ORIGINAL PAPERS

Wilson's Disease: a Challenge of Diagnosis. The 5-Year Experience of a Tertiary Centre

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Abstract

Background. Because molecular diagnosis is considered impractical and no patognomonic features have been described, diagnosis of Wilson's disease (WD) using clinical and biochemical findings is still challenging.

Patients and method. We analysed predictive factors for the diagnosis in 55 patients with WD diagnosed in our centre between 1st January 1999 and 1st April 2004. All patients presented predominant liver disease classified as: 1) asymptomatic, found incidentally, 2) chronic hepatitis or cirrhosis, or 3) fulminant hepatic failure. Diagnosis was considered as classic (two out of the three following criteria: 1) serum ceruloplasmin < 20 mg/dl, 2) the presence of Kayser-Fleischer rings and/or 3) hepatic copper >250 mg/g dry weight liver tissue), and non-classic (clinical manifestations plus laboratory parameters suggesting impaired copper metabolism). The association between the predictive factors and non-classic diagnosis was assessed based on the level of statistical significance (p value<0.05) associated with the chi-squared test in contingency tables. Multivariate analysis was performed by logistic regression using SPSS 10.

Results. There were 31 males (56.3%) and 24 females (43.7%) with the mean age at diagnosis of 20.92 ± 9.97 years (4-52 years); 51 patients (92.7%) were younger than 40 years. Asymptomatic WD was diagnosed in 14 patients (25.4%), chronic liver disease due to WD in 29 patients (52.8%) and fulminant hepatic failure in 12 patients (21.8%). The classic diagnosis was made in 32 patients (58.18%). In the univariate analysis the non-classic diagnosis was associated with: age>18 years (p=0.03), increased copper excretion (p<0.0001), Coombs-negative hemolysis (p=0.03), absence of neurological manifestations (p<0.0001). Multivariate analysis identified age over 18 years, increased urinary copper, and isolated hepatic involvement as independent predictors.

Conclusion. In clinical practice, WD should be considered also in patients who do not fulfil classic criteria. Independent factors associated with non-classic diagnosis were age over 18 years, increased cupruresis and isolated liver disease.

Key words

Wilson's disease – diagnosis - ceruloplasmin - Kayser-Fleischer ring

Rezumat

Introducere. Deoarece disponibilitatea şi eficienţa diagnosticului molecular este limitată, în practica medicală curentă diagnosticul bolii Wilson este fundamentat pe combinaţia dintre o serie de criterii clinice şi biochimice.

Scop şi metodologie de studiu. Am analizat factorii predictivi pentru diagnostic în cazul a 55 de pacienţi cu boală Wilson diagnosticaţi în centrul nostru între 1 ianuarie 1999 şi 1 aprilie 2004. Toti pacienţii au prezentat afectare hepatică predominantă, clasificată ca: 1) asimptomatică, descoperită incidental, 2) hepatită cronică/ciroză sau 3) insuficienţă hepatică fulminantă. Diagnosticul clasic a fost fundamentat pe existenţa a două din următoarele trei criterii: 1) ceruloplasmina serică < 20 mg/dl, 2) prezenţa inelului cornean Kayser-Fleischer şi/sau 3) concentraţia de cupru >250 mg/g ţesut hepatic uscat. Diagnosticul non-clasic s-a realizat pe baza manifestărilor clinice evocatoare asociate cu modificări paraclinice sugestive pentru anomalii ale metabolismului cuprului. Asocierea dintre factorii predictivi analizaţi şi diagnosticul non-clasic a fost evaluată pe baza nivelului de semnificaţie statistică (p<0.05) asociat cu testul chi[2] în tabele de contingenţă. Analiza multivariată a fost efectaută prin regresie logistică utilizând SPSS 10.

Rezultate. Au fost detectaţi 31 de bărbaţi (56,3%) şi 24 de femei (43,7%) cu vârsta medie la diagnostic de 20,92 ±

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9,97 ani (4-52 ani); 51 de pacienți (92,7%) au avut sub 40 de ani. Boala Wilson asimptomatică a fost diagnosticată la 14 pacienți (25,4%), hepatita cronică sau ciroza hepatică la 29 de pacienți (52,8%), iar insuficiența hepatică fulminantă la 12 pacienți (21,8%). Diagnosticul clasic a fost formulat la 32 pacienți (58,18%). În analiza univariată diagnosticul non-classic s-a asociat cu vârsta>18 ani (p=0,03), excreția crescută de cupru (p<0,0001), anemia hemolitică Coombs-negativă (p=0,03), absența manifestărilor neurologice (p<0,0001). Analiza multivariată a identificat următorii parametri independenți predictivi pentru diagnostic: vârstă > 18 ani, excreția excesivă de cupru şi afectarea hepatică izolată.

Concluzie. În practică, diagnosticul de boală Wilson trebuie considerat şi în cazul pacienților care nu îndeplinesc criteriile clasice. Factorii independenți asociați cu diagnosticul non-clasic sunt vârsta peste 18 ani, creştera cupruriei şi afectarea hepatică izolată.

Background and aim

Wilson's disease (WD) is an autosomal recessive condition which occurs worldwide with an average prevalence of 1:30,000 population (1). In 1993 the WD gene (known as *WND* gene) was identified and cloned (2-5). Also referred as *ATP7B* gene, it encodes a metal-transporting P-type ATP-ase, which is expressed mainly in hepatocytes and functions as a transmembrane transporter of copper coupled with ceruloplasmin synthesis and biliary copper excretion. Absence or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into the bile resulting in hepatic copper accumulation and injury, as well as copper deposits and damage of other organs, notably the brain, cornea, and kidney (6). This may explain, in part, the clinical heterogeneity of the disease (7). Molecular analysis of the *ATP7B* gene in patients with WD has detected more than 200 distinct mutations (8). Although due to the large coding region of the *ATP7B* gene and the extreme diversity of mutations, molecular diagnosis of WD based on DNA studies is not routinely performed (9), studies in patients homozygous for specific alleles have shown little correlation between an individual mutation and clinical or laboratory features of the disease, age of onset, or disease severity (8,10). Taken all these data together, genetic detection of WD is considered impractical and clinicians still have to base their current diagnosis of WD on clinical and laboratory features.

Classic diagnosis of WD is usually based on typical hepatic and/or neurological manifestations, demonstration of corneal Kayser-Fleischer rings, serum ceruloplasmin level less than 20 mg/dl, and hepatic copper content greater than 250 mg/g dry weight liver tissue (11). Establishing the diagnosis of WD is difficult in some patients due to the non-classical pattern of disease presentation and the absence of patognomonic features.

We present our experience in 55 patients with WD hospitalized over the last 5 years in our centre, analysing disease presentation, difficulties involving the diagnosis (classic vs non-classic), as well as the predictive value of different clinical and laboratory features for the non-classic diagnosis of WD.

Subjects and methods

Demographic, clinical and laboratory data at diagnosis were obtained from the review of the records of patients with WD hospitalized at the centre of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest between 1st January 1999 and 1st April 2004. Our centre is a tertiary referral academic institution, part of the health care system in Romania, ensuring assistance of gastroenterology and hepatology for patients from Southern Romania (population of approximately five million). We represent the only centre for liver transplantation in our country (population of approximately 21 million), caring for many patients with WD awaiting for liver transplantation. The liver transplantation program was succesfully initiated in our institution in January 2000.

All patients in our study were admitted for liver disease with or without neurologic or psychiatric disorders, Coombs-negative hemolysis or other extrahepatic manifestations of WD. The spectrum of liver disease comprised: 1) asymptomatic liver disease found incidentally (elevated aminotransferases, isolated hepatomegaly and/or splenomegaly), 2) chronic liver disease (hepatitis or cirrhosis) or 3) fulminant hepatic failure. The classic diagnosis of WD according to Sternlieb (11) was based on the presence of at least two out of the three following criteria: 1) serum ceruloplasmin level < 20 mg/dl and/or 2) presence of Kayser-Fleischer rings by slit lamp examination and/or 3) hepatic copper content > 250 mg/g dry weight liver tissue in the presence of hepatic and/or neurological clinical manifestations consistent with WD. In patients who did not fulfil these criteria, the non-classic diagnosis of WD was based on clinical manifestations in conjunction with various laboratory parameters suggesting impaired copper metabolism (9): low serum ceruloplasmin levels, increased urinary copper excretion (usually > 100mg/24h), serum copper level < 60 mg/dl, hepatic copper content > 250 mg/g dry weight liver tissue, favourable response to D-penicillamine, and absence of other etiology of liver injury.

At diagnosis, all patients underwent a slit-lamp ophtalmologic examination in order to detect Kayser-Fleischer rings, as well as a neurological examination. Serum ceruloplasmin level was measured by immunoprecipitation (normal range 30-50 mg/dl). The 24-hour urinary excretion of copper and the total serum copper were measured by standard methodology.

When not contraindicated, liver biopsy was obtained (19 patients) before the initiation of the treatment in order to detect histological changes compatible with WD (micro- and macrovesicular steatosis, ballooned hepatocytes, glycogenated nuclei, focal hepatocellular necrosis, piecemeal necrosis, fibrosis and cirrhosis) and to assay the copper content in liver tissue by absorption spectroscopy (8 patients) (normal<50 mg/g dry weight liver tissue). Echo-guided liver biopsies were performed by the Menghini technique using a disposable Autovac device (Bard Inc., angiomed GmBH & Co. Medizintechnik KG). Molecular analysis for the His1069Gln mutation of the WD gene by polymerase chain reaction (PCR) was available in five patients.

Most patients received therapy with D-penicillamine with/without zinc salts and regular supplementation with pyridoxine. Four patients received trientine due to the side effects to D-penicillamine. Response to chelator therapy was defined as increasing in urinary copper excretion at least twice after two weeks. Orthotopic and living-donor liver transplantation was offered to patients with fulminant hepatic failure, as well as to patients with chronic decompensated liver disease.

The study methodology was approved by the local Ethical Committee of the Fundeni Clinical Institute.

Statistical analysis

Continuous data were expressed as means ± SD. Categorical data were expressed as number of subjects or proportion of the subjects with a specific condition or clinical feature. Chi-square test or Fisher's exact test, when appropriate, were used to compare categorical data. In order to identify the independent variables associated with the non-classic diagnosis, a multivariate analysis was conducted by logistic regression, considering the non-classic diagnosis as the dependent variable. A two-tailed p value of less than 0.05 was required for statistical significance.

Results

Clinical, biochemical and histologic features

Fifty five patients, 31 men (56.3%) and 24 women (43.7%), were diagnosed with WD at the centre of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest between 1st January 1999 and 1st April 2004. The age ranged between 4 and 52 years, with the mean age at diagnosis of 20.9±9.9 years. Fifty one patients (92.7%) were younger than 40.

Four patients in our study population (7.4%) had co-morbidities such as chronic hepatitis B virus (HBV) infection (one patient), chronic hepatitis C virus (HCV) infection (1), acute hepatitis E virus infection (HEV) (1) and Crohn's disease (1). The outcome was fatal in the patient with concurrent acute HEV infection; slow recovery from acute liver failure was noted in the patients with concurrent chronic hepatitis B and C. The patient with Crohn's disease was diagnosed 11 years after the initial diagnosis of WD as severe refractory ileo-colitis requiring Infliximab for the induction of the remission and maintenance therapy.

Neurological or psychiatric manifestations were detected in 31 patients (56.36%) (Table I). The presence of Kayser-Fleischer rings was found in 26 of these patients (83.8%). Six patients with Kayser-Fleischer rings had no neuro-psychiatric manifestations. Renal involvement associated with WD was noted in 8 patients (14.5%): urinary stones (3), microscopic hematuria and proteinuria (3), phosphaturia and tubular acidosis (2). Other extrahepatic conditions associated with WD were detected in 8 patients (14.5%): cardiomyopathy (1), osteoporosis (2), arthritis (1), infertility (1) and repeated miscarriages (1). Coombs-negative hemolytic anemia was diagnosed in 20 patients (36.36%).

Table I Patients' characteristics

Parameter	Value
Gender (M/F)	31/24 pts.
Age ± SD (yrs)	20.9 ± 9.9
ALT (UI/l) (normal ≤ 42 UI/l)	132 ± 98
Bilirubin (mg/dl) (reference value≤1 mg/dl)	19.4 ± 12.5
ALP (UI/l) (normal< 82 UI/l)	84.74 ± 19.5
ALP/ BT < 2	16 (29.09%)
INR (normal<1.12)	3.5 ± 2.7
Ceruloplasmin < 20 mg/dl	31 (56.36%)
Urinary copper > 100 mg/day	24 (43.63%)
Serum copper < 60 mg/dl	35 (63.63%)
Chronic liver disease at presentation	29 (52.8%)
Fulminant hepatic failure at presentation	12 (21.8%)
Asymptomatic patients at presentation	14 (25.4%)
Detectable Kayser Fleisher ring	32 (58.18%)
Neurologic/psychiatric symptoms	31 (56.36%)
Coombs negative hemolytic anemia	20 (36.36%)
Renal involvement	8 (14.54%)
Other extrahepatic disorders	8 (14.54%)
Relatives with Wilson disease	26 (47.27%)
Good response to specific treatment	31 (56.36%)

The serum alanine aminotransferase (ALT) was only moderately raised, with a mean value of 132 UI/l (ranging: normal to 431 UI/l). Increased total serum bilirubin was noted in 38 patients (69%) (mean 19.4 mg/dl, range 0.7-66 mg/dl) and prolongation of the prothrombin time in 23 patients (42%) (INR 3.5, range 1-7.8). Serum alkaline phosphatase activity was normal in 21 patients (38.18%), and slightly to moderately increased (84.74 UI/l, range 44-405 UI/l) in the remaining 34 patients. Markers of abnormal copper metabolism were present in all patients. Ceruloplasmin level < 20 mg/dl was noted in 31 patients (56.36%), urinary copper excretion > 100 mg/day in 24 (43.63%) and serum copper concentration < 60 mg/dl in 35 (63.63%).

Liver biopsy was performed in 19 patients (34.5%). Liver copper was assessed in 8 patients. All of them had increased liver copper deposits (> 250 mg/g dry weight liver tissue). Out of the 19 biopsied patients, 13 patients (68.4%) had steatosis, 16 (84.21%) had necrosis and inflammation, 9 (47.3%) associated fibrosis and 4 patients (21.0%) had cirrhosis.

Clinical presentation

All patients in our study had predominant liver disease, manifested as unexplained asymptomatic liver disease

Table II Diagnosis of Wilson disease in our patients. Results of univariate analysis

		Classic diagnosis	Nonclassic diagnosis	p value
Age > 18 yrs		16 (50 %)	18 (78.3 %)	0.03
< 18 yrs		16 (50 %)	5 (21.7 %)	
Sex Female		12 (37.5 %)	12 (52.2 %)	0.27
Male		20 (62.5 %)	11 (47.8 %)	
Neurologic symptoms	No	5 (15.6%)	18 (78.3%)	< 0.0001
	Yes	27 (84.4%)	5 (21.7%)	
Serum copper < 60 mg/l	No	13 (40.6 %)	7 (30.4 %)	0.43
	Yes	19 (59.4 %)	16 (69.6 %)	
Urinary copper > 100 mg/day	No	26 (81.3 %)	5 (21.7 %)	< 0.0001
	Yes	6 (18.7 %)	18 (78.3 %)	
Siblings with WD	No	18 (56.3 %)	11 (47.8 %)	0.53
	Yes	14 (43.7 %)	12 (52.2 %)	
Favorable response to therapy	No	16 (50 %)	8 (34.8 %)	0.26
	Yes	16 (50 %)	15 (65.2 %)	
Hemolysis	No	24 (75 %)	11 (47.8 %)	0.03
	Yes	8 (25 %)	12 (52.2 %)	
Coagulopathy	No	27 (84.4 %)	15 (65.2 %)	0.09
	Yes	5 (15.6 %)	8 (34.8 %)	
Asymptomatic presentation	No	23 (71.9 %)	18 (78.5 %)	0.59
	Yes	9 (28.1 %)	5 (21.7 %)	
Chronic hepatitis/ cirrhosis	No	15 (46.9 %)	11 (47.8%)	0.94
	Yes	17 (53.1 %)	12 (52.2 %)	
Fulminant hepatic failure	No	26 (81.3 %)	17 (73.9 %)	0.51
	Yes	6 (18.7 %)	6 (26.1 %)	
Exclusive hepatic disease	No	27 (84.4 %)	4 (17.4 %)	< 0.0001
	Yes	5 (15.6 %)	19 (82.6 %)	
Renal dysfunction	No	29 (90.6 %)	18 (78.3 %)	0.19
	Yes	3 (9.4 %)	5 (21.7 %)	

(elevated ALT and/or isolated hepatomegaly) in 14 patients (25.4%), chronic liver disease in 29 patients (52.8%), and fulminant hepatic failure in 12 patients (21.8%).

Predictive factors for the diagnosis of Wilson's disease

Diagnosis of WD was made by Sternlieb's criteria in 32 patients (58.18%). In the remaining 23 patients the non-classic diagnosis was based on the following criteria: low ceruloplasmin level and/or elevated 24-hour urinary copper excretion and/or low serum copper concentration (8 patients); increased urinary copper excretion and/or low serum copper concentration and/or response to D-penicillamine therapy (5 patients); increased urinary copper excretion and increased hepatic copper content > 250 mg/g dry weight liver tissue (3 patients); increased hepatic copper deposits > 250 mg/g dry weight liver tissue and response to D-penicillamine therapy (4 patients); increased hepatic copper content > 250 mg/g dry weight liver tissue and positive molecular testing (1 patient); increased urinary copper excretion and positive molecular analysis (2 patients).

We included in the univariate analysis the parameters shown in Table II. The non-classic diagnosis of WD showed a positive correlation with age over 18 years at the onset of disease ($p=0.03$), absence of neurological manifestations ($p<0.0001$), increased urinary copper excretion ($p<0.0001$), and Coombs-negative hemolytic anemia ($p=0.03$). The association between the non-classic diagnosis and the presence of isolated liver disease was also statistically significant ($p<0.0001$). Clinical presentation (asymptomatic, chronic liver disease or fulminant hepatic failure) showed no association with the non-classic diagnosis.

Age over 18, absence of neurologic symptoms, increased urinary copper, Coombs negative hemolysis, and isolated hepatic disorder were included in the multivariate analysis. Age over 18, increased copper excretion and isolated hepatic disease have been identified by the multivariate logistic regression analysis as independent predictors of the non-classic diagnosis of WD (Table III).

Table III Results of multivariate analysis

Variable	Regression coefficient	Standard error	Chi-square (β=0)	p value
Intercept (β0)	-2.45	0.82	8.84	0.002
Age > 18 yrs	2.46	1.08	5.2	0.02
Exclusive liver disease	3.51	1.03	11.53	0.0006
Increased urinary copper	3.17	1.05	9.08	0.002

The outcome was fatal in 10 patients (7 due to fulminant hepatic failure, 2 due to decompensated liver cirrhosis, 1 due to accidental cranio-cerebral trauma) and a liver transplantation was performed in 4 patients: orthotopic liver transplantation in two and living donor liver transplantation in the other two WD children for acute liver failure and decompensated liver cirrhosis, respectively. All the transplanted patients are alive at a mean of 22 months after post-transplant, in a very good condition. Twelve patients are currently included on the waiting list for liver transplantation.

Discussion

Patients with WD usually present at ages 5 to 40 years, but age at diagnosis may be both younger and older than is generally reported (6). The youngest patient reported with cirrhosis secondary to WD was 3-year old (12), acute liver failure from WD being also reported in the preschool age (13). The oldest patients with WD reported in the literature had 55 to 62 years at the time of diagnosis (10,14). A 44-year old female represents the oldest patient reported with acute liver failure due to WD (15). As in the literature, most of our patients were under 40 (92.6%), with only four patients (7.4%) over 40 and three patients (5.45%) younger than 7 years. The youngest patient in our study was 3-year old. Although the age limit for considering WD is generally lower than 40 years, in the setting of unexplained liver disease associated with suggestive manifestations, further evaluation should be carried out even in older patients.

As anti-nuclear autoantibody (ANA) seropositivity and histological features of steatohepatitis could be found in association with WD, this condition may be misdiagnosed as autoimmune hepatitis or nonalcoholic steatohepatitis at the time of its first presentation (16,17). True co-morbidity of WD at the time of diagnosis is rarely reported, no more frequently than expected by chance (6). Coexistence of WD and viral infections may lead to an early onset, severe presentation and rapidly progressive liver disease (18-20). In our patients with concurrent viral hepatitis infection (HBV, HCV, HEV), the liver disease was severe and rapidly progressive, leading to fulminant liver failure and death in one patient and slow recovery in the other two. A case of concurrent hepatic involvement of systemic lupus erithematosus in association with WD presented as fulminant hepatic failure in a juvenile patient was recently reported in the literature (21). These figures suggest that a mixed etiology of the hepatic injury involving hepatotropic viral infections, systemic lupus erithematosus or hepatotoxic drugs in association with WD may lead to a more severe, fulminant presentation. The association between WD and inflammatory bowel disease was recently reported by Japanese authors as a rare case of corticoresistant ulcerative colitis occurred 12 years after the diagnosis of WD (22). Similarly, in our patient with Crohn's disease, it occurred late in the evolution of WD as a severe refractory ileo-colitis requiring Infliximab. Because altered copper metabolism impairs antioxidant defence mechanisms during inflammatory process, the co-existence of WD may contribute to the refractoriness of the inflammatory bowel disease.

Neurological and psychiatric modality of presentation in WD varies between 10% and 36.3% in different studies (7, 10). Because it occurs later in life, most of these patients already have serious liver involvement even if asymptomatic. In our study, neuro-psychiatric manifestations were noted in 31 (56.36%) patients with predominant liver disease. Kayser-Fleischer rings, usually associated with neurologic presentation, were found in 83.8% of these patients in our study. Coombs-negative hemolytic anemia in 20 patients (36.3%) and renal involvement in 8 patients (14.5%) with WD.

The spectrum of liver disease in WD is highly variable, ranging from asymptomatic with biochemical abnormalities or hepato-splenomegaly to chronic liver disease and fulminant hepatic failure. Nowadays, more patients with WD are diagnosed incidentally as asymptomatic liver disease, due to the increasing awareness for the disease and to the routine liver function tests performed in clinical practice.

Establishing the diagnosis of WD is usually straightforward in the setting of typical criteria such as neurologic manifestations, Kayser-Fleischer rings and low serum ceruloplasmin. In some circumstances a liver biopsy may be required to quantify hepatic copper content (11). Using these criteria, the diagnosis was established in 32 patients (58.18%) in our study. However, many patients with WD do not fulfil classic criteria. In this case, no single diagnostic test can exclude or confirm the diagnosis of WD with 100% certainty and a combination of various laboratory parameters is necessary to firmly establish it (23). Exclusion of other liver diseases, presence of abnormalities of copper metabolism, and the favorable response to treatment with D-penicillamine are important for the diagnosis of WD.

More than 40% of our patients were diagnosed based on non-classic criteria. Features such as increase of copper excretion, isolated hepatic disorder and age over 18 years have been identified by the multivariate logistic regression analysis as independent predictors of the WD in our study. Confirming the difficulties of diagnosis in the absence of classic criteria, recently, the group of experts on WD proposed an integrated scoring system based on the combination of clinical symptoms and laboratory test results such as urinary and liver copper, serum ceruloplasmin, rhodanine positive stain in hepatocytes, and mutation analysis (24). A cumulative score higher than 4 points is strongly suggestive for WD, a score between 2-3 points does not exclude WD indicating that further tests are required if clinical suspicion is high, while a score of 0-1 points is unlikely to be associated with WD. This scoring system may be particularly useful in patients with non-classic diagnosis of WD. Before accepting this score as gold standard diagnosis in WD, it has to be prospectively validated in WD patients (24).

The amount of copper excreted in urine in a 24-hour period may be very helpful for diagnosing WD and for monitoring of the treatment. It reflects the amount of nonceruloplasmin-bound copper in the circulation (6). The conventional level taken as diagnostic of WD is greater than 100 mg/day in symptomatic patients (25). Recent studies indicate that basal 24-hour urinary copper excretion may be < 100 mg/day in 10 to 25% of patients diagnosed with WD (26,27). Increased 24-hour urinary copper excretion may be difficult to interpret due to the overlap of this finding with other chronic liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis and acute liver failure (28-30). Heterozygotes with WD may also have intermediate level of cupruria (28). Many laboratories consider 40 mg/day as the upper limit of the normal range; therefore a finding of basal 24-hour urinary excretion of copper > 40 mg/day might indicate WD and requires further investigations.

Usually, liver disease (fulminant liver failure or chronic liver disease) represents the initial manifestation of WD. Neurologic (31) and other extrahepatic manifestations of WD typically occur later than liver disease, most often in the third decade of life (6). The association between atypical diagnosis characterized by frust abnormalities of copper metabolism, and the absence of extrahepatic manifestations suggests an early phase of the disease.

In conclusion, WD in patients presenting with liver disease is a complex diagnosis. As none of the diagnostic features alone allows a certain diagnosis, a combination of various clinical traits and laboratory parameters is necessary to confirm the disease. Although the vast majority of our patients with WD were young, our study alerts clinicians to suspect WD also in patients older than 40 years. Our study confirmed that the clinical spectrum of presentation is dominated by chronic liver disease, but an increasing number of asymptomatic patients is currently diagnosed (more than 25% in our study). Isolated unexplained liver disease and increased cupruresis in patients older than 18 years strongly predict WD, even in the absence of classic criteria.

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