Advances in Medicine and Engineering Interdisciplinary Research, 2026, Volume 4, Issue 1
DOI: 10.32629/ameir.v4i1.4932
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Wilson's disease: experience of a reference center in Colombia

Octavio Muñoz-Maya[1,*], Juan Esteban Vélez-Hernández[2], Óscar Mauricio Santos[1], Juan Ignacio Marín[1], Juan Carlos Restrepo-Gutiérrez[1]

1. Clinical Hepatology and Gastrohepatology Group, University of Antioquia. Pablo Tobón Uribe Hospital, Medellín, Colombia
2. Gastrohepatology Group, University of Antioquia, Medellín, Colombia
*Corresponding author.
Email address: octavio.g.munoz@gmail.com

Abstract: Introduction: Wilson's disease is a heterogeneous disorder caused by mutations in the ATP7B gene. Its clinical presentation is variable in hepatic and neuropsychiatric phenotypes. The aim of this study is to describe a retrospective cohort of patients. Materials and methods: A descriptive retrospective study was carried out in patients treated at the Hospital Pablo Tobón Uribe from January 2004 to September 2017. Results: 27 patients were reported, 17 men and 10 women. The mean follow-up time was 2.18 years. 40 % of the patients had neurological symptoms, 29 % psychiatric symptoms, and 85 % hepatic impairment. Lab tests showed that 85 % had low ceruloplasmin and 55 % had increased urinary copper. In cases that underwent liver biopsy, 7 had special copper colorations. Neuroimaging revealed that 84 % had findings suggestive of Wilson's disease and a pathogenic genetic mutation was documented in 3 cases. During follow-up, 51 % improved clinically or biochemically, 11 % remained stable, and 18 % deteriorated. 88 % of cases survived at the end of follow-up. Conclusions: This study is the largest retrospective cohort carried out in Colombia. The results are the basis for new population-based studies actively seeking this disease to describe its preclinical development and thus impact prognosis.

Key words: hepatolenticular degeneration; copper-transporter ATPases; liver cirrhosis; acute liver failure; human ATP7B protein; basal ganglia diseases

1 Introduction

Copper is an essential trace element in living organisms, and its consumption exceeds the basal requirement [1]. The ATP7B protein is found in hepatocytes and is responsible for the excretion of copper through bile, adding it to apoceruloplasmin for distribution [2,3]. This protein is mutated in Wilson's disease, which leads to the accumulation of copper, causing multi-organ disease. Currently, more than 600 pathogenic mutations have been described, and its inheritance pattern is autosomal recessive [4,5]. In Colombia, it is considered an orphan disease [6], with an estimated global prevalence of 0.5 cases per 100,000 inhabitants and an incidence in most populations of 1 per 30,000 live births [7, 8].

The clinical presentation is highly variable and can appear at any age, although it is more common between the ages of 5 and 35, with both acute and chronic symptoms and multi-organ involvement, predominantly hepatic, neurological and

psychiatric [9, 10]. There is no single test to confirm the diagnosis, so a series of tests must be performed which, together with clinical findings, form the diagnosis.

Although its distribution is global, areas of higher prevalence have been described, which correspond to closed areas with little genetic variability and high rates of inbreeding. In Latin America, there are reports of isolated cases and small series in most countries; however, the experience of Costa Rica should be highlighted. In this country, there are areas where the incidence can reach 60 cases per 100,000 inhabitants [11]. In Colombia, the situation is similar to that in other Latin American countries, where isolated cases are reported, but there is insufficient information on local behavior [12,13].

The objective of this study is to describe a retrospective series of cases, identifying the clinical characteristics, diagnostic tests, management plan, and outcomes in patients with Wilson's disease who were treated at our center.

Table 1. Scoring system developed at the 8th International Meeting on Wilson's Disease, Leipzig, 2001

Symptoms, signs, and tests	Points	Symptoms, signs, and tests	Points
Kayser-Fleischer ring		Hepatic copper (in the absence of cholestasis):	
-Present	2	- 5 x ULN (> 4 µ mol/g)	2
-Absent	0	- 0.8-4 µ mol/g	1
		-Normal (< 0.8 µ mol/g)	-1
		-Rhodamine-positive granules*	1
Neurological symptoms:**		Urinary copper (in the absence of acute hepatitis)	
-Severe	2	-Normal	0
-Moderate	1	-1-2 x ULN	1
-Absent	0	-> 2 x ULN	2
		-Normal, but > 5 x ULN after D-penicillamine	2
Serum ceruloplasmin:		Mutations analysis	
-Normal (> 0.2 g/L)	0	-Detected on both chromosomes	4
-0.1-0.2 g/L	1	-Detected on 1 chromosome	1
-< 0.1 g/L	2	-No mutations detected	0
Coombs negative hemolytic anemia:			
-Present	1		
-Absent	0		

Total score	Evaluation result
4 or more	Confirmed
3	Possible
2 or less	Unlikely

*If there is no quantifiable hepatic copper available. **If there are no typical abnormalities on brain magnetic resonance imaging. ULN: upper limit of normal.

1.1 Data collection

Retrospective information was obtained from the database of the Gastrohepatology Group at the University of Antioquia and the Pablo Tobón Uribe Hospital (HPTU) in Medellín, Colombia. A search was conducted of the medical

records of patients with the diagnostic code: E830: copper metabolism disorders, from January 2004 to September 2017, without any restrictions.

1.2 Diagnostic criteria

The medical records of 50 patients were collected, and patients who did not meet the Leipzig criteria for Wilson's disease were excluded from the analysis. The Leipzig criteria include the presence of Kayser-Fleischer rings, serum ceruloplasmin levels, and neurological involvement, the presence of non-immune hemolytic anemia, the quantification or detection of copper in liver biopsy, urinary copper, and the finding of mutations pathogenic conditions [14]. All patients scored more than 4 points on this diagnostic scale (Table 1).

1.3 Variables

Categorical variables were analyzed in all patients, including general demographic variables, comorbidities, age at symptom onset, age at diagnosis, presentation, laboratory characteristics, imaging, histopathological findings, follow-up time, treatment, and outcomes. Diagnostic tests, imaging, and genetic studies are described according to availability; similarly, the criteria for clinical improvement, biochemistry, stability, and survival were based on the data recorded in the medical history by the treating hepatologist.

1.4 Statistical analysis

Data collection and analysis were performed using Epidat 4.2 software. A descriptive analysis was performed for all patients with Wilson's disease.

Quantitative variables are expressed as mean or median with their respective measures of dispersion, depending on the distribution of the variable.

1.5 Ethical considerations

The study was approved by the HPTU Ethics Committee and complied with Resolution 008430 of 1993 issued by the Ministry of Health of the Republic of Colombia regarding ethical aspects of research involving human beings.

2 Results

In the medical record registry, 27 patients met the diagnostic criteria for Wilson's disease: 17 (62%) were men and 10 (37%) were women. Twenty-four (88%) were from municipalities in the department of Antioquia. The average age of patients at the time of diagnosis was 21.2 years (range 8 to 42 years). Younger ages predominated, with 81% of all patients between the ages of 10 and 30 (Figure 1).

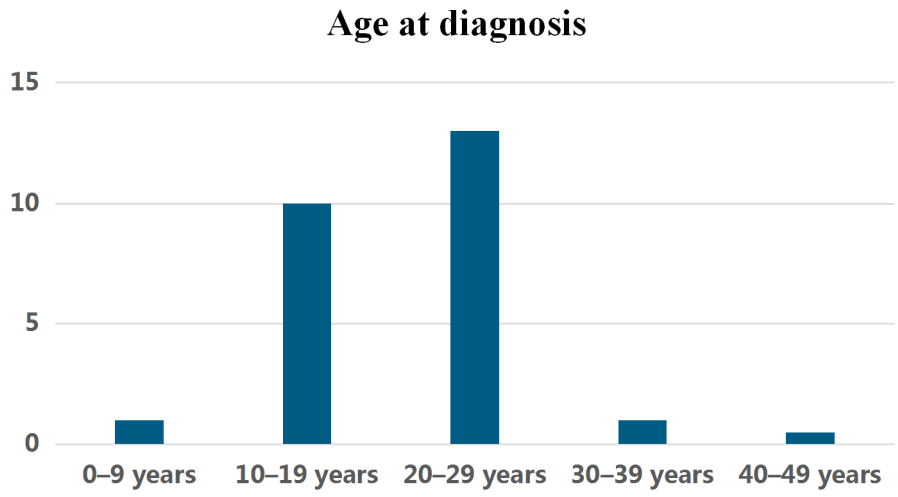

Figure 1. Age at clinical presentation

The clinical presentation was heterogeneous, and many patients had overlapping symptoms (Figure 2). The most common presentation was hepatic involvement, followed by neurological involvement and, finally, psychiatric involvement.

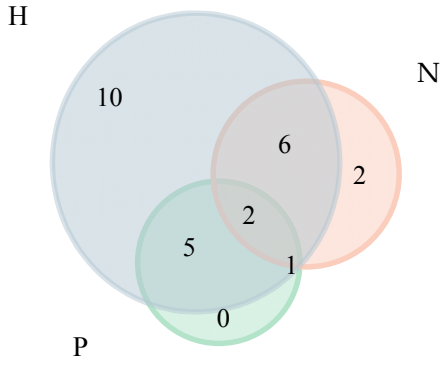

Figure 2. Initial symptoms of Wilson's disease. H: hepatic; N: neurological; P: psychiatric

2.1 Hepatic involvement

Twenty-three patients (85%) had hepatic involvement: cirrhosis (55%), steatosis (14.81%), acute liver failure (7.41%), and asymptomatic biochemical abnormalities (7.41%). A liver biopsy was performed in 16 patients, and the most frequent findings were cirrhosis (44%), steatosis (31%), and chronic hepatitis (19%). Copper deposits were documented in special stains in only 7 patients (Figure 3). The cases of acute liver failure correspond to two women aged 22 and 25 years who presented with this condition and had no neuropsychiatric manifestations. The biochemical presentation was typical, with severe hyperbilirubinemia and low alkaline phosphatase; one case presented with acute renal failure and required renal replacement therapy. Both patients received a cadaveric liver transplant and had a favorable outcome.

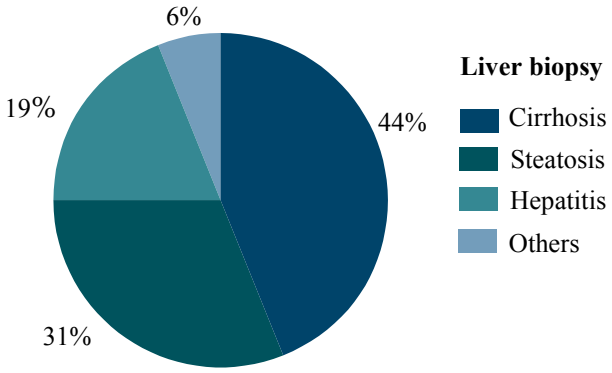

Figure 3. Findings in liver biopsy

2.2 Neurological involvement

Neurological involvement was found in 11 patients (40%), with the following manifestations:: parkinsonism (14%), ataxia (7.4%), dystonia (11%), and tremor (7%).

2.3 Psychiatric involvement

Eight patients (29%) had psychiatric symptoms. The most common were depression, anxiety, and schizophrenia.

2.4 Other associated manifestations

Four cases developed Coombs-negative hemolytic anemia, two were associated with acute liver failure, two with acute-on-chronic liver failure,, and one case of hypogonadism (Table 2).

2.5 Laboratory tests

In terms of laboratory tests, 23 patients (85%) had low ceruloplasmin and 15 (55%) had high urinary copper. In the four patients with acute presentation (two with acute liver failure and two with acute-on-chronic liver failure), alkaline phosphatase/total bilirubin (scores < 4 are positive) and alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratios (scores > 2.2 are positive) were performed; all patients had positive results for these indices. On ophthalmologic evaluation with slit-lamp examination, Kayser-Fleischer rings were found in 11 patients (40% of patients). Twelve magnetic resonance imaging scans and 2 simple computed tomography scans of the central nervous system (CNS) were performed, and findings suggestive of Wilson's disease were found in 9 patients (86%) (Table 3).

Table 2. Clinical presentation

Clinical presentation	n (%)
Average age in years	21 (8-42)
Gender	
- Male	17 (62)
- Female	10 (37)
Hepatic	23 (85)
- Cirrhosis	15
- Steatosis	4
- Acute liver failure	2
- Biochemical abnormality	2
Neurological	11 (40)
- Parkinsonism	4
- Ataxia	2
- Dystonia	3
- Tremor	2
Psychiatric	8 (29)
Asymptomatic	6 (22)

Table 3. Clinical presentation and laboratory findings

Laboratory tests	Clinical presentation		
	Hepatic (n: 24)	Neurological (n:11)	Psychiatric (n: 8)
Low ceruloplasmin < 0.2 g/L	20 (83%)	9 (81%)	6 (75%)
Urinary copper	15 (62.5%)	6 (54.5%)	3 (37.5%)
Kayser-Fleischer ring	7 (29.1%)	8 (72.7%)	4 (50%)
Hepatic biopsy copper	7 (29%)	0 (0%)	2 (25%)

A genetic test was performed with confirmatory results in three patients. The mutation found is considered a likely pathogenic, homozygous variant (c.3694 A> C, a missense mutation that replaces threonine with proline at position 1232 of the protein and affects several functional domains). Table 3 shows the distribution of positive diagnostic tests in different clinical scenarios (hepatic, neurological, and psychiatric involvement).

2.6 Treatment

With regard to treatment, 15 patients received zinc and D-penicillamine (55%), 3 received zinc alone (11%) and 3 received only D-penicillamine (11%). Six patients required liver transplantation (22%; 2 patients with liver failure without medical treatment and 4 with decompensated cirrhosis). Two adverse reactions were recorded, one of which was a severe reaction to D-penicillamine (febrile neutropenia). For this reason, trientine hydrochloride was initiated as second-line therapy in this case.

During follow-up, 14 patients (51.8%) showed clinical or biochemical improvement; 3 remained stable (11%) and 6 deteriorated (18%). No follow-up information was found for 4 patients. Of the total number of patients, 24 survived during follow-up (88%) and 4 died.

3 Discussion

This case series reports new data on Wilson's disease in Colombia. One of the most important findings is that 24 patients were from Antioquia, with clustering in subregions of the department. This is due to the founder effect in these isolated subregions of Antioquia, where poor genetic variability due to consanguinity leads to the manifestation of diseases with recessive Mendelian inheritance. This theory is supported by the fact that three patients who underwent genetic testing had the same mutation, without being family-related.

The peak age for both sexes is between 10 and 30 years old, demonstrating that this is a disease of young people; and late identification is a socioeconomic tragedy for families, as it reduces productive working life, perpetuating the socioeconomic gap.

Wilson's disease has been described as a heterogeneous disease, both clinically and genetically [15]. This is also evident in our series, where we found significant overlap between the different symptoms. With regard to liver involvement, the most common manifestation was liver cirrhosis, and the least frequent presentations were biochemical abnormalities alone and acute liver failure. An important finding in histopathology was that 31% of biopsies showed only steatosis, a finding that can be found in more common liver diseases, which means that Wilson's disease must always be considered in the compatible clinical setting. These data are similar to other series, in which there was hepatic predominance (58%–83%) and cirrhosis was the most frequent presentation (31%) [9]. In the liver biopsy of one of the series, a higher amount of steatosis [54%] was found, and cirrhosis was found in only 37% [10]. It is possible that in our region the disease is being diagnosed late or that liver biopsy is being delayed in patients with more advanced clinical symptoms.

All patients with hemolytic anemia presented with acute liver failure or acute-on-chronic liver failure; this corroborates the explanation of hemolysis in Wilson's disease, caused by the excessive release of copper ions into the blood when hepatocytes are damaged [16,17]. It was also evident that the four patients presented the classic Wilson's disease indices in acute liver failure (ALP/TB < 4 and AST/ALT > 2.2), which corroborates their usefulness and high sensitivity and specificity rates in this scenario [18].

One of the patients presented with endocrine involvement: hypogonadism associated with decreased somatomedin C and elevated growth hormone. Hypogonadotropic hypogonadism has been found in patients with Wilson's disease, but this finding is possibly associated with advanced stage of liver disease [19].

Different diagnostic methods were used in all patients, demonstrating the importance of the Leipzig criteria [14]. As

can be seen in Table 3, in neither of the two most common presentations (hepatic and neurological) was low ceruloplasmin or elevated urinary copper found in 100% of cases. The diagnostic process in general is complex and requires extensive clinical experience and an adequate interpretation of diagnostic aids.

Among the neuroimaging tests, the most prevalent finding was T2 hyperintensity in the basal ganglia and the classic finding of Wilson's disease (the panda sign in the midbrain and tegmentum) in only one patient. Interestingly, four patients were found to have T1 hyperintensity, reflecting the accumulation of manganese associated with cirrhosis or liver failure [20]. In addition, a finding observed in both magnetic resonance imaging and computed tomography [CT] was generalized cortical atrophy, leukoaraiosis, and ventriculomegaly, suggesting that there are presentations with more diffuse involvement, in addition to the possible cognitive impairment of patients with this disease, which has been evidenced in different studies [21].

The response to medical treatment is generally good. Of the patients who received combined treatment with zinc and D-penicillamine, 86% showed improvement; 6% showed stabilization of their clinical condition; and only 1 case progressed to cirrhosis and required a liver transplant. In a multicenter cohort study conducted in Germany and Austria, improvement with medical treatment was found in 91% of patients with hepatic presentation treated with D-penicillamine and in 92% treated with trientine [22]. In a similar cohort, therapeutic failure was found to be more common in patients treated with zinc [15%] compared to patients treated with chelators (1.2%) [23]. Follow-up showed that only 6 patients deteriorated and 4 died; of these, 1 died due to discontinuation of immunosuppressive treatment after liver transplantation and the other 3 due to infectious complications during hospitalization. Overall, an survival rate of 85% during follow-up, so it can be concluded that Wilson's disease can have good outcomes, as long as it is identified early and treated according to the clinical stage.

As this is a retrospective observational study, it has the limitations inherent to this methodology. However, it is an important tool for describing the behavior of Wilson's disease in our region and clearly identifying a geographical area with a higher frequency of the disease associated with the founder effect and endogamy. This serves as a starting point for conducting population studies in the field, with the aim of detecting a greater number of cases, achieving early or preclinical diagnostic confirmation to improve prognosis, and additionally, conducting genetic counseling campaigns in the region.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Pohanka M. Copper and copper nanoparticles toxicity and their impact on basic functions in the body. Bratisl Lek Listy. 2019;120(6):397-409. https://doi.org/10.4149/BLL_2019_065.

[2] Broussolle E, Trocello JM, Woimant F, Lachaux A, Quinn N. Samuel Alexander Kinnier Wilson. Wilson's disease, Queen Square and neurology. Rev Neurol (Paris). 2013;169(12):927-35. https://doi.org/10.1016/j.neurol.2013.04.006.

[3] Harada M, Kawaguchi T, Kumemura H, Terada K, Ninomiya H, Taniguchi E, Hanada S, Baba S, Maeyama M, Koga H, Ueno T, Furuta K, Suganuma T, Sugiyama T, Sata M. The Wilson disease protein ATP7B resides in the late endosomes with Rab7 and the Niemann-Pick C1 protein. Am J Pathol. 2005;166(2):499-510. https://doi.org/10.1016/S0002-9440(10)62272-9.

[4] Gomes A, Dedoussis GV. Geographic distribution of ATP7B mutations in Wilson disease. Ann Hum Biol. 2016;43(1):1-8. https://doi.org/10.3109/03014460.2015.1051492.

[5] Trocello JM, Broussolle E, Girardot-Tinant N, Pelosse M, Lachaux A, Lloyd C, Woimant F. Wilson's disease, 100

years later…. Rev Neurol (Paris). 2013;169(12):936-43. https://doi.org/10.1016/j.neurol.2013.05.002.

[6] Resolución 2048 de 2015, por la cual se actualiza el listado de enfermedades huérfanas y se define el número con el cual se identifica cada una de ellas en el sistema de información de pacientes con enfermedades huérfanas. Ministerio de salud y Protección Social, Republica de Colombia (9 de junio de 2015).

[7] Kim GH, Yang JY, Park JY, Lee JJ, Kim JH, Yoo HW. Estimation of Wilson's disease incidence and carrier frequency in the Korean population by screening ATP7B major mutations in newborn filter papers using the SYBR green intercalator method based on the amplification refractory mutation system. Genet Test. 2008;12(3):395-9. https://doi.org/10.1089/gte.2008.0016.

[8] Kumar S, Thapa B, Kaur G, Prasad R. Analysis of most common mutations R778G, R778L, R778W, I1102T and H1069Q in Indian Wilson disease patients: correlation between genotype/phenotype/copper ATPase activity. Mol Cell Biochem. 2007;294(1-2):1-10. https://doi.org/10.1007/s11010-005-9028-z.

[9] Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilsons disease: a cohort study. Gut. 2007;56(1):115-20. https://doi.org/10.1136/gut.2005.087262.

[10] Cheung KS, Seto WK, Fung J, Mak LY, Lai CL, Yuen MF. Epidemiology and natural history of Wilson's disease in the Chinese: A territory-based study in Hong Kong between 2000 and 2016. World J Gastroenterol. 2017;23(43):7716-7726. https://doi.org/10.3748/wjg.v23.i43.7716.

[11] Hevia-Urrutia, F., Alvarado-Echeverría, I., Sanabria-Castro, A. Sánchez-Molina M, Meza-Sierra L, Parajeles-Vindas A, Méndez-Blanca O, Sánchez-Siles Á, Saborío-Rocafort M, Barguil-Gallardo M, Chavarría-Quirós I, Monge-Bonilla C. National alliance for Wilson's disease: health policy in Costa Rica. Hepatology Medicine Policy 2017;2:5. https://doi.org/10.1186/s41124-016-0012-x.

[12] Pulido JN, Medina LA, De Castro A, Tamayo JG, Medina S, Restrepo JC. Enfermedad de Wilson. Acta Med Colomb. 2002;27:186-188.

[13] Castaño O, Gómez DM, Ocampo JM, Casanova ME. Degeneración hepatolenticular: a propósito de tres casos. Iatreia. 2017;30(4):436-442. http://dx.doi.org/10.17533/udea.iatreia.v30n4a07.

[14] Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. Liver Int. 2003;23(3):139-42. https://doi.org/10.1034/j.1600-0676.2003.00824.x.

[15] Thomas GR, Forbes JR, Roberts EA, Walshe JM, Cox DW. The Wilson disease gene: spectrum of mutations and their consequences. Nat Genet. 1995;9(2):210-7. https://doi.org/10.1038/ng0295-210.

[16] Kiss JE, Berman D, Van Thiel D. Effective removal of copper by plasma exchange in fulminant Wilson's disease. Transfusion. 1998;38(4):327-31. https://doi.org/10.1046/j.1537-2995.1998.38498257369.x.

[17] Hartleb M, Zahorska-Markiewicz B, Ciesielski A. Wilson's disease presenting in sisters as fulminant hepatitis with hemolytic episodes. Am J Gastroenterol. 1987;82(6):549-51.

[18] Korman JD, Volenberg I, Balko J, Webster J, Schiodt FV, Squires RH Jr, Fontana RJ, Lee WM, Schilsky ML; Pediatric and Adult Acute Liver Failure Study Groups. Screening for Wilson disease in acute liver failure: a comparison of currently available diagnostic tests. Hepatology.2008;48(4):1167-74. https://doi.org/10.1002/hep.22446.

[19] Dzieżyc K, Litwin T, Członkowska A. Other organ involvement and clinical aspects of Wilson disease. Handb Clin Neurol. 2017;142:157-169. https://doi.org/10.1016/B978-0-444-63625-6.00013-6.

[20] Yu XE, Gao S, Yang RM, Han YZ. MR Imaging of the Brain in Neurologic Wilson Disease. AJNR Am J Neuroradiol. 2019;40(1):178-183. https://doi.org/10.3174/ajnr.A5936.

[21] Wenisch E, De Tassigny A, Trocello JM, Beretti J, GirardotTinant N, Woimant F. Cognitive profile in Wilson's disease: a case series of 31 patients. Rev Neurol (Paris). 2013;169(12):944-9. https://doi.org/10.1016/j.neurol.2013.06.002.

[22] Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, Merle U, Ferenci-Foerster D, Maieron A, Stauber R, Zoller H, Schmidt HH, Reuner U, Hefter H, Trocello JM, Houwen RH, Ferenci P, Stremmel W; EUROWILSON Consortium. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol. 2013;11(8):1028-35.e1-2. https://doi.org/10.1016/j.cgh.2013.03.012.

[23] Weiss KH, Gotthardt DN, Klemm D, Merle U, FerenciFoerster D, Schaefer M, Ferenci P, Stremmel W. Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. Gastroenterology. 2011;140(4):1189-1198.e1. https://doi.org/10.1053/j.gastro.2010.12.034.