patients had persisting symptoms despite treatment.

Conclusion: Wilson disease presents with a wide spectrum of clinical manifestations and should be investigated even in older patients, as early diagnosis, close follow-up and treatment monitoring usually provide favorable outcomes. Eur J Gastroenterol Hepatol 32: 1545–1552

Introduction

Wilson disease (WD) is a rare genetic disorder of copper metabolism caused by ATP7B gene mutations located on chromosome 13 and inherited in an autosomal recessive pattern [1–3]. Over 600 mutations related to WD have been described [4] while mutation carrier frequency is estimated to be between 1/25 and 1/31, a proportion higher than initially expected according to recent European studies [5,6]. The disease prevalence rates depend on the geographic area and can reach 2/100 000 [4]. ATP7B is a metalloproteinase located in the trans-Golgi network of hepatocytes and it is responsible for transmembrane copper transfer either by binding copper to ceruloplasmin to be excreted to blood circulation or by direct excretion to bile [1]. When ATP7B function is impaired, excess copper is not efficiently metabolized and thus it accumulates in the liver, central nervous system, cornea and other organs. The clinical complications of copper accumulation vary from asymptomatic liver disease to severe hepatic impairment, neurological manifestations or even psychiatric disorders [1].

Based on the above, WD is a rare clinical entity with a wide spectrum of clinical manifestations that could sometimes elude immediate diagnosis due to limited experience. The aim of this study is to analyze the 30-year data of a relatively large cohort of 63 patients followed at two tertiary Greek centers of referral: Hippokrateio General Hospital of Athens (HGHA) and Department of Medicine and Research Laboratory of Internal Medicine, University Hospital of Larissa (UHL). The geographic distribution of the disease, the heterogeneity of clinical presentation at diagnosis, its correlation to laboratory findings and treatment outcomes will be discussed.

Materials and methods

A retrospective chart review was performed in the outpatient visit files of both HGHA and UHL to identify all past and present patients diagnosed with WD during the last 30 years. Once identified, every chart review was individually studied. The place of birth and the presence of first-degree relatives with a diagnosis of WD were reviewed. Clinical presentation at time of diagnosis including asymptomatic

European Journal of Gastroenterology & Hepatology 2020, 32:1545–1552

Keywords: ceruloplasmin, cirrhosis, Kayser–Fleischer rings, neurologic manifestations, Wilson disease

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Received 1 September 2019 **Accepted** 18 November 2019

disease, the presence and severity of hepatic disease, neurological manifestations or psychiatric disorders were recorded. The diagnosis of cirrhosis was based on a combination of imaging and laboratory findings and biopsy results when available (histological findings were available in 29/63 patients). The differential diagnosis of neurological disease was based on neurological examination, brain MRI findings and the presence of typical neurological symptoms (motor abnormalities with Parkinsonian characteristics of dystonia, hypertonia and rigidity, tremor and dysarthria). The presence of Kayser–Fleischer (KF) rings was also evaluated at first or following visits. Laboratory findings in the initial work-up of each patient as well as ultrasound and biopsy results were reviewed. The administered treatment and every switch during follow-up were recorded. In cases of treatment alteration such as dose reduction or complete discontinuation, the exact cause was noted. The response to treatment, the development of cirrhosis, any event of liver decompensation, the occurrence of hepatocellular cancer (HCC) and orthotopic liver transplantation (OLT) were also documented when encountered in the patients' history. In cases of neurological or psychiatric symptoms related to WD, any improvement or deterioration was recorded until the end of follow-up.

The Leipzig scoring (LS) system which is based on seven clinical, laboratory and genetic parameters (presence of KF rings, neurological symptoms, hemolytic anemia, levels of ceruloplasmin, urinary copper, liver copper and mutation analysis) was evaluated for each identified patient [7]. However, the exact Leipzig score could not be estimated in most of the patients due to the lack of liver copper values and missing mutation analysis. It should be mentioned that the estimation of liver copper was not available until recently and the mutation analysis is not reimbursed in Greece. As a result, only the patients with LS ≥4 based on available parameters were included in the study, while patients with indefinite results (score < 4) or missing data were excluded from the analysis.

For the final analysis, types of WD presentation at diagnosis were divided into three groups: (1) patients with liver disease including asymptomatic transaminase elevation, acute liver failure (ALF), acute liver injury (ALI) and decompensated cirrhosis, (2) neurologic patients including those presenting with at least one WD-related neurological manifestation with or without typical MRI findings and (3) other including the patients with atypical presentation at diagnosis, without the findings that are described in the previous groups. The association between the types of clinical manifestations and serum ceruloplasmin, 24-hour urine copper and serum copper concentrations were based on the non-parametric ranking Kruskal–Wallis test. Serum ceruloplasmin values were compared among cirrhotic and non-cirrhotic patients with nonparametric Mann–Whitney test. The χ^2 test was used for the association of KF rings with neurological disease. Statistical significance was set at $P < 0.05$.

Results

Clinical presentation

The retrospective chart review identified 72 patients with WD diagnosis. Nine patients out of 72 were excluded from the analysis due to LS <4. Of 63 patients (22 males and 41 females) finally included in the study, 23 were followed at UHL and 40 at HGHA. Baseline demographic, clinical and laboratory parameters of the patients are shown in Table 1.

Age at time of diagnosis ranged from 3 to 59 years with a median value of 19 years. The youngest patient diagnosed with WD was a 3-year-old girl from Kalymnos Island who had a family history of WD and had a positive genetic testing (I1148T/R969Q). The girl was asymptomatic, with normal liver enzymes, negative slit-lamp examination, borderline ceruloplasmin value and slightly elevated 24-hour urine copper excretion. On the other hand, the oldest patient presenting with WD diagnosis was a 59-year-old man who was asymptomatic but presented at the outpatient clinic because of abnormal transaminase values. The diagnosis was based on high 24-hour urine copper levels, presence of KF rings and positive mutation analysis (H1069Q/Arg616Gln). His two sons were also later diagnosed with WD. Interestingly, in our study, nine patients (14%) were diagnosed after the age of 40. The median time of follow-up was 185 months (1–466).

Liver dysfunction (symptomatic or asymptomatic) was the most common type of clinical presentation (48/63, 76.2%). Specifically, 23/63 (36.5%) patients were already cirrhotic at time of diagnosis (Fig. 1). The majority of patients who presented with hepatic disease (36/48, 75%) were asymptomatic and were referred to the outpatient clinic due to mild transaminase elevation. Symptomatic liver disease affected 19% of the study population and included ALF in four patients, ALI in two and decompensated cirrhosis in six patients (Fig. 1). Interestingly, two out of six patients with decompensated cirrhosis were older than 40 years at diagnosis ($P = 0.352$). Twenty patients (32%) presented with transaminase levels higher than two times upper normal limit (>2 × UNL) and 19 patients (30%) had elevated alkaline phosphatase levels. Ultrasound examination (U/S) at baseline visit revealed increased liver echogenicity indicative of liver steatosis in 11 out of 59 (19%) patients with available results. Splenomegaly and ascites were present in 17 (29%) and five patients (8%), respectively.

The second most common type of clinical presentation at diagnosis was neurological disease manifested as tremor, ataxia or speech disorder which was reported in 13 out of 63 patients (20.6%). Ten patients (15.8%) reported psychiatric symptoms including mainly depression and

Table 1. Baseline patient characteristics

Male sex (%)	22 (34.9%)
Age (median, range) (years)	19 (3–59)
Clinical presentation	
Liver disease, n (%)	48 (76.2%)
Asymptomatic	36 (57.1%)
Overt liver disease	8 (12.7%)
Acute hepatic failure	4 (6.3%)
Neurological disease, n (%)	13 (20.6%)
Neurologic and liver disease, n (%)	5 (8%)
Hemolysis, n (%)	1 (1.6%)
Arthralgias, n (%)	1 (1.6%)
Positive KF rings, n (%)	27/62 (43.5%)
Increased transaminase levels, n (%)	53 (84%)
Increased total bilirubin, n (%)	15 (24%)
Low serum ceruloplasmin (<20 mg/dl), n (%)	55 (87.3%)
High 24-hour urine copper (>40 μg/24 hour), n (%)	59 (93.6%)

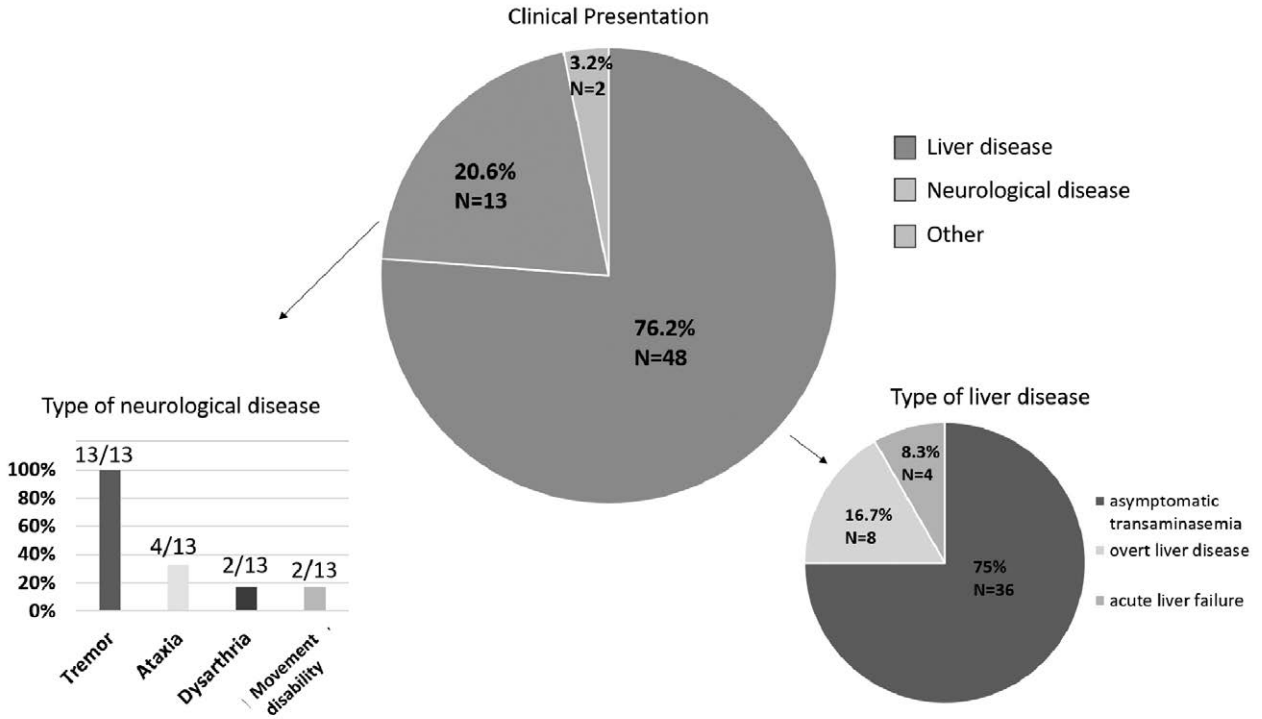

Fig. 1. Types of clinical presentation at diagnosis and subtypes of liver and neurological disease.

Table 2. Patient characteristics according to clinical presentation

Presenting symptom	Liver disease (n = 48)	Neurologic disease (n = 13)	Other[a] (n = 2)	Total (n = 63)	*P* value
KF rings, N (%)	14 (29.8)	11 (84.6)	2 (100)	27 (42.8)	<0.001
Ceruloplasmin mg/dl, median (range) (normal: >20 mg/dl)	14.1 (0.5–32)	10 (1–17)	11 (8–14)	13 (0.5–32)	0.048
24-hour-urine copper μg/24 hour, median (range) (normal < 40 μg/24 hour)	208 (20–1838)	389 (98–1216)	N/A	268 (20–1838)	0.08
Serum copper (μg/dl), median (range) (normal: 70–140 μg/dl)	67 (9–235)	43 (17–184)	41	57 (9–235)	0.506
Free serum copper (μg/dl), median (range) (normal: <20 μg/dl)	26 (1–232)	17.5 (1–181)	17	28 (1–232)	0.755

P values are based on comparisons between presentation groups using the χ^2 test for KF rings and Kruskal–Wallis test.
KF, Kayser–Fleischer; N/A, not available.
[a]Hemolytic anemia, arthralgias.

episodes of panic attack. Simultaneous presentation of hepatic and neurological disease was presented in 5/63 (8%) of patients at initial visit (these patients are included in the group of neurological disease). Other types of WD clinical presentation included one patient who presented with acute hemolysis and one with arthralgias. Both patients had a positive family history of WD and were referred to the outpatient clinic in order to exclude WD diagnosis. Further examination of their medical history revealed occasionally abnormal liver enzymes in the past. Their ceruloplasmin value was tested and found to be low, while the slit-lamp examination for KF was positive for both (Table 2). There was no correlation between the type of WD clinical presentation and the patients' age or detected mutations.

Mutation analysis

The geographic distribution of Greek patients diagnosed with WD is depicted in Fig. 2. All patients were Greek apart from two patients from Albania and one from Bulgaria. The Bulgarian patient had a positive mutation analysis (H1069Q/Arg616Gln), whereas among the two Albanian patients only one was tested and proved to be negative for any mutation. Genetic analysis was available in 37 patients of whom 30 (81%) were positive for ATP7B gene mutations. Nine patients were homozygotes for the following mutated alleles: one patient homozygous for c3252delA, one patient for X1466Arg, three for H1069, three for I1148T and one for R969Q (Table 3). Eighteen patients were compound heterozygotes and three patients had only one abnormal allele (single heterozygotes). Interestingly, seven patients were negative for any known mutation (wild-type mutations). In total, the most common mutation of the *ATP7B* gene in the study population was H1069Q (16/74, 21.6%), followed by I1148T (8/74, 10.8%) (Fig. 3). There was no association between the geographic origin of the patients and the detected mutations.

Kayser–Fleischer rings

KF rings were detected in 27 patients out of 62 patients (43.5%) with available slit-lamp examination results (Table 2). Presence of KF rings at diagnosis was found in 29.8% of patients with hepatic disease and in 84.6% of patients with neurological disease ($P < 0.001$).

Fig. 2. Geographic distribution of the study population. The areas with the higher numbers of patients are marked on the map.

Table 3. Mutation analysis per patient

Mutated alleles	Number of patients
Homozygotes	
c3252delA/c3252delA	N = 1
X1466Arg/X1466Arg	N = 1
H1069Q/H1069Q	N = 3
I1148T/I1148T	N = 3
R969Q/R969Q	N = 1
Compound heterozygotes	
H1069Q/Arg616Gln	N = 2
H1069Q/G943S	N = 1
H1069Q/c3252delA	N = 2
X1466Arg/Ile1230Threo	N = 2
H1069Q/X1466Arg	N = 1
GLY943Ser/MET665Ile	N = 1
845delT/G943S	N = 1
I1148T/R969Q	N = 1
H1069Q/R969Q	N = 3
X(ter)1466R/G943S	N = 1
1708-1G/I1148T	N = 1
X1466Arg/R969Q	N = 1
c3252delA/G943S	N = 1
Single heterozygotes	
M665I	N = 2
N1128Y	N = 1

Ceruloplasmin

In terms of laboratory findings, the median ceruloplasmin value at diagnosis was 13 mg/dl (range from 0.5 to 32 mg/dl) (Table 2). In 23 patients (36.5%), ceruloplasmin levels were below 10 mg/dl, a finding that increases significantly the possibility of WD diagnosis, while eight out of 63 patients (13%) had normal ceruloplasmin levels (>20 mg/dl). Importantly, all patients with normal ceruloplasmin levels were asymptomatic (P = 0.009), young adults or children (age <20 years) presenting with mild elevation of aminotransferases. Mean ceruloplasmin levels were significantly lower in patients with neurological symptoms when compared to patients without such symptoms (10 mg/dl vs. 14.1 mg/dl, P = 0.048, respectively) (Table 2). Furthermore, mean ceruloplasmin levels at baseline visit were significantly lower in cirrhotic patients versus patients without cirrhosis (9.34 mg/dl vs. 16.69 mg/dl, P = 0.017, respectively).

Twenty-four-hour urine copper levels

Median 24-hour urine copper levels at baseline were 268 μg/24 h (range from 20 to 1838 μg/24 h). Four asymptomatic patients (one child and three adults) had normal urine copper pre-treatment levels (<40 μg/24 h) but all had a positive D-penicillamine challenge test later. Interestingly, urine copper levels tended to be higher in patients with neurological disease at diagnosis when compared to other patient groups (389 vs. 208 μg/24 h, P = 0.08, respectively, Table 2). On the other hand, there was no difference between cirrhotic and non-cirrhotic patients (P = 0.965). Finally, the levels of 24-hour urine copper did not differ significantly between patients with asymptomatic vs. symptomatic liver disease (P = 0.761).

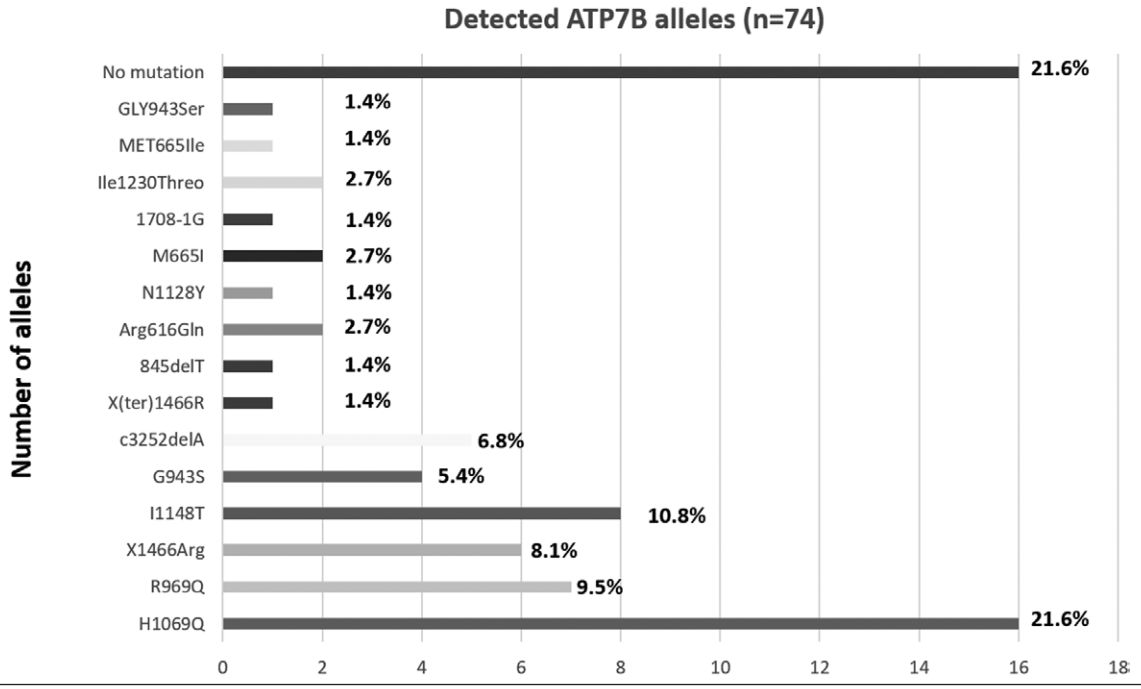

Fig. 3. Detected alleles in Wilson disease patients with available, positive mutation analysis.

Serum copper levels

Pre-treatment serum copper values were available in 29 patients with a reported median value of 57 μg/dl (range from 9 to 235 μg/dl), of whom 16/29 (55%) had lower than normal values (<70 μg/dl), 11/29 (38%) had levels within the normal range (70–140 μg/dl) and only 2/29 (6.9%) patients had higher than normal values. There was no correlation between serum copper levels and ceruloplasmin levels in the study population. Mean serum copper values at diagnosis did not differ significantly between WD patients with liver disease and patients with neurological manifestations. The presence of cirrhosis did not affect serum copper levels either (P = 0.440). On the other hand, the median value of free serum copper was 28 μg/dl (1–232 μg/dl), while 20/29 (69.9%) patients had higher than normal (>20 μg/dl) values.

Treatment

D-penicillamine was the preferred treatment for the newly diagnosed WD patients. Specifically, 56 out of 63 patients (88.8%) received D-penicillamine as first-line therapy, six patients received trientine (9.5%) and one patient was submitted to OLT due to ALF at the time of WD diagnosis. All patients who received trientine as initial treatment were asymptomatic without cirrhosis, except for one patient with psychosis and neurological disease. Zinc, which is also an approved therapeutic option for WD, was not administered to any patient as first-line treatment.

At time of last follow-up, two additional patients had received a liver transplant, 40/63 (63.4%) patients were under D-penicillamine treatment, 14/63 (22.2%) under trientine and 6/63 (9.5%) received zinc, all as monotherapy. At least one treatment switch had been performed in 18/63 (28.6%) WD patients: 12 patients switched from D-penicillamine to trientine, four from trientine to zinc and two from D-penicillamine to zinc. Two sequential treatment switches (D-penicillamine to trientine and then switch to zinc) were reported in 4/63 (6.3%). All treatment changes were made due to reported side effects (Table 4). Of the patients that were initially treated with D-penicillamine, 25/56 (44.6%) presented with at least one side effect that led either to dose reduction or discontinuation. The most frequent side effects of D-penicillamine therapy were proteinuria (21%), skin toxicity (21%) and arthralgias (17%). Depression and vitiligo were also reported in one patient under treatment with D-penicillamine. Switching from D-penicillamine to trientine led to symptom recession in all the cases except for two patients with arthralgias who were later treated with zinc. Moreover, skin rash was reported in one patient that received trientine and was later switched to zinc, resulting in symptom recession. In patients that received zinc treatment, no adverse events were reported apart from mild gastrointestinal discomfort.

Table 4. Reasons for treatment change

Adverse event	N (%)
Proteinuria	7 (38.9)
Skin toxicity[a]	5 (27.8)
Proteinuria and skin toxicity	3 (16.7)
Arthralgias	2 (11.1)
Vitiligo and depression	1 (5.6)
Total	18 (100)

[a]All treatment switches relate to D-penicillamine treatment apart from 4 patients with skin toxicity under trientine treatment.

Disease outcome

In terms of hepatic disease, all non-cirrhotic patients (25/25) patients normalized their liver enzyme values within 1 year of diagnosis and maintained normal liver function under treatment. Among 23 patients with compensated cirrhosis at presentation, four progressed to decompensation and one of them developed HCC despite

treatment initiation. These patients were included to the waiting list for liver transplant, but one of them died due to end-stage liver disease. Of six patients presenting with hepatic decompensation at baseline visit (five with ascites and one with variceal bleeding), five are still alive; two of them underwent liver transplantation within the first year after WD diagnosis due to development of acute on chronic liver failure (currently alive at 15th and 16th year post-OLT), three patients have returned to compensated disease, although one of them has developed HCC at 7th year post-diagnosis and entered the waiting list for OLT. Finally, the patient who received a liver transplant due to ALF is still alive under immunosuppressive treatment, 23 years after the transplantation.

Among 13 patients with neurological disorders at presentation, three patients (23%) responded completely to treatment, five (38.4%) improved without total remission and five (38.4%) had ongoing symptoms despite treatment. There was one case of neurological symptoms deterioration in a patient who started treatment with D-penicillamine. He was switched to trientine, but the symptoms did not improve. Among patients without neurological disease at baseline, two patients developed symptoms (tremor and ataxia) while on treatment. There was no association between the patients' laboratory findings (ceruloplasmin, urine copper) and the treatment response in terms of neurological symptoms.

Discussion

Our study summarizes the 30-year experience from diagnosis to latest follow-up visit in a total of 63 WD patients. Interestingly, there was a wide range in the age of diagnosis. Specifically, 14% of the study population was diagnosed after the age of 40. Nevertheless, these patients did not differ significantly from younger patients in terms of baseline characteristics, treatment tolerability and therapeutic outcome. However, two out of eight patients presenting with decompensated cirrhosis at diagnosis belonged to this group, indicating that a delay in diagnosis may lead to severe deterioration of liver function. It has been already reported that 6% of patients diagnosed with WD are older than 40 years old [4,11]. These findings further support the inclusion of WD in the differential diagnosis of patients presenting with abnormal liver enzymes, neurological disease or cirrhosis regardless of age [4,11].

All patients were Caucasian and resided in different areas of Greece. It should be mentioned that 10 patients of the study population were born in Kalymnos Island where a high prevalence of WD has been already reported [8]. A similar observation has been reported in the island of Crete, although only three Cretan patients were included in our study [9].

Furthermore, the mutation analysis of the study population has confirmed previous observations that H1069Q is the most common mutation in Caucasian populations and specifically more frequent in Greek WD patients [9,10,12]. However, It should be noted that a mutation analysis was not performed in 37/63 patients, mainly due to the fact that WD diagnosis was established without the need of genetic testing. Additionally, it is a costly examination which is not currently reimbursed in Greece. Seven patients with definite WD diagnosis (Leipzig score >4) were negative for the usual *ATP7* gene mutations and three patients were single heterozygotes. There is growing evidence that molecular results should be interpreted always in combination with clinical and laboratory findings to confirm diagnosis. The existence of unknown mutations must be taken into consideration especially in cases when the genetic testing is negative. Additionally, heterozygous carriers may also present with severe disease due to coexistent modifier genes that impair copper excretion [13].

According to our study, the most frequent type of clinical presentation of WD was asymptomatic liver disease in the form of elevated liver enzymes. This type of WD presentation has been also described as the most frequent in other cohorts from Europe, Canada and Asia [14–16]. A significant proportion of patients (36.5%) were already cirrhotic at time of diagnosis. These patients had mild transaminasemia in previous blood exams, but were not tested specifically for WD. On the contrary, neurological disease was relatively rare in our cohort when compared with previous studies [16]. Fifteen patients in total exhibited neurological symptoms of whom 13 (84.6%) were positive for KF rings in the slit lamp examination. KF rings are a traditional finding in neurologic WD, although in a minority of patients they may be absent [17].Based on the above, a negative slit-lamp examination should not exclude the diagnosis of WD especially in patients with liver disease without any neurological symptom.

Diagnostic biomarkers such as serum ceruloplasmin and 24-hour urine copper may be quite useful for establishing WD diagnosis. However, in our study, 13 and 6% of patients had normal baseline ceruloplasmin values and urine copper levels respectively. Serum ceruloplasmin may increase in cases of inflammation such as acute hepatitis [18] or in cases of hyperestrogenemia such as pregnancy and contraceptive treatment [23]. This increase could cause a false-negative result. In our study population, normal ceruloplasmin values were detected only in young asymptomatic patients (<20 years old) with mild transaminasemia. Normal ceruloplasmin levels have been previously described in 15–36% of children with WD [22]. On the other hand, lower median ceruloplasmin values were found in cirrhotic patients. This could be explained by the fact that ceruloplasmin is normally produced in the liver and thus, the development of cirrhosis could affect its production [19,20]. Moreover, 24-hour urine copper has been reported to be normal in 13–26% of WD patients at diagnosis and especially in children and asymptomatic patients who are tested due to family history of WD [21,22]. In case of high clinical suspicion of WD, the D-penicillamine challenge test may facilitate WD diagnosis as showed in four asymptomatic patients of our study. Nevertheless, a negative D-penicillamine challenge cannot exclude WD diagnosis [23]. Finally, serum copper was found to be lower than normal in most of the patients in our cohort, a finding that has been associated to the decrease of circulating ceruloplasmin [23]. High serum copper values have been reported in cases of ALF in WD, although this was not observed in our cohort [23]. In general, serum copper is not considered to be a valid diagnostic marker for WD and it is not included in the Leipzig score [23]. In contrast to total serum copper, 'free serum copper' was found to be higher than normal in 68.9% of the patients. The calculation of 'free copper' (3.18 × ceruloplasmin subtracted

from total serum copper), which represents non-ceruloplasmin-bound copper, may be helpful for WD diagnosis and assessment of treatment efficacy, although it is often dependent on the accuracy of laboratory methods that are used for copper and ceruloplasmin measurements [23]. Finally, ALP values were normal in 70% of our patients, a finding which is consistent with the previous observations of low ALP activity in WD patients and particularly in cases of ALF [23]. Specifically, according to existing data, an ALP to total bilirubin ratio <4 may yield a sensitivity up to 94% for the diagnosis of ALF in WD [23].

Considering the treatment trends of WD in Greece, D-penicillamine was the prevalent choice of treatment for newly diagnosed patients (88.8%) in our cohort. Chelating agents (D-penicillamine and trientine) are recommended by European Guidelines as first-line treatment to achieve induction of response, while Zinc can be used in patients with neurological symptoms [23]. D-penicillamine, trientine and zinc are reimbursed for the treatment of WD in Greece. The fact that our study included patients who were diagnosed in the last 30 years could explain the high proportion of D-penicillamine-treated patients. Among 56 patients who received D-penicillamine as initial therapy, 25 patients (44.6%) reported side-effects of whom 11 patients received a lower dose and 14 patients were eventually switched to other treatments. This reflects the current trend of WD maintenance treatment either with trientine or zinc monotherapy in order to avoid D-penicillamine undesired effects [16,24]. In fact, according to a recent Canadian study, an even higher proportion of patients (41%) who received D-penicillamine experienced at least one side-effect (mainly skin rash and proteinuria) and 64.5% were switched to other treatments during follow-up [16]. According to our clinical experience, the available treatments for WD are adequately effective and safe. The management of the frequent adverse effects is the main challenge, especially when it leads to poor patients' compliance. Based on the above, an approach to optimize therapeutic outcomes is to apply a close patient follow-up, monitor treatment response and identify adverse effects as early as possible. The timely adjustment of the prescribed dose especially for D-penicillamine, or the switch to other available treatments is frequently required. Additionally, since trientine causes significantly lower side effects, it could be advisable to use it as a first-line treatment especially in non-cirrhotic, asymptomatic patients.

Newer chelators such as tetrathiomolybdate ammonium are currently under investigation and could provide additional options in cases of drug toxicity [4]. Moreover, gene therapy via HIV-derived lentiviral vectors may restore copper metabolism at an early stage, before the establishment of liver or neurological disease [4]. Further studies are needed to confirm the initial, promising results of this therapeutic approach.

Initiation of treatment led to favorable outcomes in most of the patients in our study. It has been reported that treatment with chelating agents is quite effective in the majority of WD patients and may reverse the liver injury and restore the synthetic function within the first 6 months of therapy [25,26]. Even so, the patients with cirrhosis at presentation should be closely monitored for signs of hepatic decompensation and for the development of HCC. As observed in our study, 4/23 (17.3%) cirrhotic patients progressed to decompensated disease despite initiation of treatment and one of them developed HCC. A similar observation was reported in a French cohort [30], where liver disease progressed in 8/249 (3.2%) patients despite chelation treatment. This raises the issue of multifactorial causation of decompensation such as advanced liver disease, presence of comorbidities and compliance to diet and chelation therapy. In cases of advanced liver disease, acute hepatic failure or hepatic decompensation at diagnosis, OLT is the mainstay of therapy to prolong life expectancy [27]. Severe deterioration of neurological disease has been also suggested as an indication for OLT [28]. However, neurological disease remains a challenge in the treatment of WD patients. In our study, 38.4% of neurologic patients had no significant improvement of their symptoms despite treatment, while two patients developed neurological symptoms following initiation of therapy. Worsening of neurological disease at treatment initiation and inadequate response to therapy has been attributed to abrupt copper mobilization and low intracerebral chelating efficiency, respectively [29].

Conclusion

In this retrospective chart review study, we depict the 30-year clinical experience of two tertiary Greek centers on the management of WD patients and provide some useful examples of the challenges in WD diagnosis and treatment. Despite their great range and diversity, the patients' clinical manifestations, laboratory findings and genetic profiles were combined to establish a definite WD diagnosis. The availability of efficient treatments and the securing of proper compliance in the study population rendered positive disease outcomes except for a minority of patients with persisting neurological symptoms. Close patient monitoring and lifelong treatment are essential to minimize WD complications.

Acknowledgements

No financial support was provided for this study.

Conflicts of interest

There are no conflicts of interest.

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