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Wilson disease: the diagnostic challenge and treatment outcomes in a series of 262 cases

Doença de Wilson: o desafio diagnóstico e resultados do tratamento em uma série de 262 casos

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Abstract

Background Wilson disease (WD) is an autosomal recessive disorder that leads to organ toxicity due to copper overload. Early diagnosis is complicated by the rarity and diversity of manifestations.

Objective To describe the diagnostic features and response to treatment in our cohort of WD patients.

Methods This was a retrospective analysis of 262 WD patients stratified by clinical presentation, complementary exams, *ATP7B* genotyping, and response to treatment.

Results Symptoms occurred at an average age of 17.4 (7–49) years, and patients were followed up for an average of 9.6 (0–45) years. Patients presented mainly with hepatic (36.3%), neurologic (34.7%), and neuropsychiatric (8.3%) forms. Other presentations were hematologic, renal, or musculoskeletal, and 16.8% of the patients were asymptomatic. Kayser-Fleischer rings occurred in 78.3% of the patients, hypoceruloplasminemia in 98.3%, and elevated cupruria/24h in 73.0%, with an increase after D-penicillamine in 54.0%. Mutations of the *ATP7B* gene were detected in 84.4% of alleles. Brain magnetic resonance imaging showed abnormalities in the basal ganglia in 77.7% of patients. D-penicillamine was the first choice in 93.6% of the 245 patients, and 21.1% of these patients were switched due to adverse effects. The second-line therapies were zinc and trientine. The therapeutic response did not differ significantly between the drugs ($p = 0.2$). Nine patients underwent liver transplantation and 82 died.

Conclusion Wilson disease is diagnosed at a late stage, and therapeutic options are limited. In people under 40 years of age with compatible manifestations, WD could be

Keywords
- Hepatolenticular Degeneration
- Copper-Transporting ATPases
- Movement Disorders
- Penicillamine
- Liver Cirrhosis

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considered earlier in the differential diagnosis. There is a need to include *ATP7B* genotyping and therapeutic alternatives in clinical practice.

Resumo

Antecedentes A doença de Wilson (DW) é um distúrbio autossômico recessivo caracterizado por acúmulo de cobre lesivo aos órgãos. O diagnóstico precoce é dificultado pela raridade e diversidade de apresentações.

Objetivo Descrever características ao diagnóstico e resposta ao tratamento em uma coorte de DW.

Métodos Análise retrospectiva de 262 casos de DW quanto à apresentação clínica, exames complementares, genotipagem e resposta ao tratamento.

Resultados Os sintomas surgiram em uma média aos 17,4 (7–49) anos, e os pacientes foram acompanhados por uma média de 9,6 (0–45) anos. Os pacientes apresentaram principalmente formas hepáticas (36,3%), neurológicas (34,7%) e neuropsiquiátricas (8,3%). Outras apresentações foram hematológicas, renais e musculoesqueléticas. Apenas 16,8% eram assintomáticos. Anéis de Kayser-Fleischer ocorreram em 78,3% dos pacientes, hipoceruloplasminemia em 98,3%, e cuprúria elevada/24h em 73,0%, com aumento após D-penicilamina em 54,0%. Mutações do gene *ATP7B* foram detectadas em 84,4% dos alelos pesquisados. A ressonância magnética cerebral mostrou alterações em gânglios da base em 77,7% dos pacientes. O tratamento com D-penicilamina foi a escolha inicial em 93,6% dos 245 casos e foi trocado em 21,1% devido a efeitos adversos. Terapias de segunda linha foram zinco e trientina. A resposta terapêutica não diferiu significativamente entre os medicamentos ($p = 0,2$). Nove pacientes receberam transplante hepático e 82 faleceram.

Conclusão O diagnóstico da DW ainda ocorre em estágios tardios, e as opções terapêuticas são limitadas. A DW deve ser considerada precocemente no diagnóstico diferencial de pessoas com menos de 40 anos com manifestações compatíveis. É necessário incorporar na prática clínica a genotipagem do *ATP7B* e alternativas terapêuticas à penicilamina.

Palavras-chave
- Degeneração Hepatolenticular
- ATPases Transportadoras de Cobre
- Transtornos dos Movimentos
- Penicilamina
- Cirrose Hepática

INTRODUCTION

Wilson disease (WD) is an autosomal recessive disorder caused by mutations in the *ATP7B* gene that leads to an accumulation of copper (Cu), particularly in the liver, brain, and cornea. It is most commonly diagnosed between the ages of 5 and 35 and can be fatal if not treated in time.[1–4]

In the 1940s, the WD diagnosis was based on typical neurologic and hepatic findings, the presence of Kayser-Fleischer (KF) rings detected on the biomicroscopic examination with the slit-lamp, family history, and *postmortem* liver histology. In the 1950s, WD diagnosis was confirmed by hypoceruloplasminemia, increased 24-hour urinary Cu excretion, and increased Cu content in biopsy-derived liver tissue.[5] However, in many cases, these parameters are not sufficient to establish a diagnosis. The identification of the WD gene in 1993[6,7] opened up a new approach that is also helpful in the screening of asymptomatic relatives.[4–6]

Medications to be taken orally include Cu chelating agents and metallothionein inducers. Liver transplantation is appropriate in patients with decompensated liver disease who do not respond to oral medications and do not have severe neurological impairment, or in patients with severe acute liver failure.[5,8]

However, few large series with long-term follow-up can be found in the literature.[9–17] Given the complexity of WD and the difficulty in diagnosing it, the aim of this study was to describe the clinical presentation, results of diagnostic tests, patterns of response to treatment, and outcomes of WD patients treated at our center.

METHODS

A cohort of WD patients (n = 262) from 198 distinct families was analyzed. Data were obtained from a database (n = 280) of patients treated between 1946 and 2020 in the departments of gastroenterology, neurology, or pediatrics of Hospital das Clínicas of the School of Medicine of Universidade de São Paulo. After 18 patients were excluded due to insufficient records, the data were collected retrospectively by reviewing the medical charts.

The diagnosis of WD was based on typical clinical manifestations or familial screening confirmed by complementary exams. Diagnostic parameters, including neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI] of the brain), and 24 h urinary Cu stimulated by D-penicillamine (DPA), have evolved over the years, as standardized in

children[18], with a cutoff ≥ 1,600 µg/24h.[19] The *ATP7B* gene was sequenced as described elsewhere.[20] Results were categorized according to predominant features: hepatic, neurological, psychiatric, and others. Patients were categorized as asymptomatic even if there were only changes in liver enzymes and imaging findings. Hepatic features were differentiated between acute, compensated chronic disease, and decompensated cirrhosis. A *postmortem* liver sample was obtained from 18 patients.

Kayser-Fleischer rings were seen on biomicroscopic examination with the slit-lamp. Response to treatment response at ≥ 12 to 18 months was determined by history and laboratory tests. Response was complete if there was a complete improvement in symptoms, laboratory changes, disappearance of KF rings, and stabilization of urinary Cu excretion at 200 to 500 µg/24h. It was incomplete when some of these parameters remained abnormal, and it was inefficient when these parameters worsened. Adherence was good if the medication was not interrupted for > 7 days, irregular if the interruption time was between 8 and 30 days, and poor if it was interrupted frequently or ≥ 30 days. The χ^2 test, Fisher test, and unpaired t test were used for the statistical analyses (significance at $p < 0.05$).

RESULTS

We included 262 individuals from 198 families diagnosed with WD, 154 men (18.7; 5–53 years) and 108 women (8.6; 4–51 years). There was no overall gender difference ($p > 0.05$), but males predominated in neurological manifestations ($p = 0.02$). Symptoms appeared at 17.6 ± 6.5 (6–49) years, while the diagnosis was made at 18.7 ± 7.5 (4–53) years. The psychiatric form was invariably accompanied by neurological symptoms; therefore, it is referred to as the 'neuropsychiatric' form. ►**Figure 1** illustrates the age at onset of symptoms and at diagnosis.

►**Table 1** illustrates the time between symptom onset and diagnosis over the decades.

Clinical presentation

►**Table 2** illustrates the distribution of clinical presentations. Dysarthria (89.0%) was the most common neurologic manifestation, as previously reported.[21] During follow-up, motor impairment disorders were noted in 155 patients, classified as mild in 20.6%, moderate in 45.8% or severe in 33.6% (►**Figure 2**).

Decompensated chronic liver disease was found in 57.9% of patients with the hepatic form. Acute liver failure occurred in 5 patients (4 women, 2 of whom had Coombs-negative hemolytic anemia, mean age 13.2 (9–18) years.

Correlations of clinical presentation with diagnostic parameters are shown in ►**Table 3**. Mutations of the *ATP7B* gene were detected in 78.3% of alleles (191/244). Kayser-Fleischer rings were present in all hematologic patients and remarkably also in 5 asymptomatic patients, while they were absent in only 2 neurologic/neuropsychiatric patients ($p < 0.001$).

Laboratory tests

Liver enzymes were elevated in 73.4% of patients (n = 226 before treatment). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were elevated in 98/214 (45.8%) and 114/213 (53.5%) patients, respectively.

In patients with acute liver failure (n = 5), ALT levels were twice the reference value, with a median of 29 (22–67) IU/L and a mean alkaline phosphatase (AP) level of 85 (9–883) IU/L. These patients had AST values 5 times higher than the upper reference, with a median of 135 (58–195)

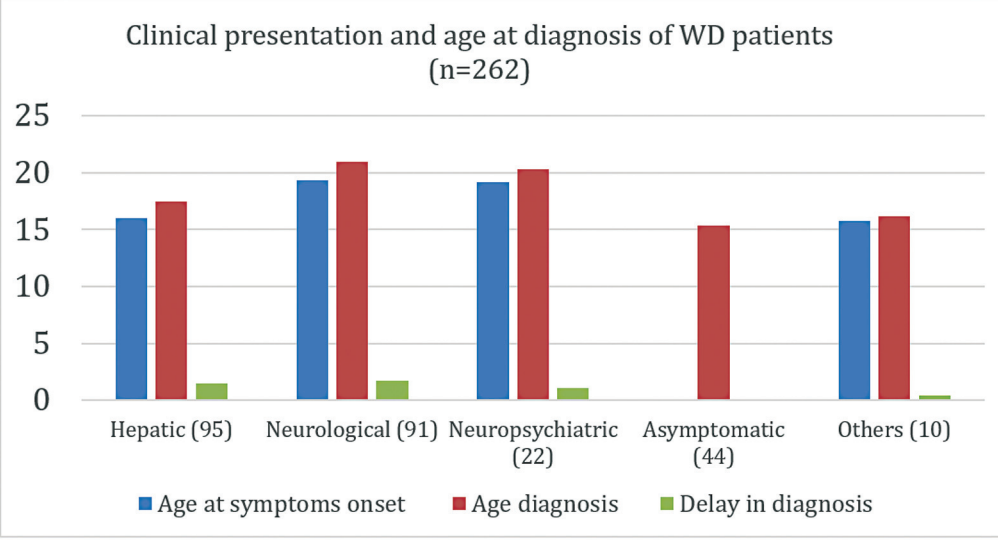

Figure 1 WD patients with hepatic presentation were younger (16.0 ± 6.3; 7–37 years) than those with neurologic (19.3 ± 6.7; 9–49 years, $p < 0.001$) or neuropsychiatric (19.2 ± 5.8; 6-30 years, $p = 0.007$) presentation. Neurological presentation did not significantly delay diagnosis compared to hepatic presentation (1.8 ± 2.5, 0–16 years vs 1.6 ± 2.3; 0–12 years, $p > 0.05$). In "other forms" group, 5 cases of hematological form had a severe acute onset with Kayser-Fleischer rings, which shortened the interval from symptom onset to diagnosis. Forty-four patients were diagnosed while they were asymptomatic.

Table 1 Wilson disease onset and time to diagnosis in a cohort of 262 patients

Decade	N	Age at diagnosis (years) (mean ± SD)	Median	Time between disease onset to diagnosis (years) (mean ± SD)	Median
1940	1	20	20	2	2
1950	3	25.7 ± 7.3	23.0 (20–34)	6.0 ± 8.7	1.0 (1–16)
1960	16	25.5 ± 10	24.0 (14–53)	3.6 ± 5.1	2.0 (1–22)
1970	59	18.3 ± 6.8	16.0 (7–35)	2.0 ± 2.3	1.0 (0–8)
1980	36	16.6 ± 6.5	16.0 (5–33)	1.0 ± 1.3	0.5 (0–4)
1990	62	17.5 ± 6.2	17.0 (8–33)	1.0 ± 2.0	0 (0–11)
2000–2021	85	19.0 ± 8.0	18.0 (4–51)	0.7 ± 1.2	0 (0–6)

Abbreviation: SD, standard deviation.

Table 2 Clinical presentation at disease onset in Wilson disease patients (n = 262)

The main presentation at disease onset (N)	Clinical manifestation (n)
Hepatic (95)	Acute hepatitis (10)
	Acute liver failure (5)
	Compensated chronic liver disease (25)
	Decompensated chronic liver disease (55)
Neurological (91)*	Dysarthria (81)
	Tremor (66)
	Gait disturbance (52)
	Dystonia (49)
	Rigidity (45)
	Cerebellar disturbances others then dysarthria and tremor (27)
	Seizures (9)
Psychiatric (22)*	Behavioral and emotional disorders (12)
	Schizophrenia (5)
	Major depression (3)
	Bipolar disorder (2)
Neurohepatic (2)	Compensated chronic liver disease/ dysarthria, dystonia, rigidity, gait disturbance (44)
Hematological (5)	Hemolytic anemia (1)
Renal (2)	Fanconi syndrome (1)
	Hematuria (1)
Osteoarticular (1)	Arthritis (1)
Asymptomatic	- (44)

Note: *see reference (19).

IU/L and hyperbilirubinemia, with a median of 28.6 (5.3–46.3) mg/dL. In 3 patients, the AST/ALT ratio was > 2.2, and in 2 patients, the AP/total bilirubin ratio was < 4. Hypoceruloplasminemia was found in 98.7% of patients (207/257) and was mostly < 10 mg/dL, with a median of 4.2 (0–26) mg/dL. The neuropsychiatric patients had the lowest values (►**Table 3**).

The mean basal urinary Cu excretion was 423.2 (10–3,870) µg/24 hours, and 119/163 tests (73%) were > 100 µg/24 hours. Asymptomatic patients had lower urinary Cu excretion than patients with neurologic and hepatic symptoms ($p < 0.001$ and $p = 0.01$, respectively).

The median 24-hour urinary Cu excretion after penicillamine challenge was 1,575 (36–6,377) µg/24 h. Urinary Cu

Figure 2 Neurological presentation of WD. A severely disabled young man presents with rigid dystonic posture, dysarthria, dysphagia requiring feeding through a gastrostomy tube.

levels were higher in patients with hepatic and neurological forms than in asymptomatic patients ($p = 0.008$ and $p = 0.007$, respectively). More than half (34/65; 52.3%) of the patients responded to penicillamine challenge with cupruria > 1,600 µg/24 hours, including one asymptomatic patient and 5 others with normal basal levels.

Radiological imaging of the brain

Magnetic resonance imaging of the brain showed abnormalities in the basal ganglia in 42/54 (77.7%) patients. In five neurological cases, no imaging signs were detected. One patient with a neuropsychiatric form had pontine myelinolysis. Changes in signal intensity in the cerebellum were observed in seven patients. Magnetic resonance imaging was normal in four neurological cases. Cranial CT showed cortical atrophy in 11/32 (34.4%), basal ganglionic hypodensity in 9/32 (28.1%), and ventricular dilatation in 7/32 (21.9%).

Liver parenchymal findings

Liver biopsies were performed in 100 cases. Seven samples were obtained from liver explants and 18 came from necropsies. Cirrhosis was already present in 64% of the samples. Steatosis was found in 33% and glycogenotic nuclei in 20% of the samples. Rhodanine staining was performed in 33 specimens, 18 of which were positive (54.5%), and in 3 cases changes suggestive of autoimmune hepatitis were detected.

Table 3 Clinical presentation form and diagnostic parameters in Wilson disease (n = 257)

Parameters	Clinical presentation*				*P*-value
	H (N = 95)	N (N = 91)	NP (N = 22)	HEM (N = 5)	A (N = 44)	
KF rings (%)	71/88 (80.7)	88/89 (98.9)	19/20 (95)	5/5 (100)	5/38 (13.2)	H x N; H x A; A x N; A x NP < 0.001
Ceruloplasmin < 20 mg/dL (%)**	5.3 ± 5.0 82/84 (97.6)	3.5 ± 4.4 77/78 (98.7)	2.9 ± 3.1 20/20 (100)	5.5 ± 2.4 4/4 (100)	4.0 ± 4.7 39/40 (97.5)	H X N = 0.03; H x NP = 0.01
Urinary copper > 100 µg/24 hours (%)**	422.9 ± 707.6 43/58 (74.1)	526.4 ± 519.0 53/64 (82.8)	291.5 ± 532.0 6/13 (46.2)	213 ± 184.9 2/4 (50)	156.1 ± 206.7 14/28 (50)	A x H = 0.02; A x N = 0.001; N x NP = 0.009
Penicillamine hallenge test (%)***	1,703 (114–4,034) 15/24 (62)	1,865 (150–6,377) 17/26 (65)	1,377 (800–3,175) 2/4 (50)	196 0/1 (0)	884 (36–1,600) 1/10 (10)	H x A = 0.016; A x N = 0.007
ATP7B mutations& 2 alleles (%) 1 allele (%) Absent (%)	44/50 (88) 6/50 (12) -	26/32 (81.2) 3/32 (9.4) 3/32 (9.4)	11/12 (91.7) 1/12 (8.3) -	2/3 (67) - 1/3 (33)	24/30 (80) 4/30 (13.3) 2/30 (6.7)	≥ 0.05

Abbreviations: H, hepatic; N, neurological; NP, neuropsychiatric; HEM, hematological; KF, Kayser-Fleischer; A, asymptomatic.
Notes: **mean ± standard deviation; ***median and range; cut off > 1,600 µg/24 h (children) after penicillamine challenge; > 100 µg/24 h (adults); &Sanger sequencing as previously described.[20]

Copper levels were quantified in 10 patients, 2 of them in a *postmortem* sample. Four individuals had hepatic Cu concentrations < 250 µg/g dry weight.

Analysis of the *ATP7B* gene

In the sequencing of the *ATP7B* gene, 37 distinct mutations were identified, and a detection rate of 89.8% (230/256 alleles) was achieved. Mutations were found in both alleles in a total of 108 individuals (84.4%), while no mutations were detected in 3.1% patients. There was no significant difference in clinical presentation or number of alleles affected (►**Table 3**). The most frequent mutation was p.A1135Q*fs* (32.8%), followed by p.L708P (14.8%), while p.H1069Q had an allelic frequency of 5.1%.

Treatment

The patients were followed up for 9.6 years (range 0–45 years). Unfortunately, 55 patients were lost to follow-up, and 82 patients (39.6%) died.

The first case of WD occurred in the neurological clinic in 1946. The first 3 patients in this study died within 5 years of symptom onset, prior to the introduction of specific WD therapy. During this time, treatment options were limited to palliative measures or dimercaprol, which proved ineffective. Nine patients receive no treatment as they died during the investigative period.

D-penicillamine (DPA) was the mainstay of therapy in 229 of 245 (93.6%) drug-treated patients. After an initial dose of 250 mg/day, it was gradually increased to 750 to 1,500 mg/day. In pediatric patients, the starting dose is usually 20 mg/kg/day. Pyridoxine was consistently administered in combination with DPA at a dose of 25 to 50 mg/day. Trientine was the treatment of first choice in four patients and was prescribed at a similar dose to DPA. Elemental zinc at a dose of 150 mg/day was given to 10 patients. One patient was given dimercaprol at a daily dose of 200 mg via the intramuscular route. All patients were advised to avoid foods with a high Cu content for at least the 1st year.

During the follow-up, DPA was used in 236 patients, zinc in 55, and trientine in 30. Seventy-nine patients had changed their treatment at the end of the study. Side effects were noted in 125 (53%) patients treated with DPA, in 20 (35.7%) patients treated with zinc salts, in 6 (20%) patients treated with trientine, and in 1 patient treated with dimercaprol. D-penicillamine was changed in 50 (19.1%) patients due to proteinuria (16), neurological deterioration (8), leukopenia (7), hypersensitivity (7), *elastosis perforans serpiginosa* (6), dyspepsia (2), thrombocytopenia (2), depression (1), or retinitis pigmentosa (1). Two patients taking zinc sulfate switched to zinc acetate due to dyspepsia. Trientine causes no serious adverse effects. D-penicillamine was the last recorded pharmacotherapy in 183 patients, zinc salts in 29 patients, and trientine in 16 patients. Nine patients were taking a Cu chelator in combination with zinc.

Data on the results of pharmacotherapy were available for 183 people, of whom 29 (15.8%) responded completely and 78 (42.6%) incompletely to the therapy. It was ineffective in 41.5%. Adherence to therapy was good in 112 (61.2%) patients, irregular in 37 (20.2%), and poor in 34 (18.6%). Clinical deterioration was observed in 29 (85.3%) patients with poor adherence, while 35 (31.3%) had good adherence ($p < 0.001$). There was no significant difference between the therapeutic outcomes of the 3 main drugs ($p = 0.2$). All patients in the asymptomatic group who showed good adherence were healthy. There were significant differences between the asymptomatic patients treated with DPA and those treated with neurological ($p = 0.012$) or hepatic symptoms ($p < 0.001$).

Two out of 5 patients with acute liver failure died before undergoing liver transplantation. Nine patients were successfully treated by transplantation (3 with acute liver failure and 6 with decompensated chronic liver disease). One patient died 3 years after transplantation due to bronchoaspiration.

Of the 42 patients with a hepatic presentation and good compliance with drug therapy and dietary restrictions, 31 (73.8%) had a complete response. Although they were asymptomatic, 20/31 (64.5%) patients had abnormal liver test results. Eighty-six of the 111 neurological patients (77.5%) achieved clinical improvement, 9 (8.1%) remained stable, and 16 (14.4%) worsened.

DISCUSSION

The current series provides a comprehensive overview of our experience with WD, from diagnosis to treatment and outcomes over the past 7 decades. Previous publications have focused on specific aspects of subgroups of this cohort,[20–24] such as genotype-phenotype correlation, neurologic manifestations, and rare presentations. However, long-term follow-up data could provide food for thought for better management of WD.

Patients with a hepatic presentation were younger than patients with neurological symptoms.[12,25,26] One possible explanation could be the natural course of the disease. However, the oldest (53 years old) patient in this cohort who started with extrapyramidal manifestations had no signs of clinical or histologic liver disease. Another patient from a familial screening at age 51 had a ceruloplasmin level of 3 mg/dL with no other signs of WD; therefore, she was taken off medication and monitored every 6 months. It was not until the 6th year of follow-up that a slight increase in AST/ALT ratio and changes in liver imaging were noted. Liver histology revealed steatohepatitis that did not react to rhodanine staining. *ATP7B* genotyping revealed p.A1135-Qfs/p.M645R mutations. The patient's brother had been diagnosed with decompensated cirrhosis at the age of 34. It is known that WD can occur at any age and tends to be less severe when symptoms begin at an older age. This indeterminate pattern may be due to various environmental factors (such as dietary Cu levels), which are associated with genetic factors. Compound heterozygosity, including the p.M645R mutation, has been found in patients with hypoceruloplasminemia, but the findings are unusual.[27] Unfortunately, in WD patients diagnosed by familial screening, with the exception of asymptomatic patients, the time between the onset of symptoms and the start of treatment was not shortened.

Direct sequencing of the first 60 patients in this series showed a mutation detection rate of 90% (108/120 alleles), and mutation in both alleles were detected in 81.7% of patients, as previously reported.[20] In the present study, 68 subjects were added to this cohort using the same techniques; the detection rate was 89.8% (230/256), and mutations in both alleles were detected in 108 patients (84.4%). We emphasize that the 3 patients from 2 different families in whom no *ATP7B* mutation was detected were diagnosed as definite WD cases, with typical clinical, laboratory, and imaging features and adequate response to treatment. Our mutation detection rate is in the range of 77 to 98% reported by other groups from America, Europe, and Asia.[28–32] The improvement of primer design and amplification techniques could contribute to a higher yield. In addition, there are mutations in promoters and intronic regions that are not accessible by direct sequencing. Recently, next-generation sequencing (NGS) has emerged as a technique that can elucidate many of these cases.[33]

Epigenetic factors causing genomic imprinting and other genetic disorders that mimic WD may also be considered. The large number of different mutations in patients with very different clinical features does not yet allow to establish clear genotype—phenotype associations. Although more than 900 *ATP7B* mutations have been described in the literature over the last 2 decades, the mechanisms involved in the development of WD are not yet fully understood.[17,34] Interestingly, the group from Austria claims that age and gender actually influence the WD phenotype more than the A*TP7B* genotype does.[32]

Kayser-Fleischer rings were detected in 78.3% of patients but were absent in 2 (1.1%) patients with the neurologic form. As expected, 86.8% of the asymptomatic patients did not have these symptoms. Hypoceruloplasminemia was detected in 98.7% of patients.[13] The penicillamine challenge test was positive in 18/33 adults (54.5%). Based on the European scoring system[19] criteria, five patients were definitively diagnosed with WD after the penicillamine challenge test. Although this is helpful, we emphasize that most healthy parents of WD patients also show a pronounced reaction to penicillamine, sometimes more than 15 times the reference value.[35]

Among the patients with neurological symptoms, most were male (68.1%). One hypothesis is that men have higher concentrations of ferritin-bound iron in the brain, and that this metal is associated with neurodegenerative diseases.[36] However, only 1/6 of patients with hepatic siderosis had neurological symptoms.

Both Cu excess and deficiency correlate with fatty liver disease.[37] In this cohort, 28 patients with liver biopsy had steatosis and inflammation. Liver biopsy was performed on admission (n = 21), during Cu chelator therapy (n = 7), or after removal of excess Cu (n = 5).

Interestingly, 2 patients had smooth muscle antibody levels > 1/320 (female) and > 1/160 (male). Both patients responded well to Cu chelator without immunosuppressive drugs; thus, the antibodies are rare epiphenomena.[38]

D-Penicillamin was the first choice as trientine is not yet easily accessible for the vast majority of patients. Zinc salts were used in the early 1980s as a second option for the treatment of WD in patients who could not tolerate DPA. Since the 1990s, zinc salts have been used as first-line treatment for severe neurological conditions and asymptomatic patients.

Although 77.3% improved liver function after starting treatment, 20% deteriorated. Liver biochemical tests improved in 39.7%, but worsened in 17%. There was a clear distinction between clinical and laboratory improvement; however, when patients deteriorated clinically, laboratory parameters reflected this trend. Iorio et al.[39] also observed persistent elevation of alanine transaminase (ALT) in patients who remained clinically stable. Therefore, lowering AST/ALT levels may not be the goal of successful therapy.

In the subgroup of decompensated chronic liver disease treated with DPA, 11 patients died within 6 months of starting therapy, 7 died between 7 months and 4 years, and 1 patient did not respond satisfactorily to therapy. Thus, some patients may not respond to copper chelation and liver transplantation is a plausible alternative for non-responders when liver function deteriorates.[40]

Of the 33 patients who continued with KF rings, 21 (63.6%) experienced clinical deterioration, while the 28/29 (96.6%) in whom the KF rings disappeared also showed a regression of neurological symptoms. Kayser-Fleischer rings can, therefore, indicate treatment compliance and response.

Three asymptomatic patients had poor adherence to Cu chelators and manifested liver disease in the follow-up. All asymptomatic patients with satisfactory adherence had a good outcome.

While therapeutic response did not differ between the three drugs, 53% of patients treated with DPA experienced adverse reactions, 21.1% experienced significant reactions requiring drug substitution, and one patient died from nephrotoxicity. One patient reported elsewhere developed myeloneuropathy after 14 years of zinc therapy.[22] This could be due to Cu deficiency or the toxic effects of zinc, as both excess and deficiency are harmful.

In conclusion, WD still mainly affects young patients, who also find it difficult to adhere to treatment. *ATP7B* genotyping can help with early diagnosis but cannot predict severity or presentation. A high suspicion of WD is crucial for early diagnosis. Penicillamine is the most commonly prescribed treatment, although it does not work satisfactorily. Another challenge in the treatment of WD patients is the identification of better tolerated medications and the development of strategies to improve adherence.

Authors' Contributions

MMD: conceptualization, data curation, funding acquisition, investigation, methodology, resources, writing – original draft, review, and editing; FCA: conceptualization, data curation, formal analysis, investigation, methodology, and writing – original draft; DRBT: data curation, investigation, and visualization; TFA: data curation and

formal analysis; GP: conceptualization, data curation, formal analysis, and investigation visualization; ERB: conceptualization, data curation, formal analysis, investigation, methodology, supervision, and visualization; ELRC: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, and writing – review & editing.

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Conflict of Interest
There is no conflict of interest to declare.

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