

Archives of Clinical Case Reports

Review Article

Delayed Diagnosis of Wilson Disease Presenting as Isolated Psychiatric Symptoms: A Review of Published Cases

Benesova K^{1*}, Jankauskas M² and Verhoeven W³

¹Department of Psychiatry, Charles University, Prague, Czech Republic

²Department of Neurology, Vilnius University, Vilnius, Lithuania

³Department of Clinical Biochemistry, Ghent University, Ghent, Belgium

*Address for Correspondence: Klara Benesova, Department of Psychiatry, Charles University, Prague, Czech Republic; E-mail: klara.benesova@charlesuniversity.edu

Received: 17 February 2024; Accepted: 5 May 2024; Published: 18 July 2024; DOI: 10.5281/zenodo.22278896

Citation of this article: Benesova K, Jankauskas M, Verhoeven W (2024) Delayed Diagnosis of Wilson Disease Presenting as Isolated Psychiatric Symptoms: A Review of Published Cases. Arch Clin Case Rep, 7(1): 01-06.

Copyright: © 2024 Klara Benesova, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Wilson disease is a treatable disorder of copper transport in which psychiatric symptoms may be the only presenting feature, with no hepatic or neurological sign alongside them.

Objective: To describe the scale of diagnostic delay in psychiatric presentations and the documented failure modes of each test on the diagnostic pathway.

Methods: Narrative review of published cohort studies, systematic reviews and individual case reports.

Findings: In 268 adults, mean time from first symptom to diagnosis was 65 months for psychiatric presentations, 26.8 months for neurological and 18.3 months for hepatic. Caeruloplasmin below 0.20 g/L had a positive predictive value of 48.3%, and the Kayser-Fleischer ring was present in 27% of 67 patients. Testing typically followed a motor sign, often unmasked by an antipsychotic.

Conclusions: The published record supports early copper studies in atypical or drug-intolerant psychiatric illness; it does not establish how often psychiatric symptoms are the sole presentation.

Keywords: Wilson disease; Delayed diagnosis; Psychiatric symptoms; Caeruloplasmin; Copper metabolism

Introduction

Wilson disease is an inherited disorder of copper transport in which loss of ATP7B function impairs the incorporation of copper into caeruloplasmin and its excretion into bile, so that copper accumulates first in the liver and then in the brain and cornea [1]. It is one of the few inherited neuropsychiatric disorders for which effective pharmacological treatment exists, and the case for finding it early rests entirely on that fact [2].

Psychiatric symptoms are not a marginal feature of the disease. Between 30% and 40% of patients have psychiatric manifestations at the time of diagnosis, and 20% have consulted a psychiatrist before the diagnosis of Wilson disease is made [3]. In a chart review of 218 patients treated in the United States, 117 (53.7%) had at least one psychiatric sign or symptom at diagnosis, most commonly anxiety, depression or another mood change (36.2%), emotional lability (12.8%) and increased irritability or anger outbursts (9.2%) [4]. Major depressive disorder in Wilson disease has been characterised prospectively in an international multisite registry [5], and reported prevalence within the disease ranges from 4% to 47% for major depression and from 1.4% to 11.3% for psychosis [3].

How often psychiatric illness is the sole presenting feature, with no hepatic or neurological sign to accompany it, is not securely established; published figures measure different things and cannot be combined into a single rate. What can be established is what happens to those patients once they enter psychiatric care. This article reviews published cohorts, systematic reviews and individual published case reports. It describes no patient of the authors. Its argument is that in this group the diagnostic delay is itself the clinical signature of the disease, and that the delay persists because every test on the diagnostic pathway has a documented failure mode in exactly this population.

The Scale of the Delay in Psychiatric Presentations

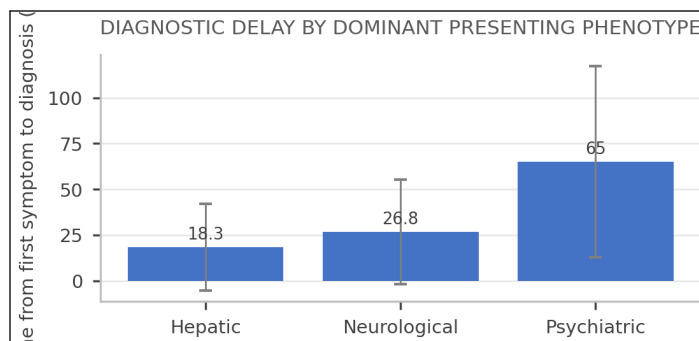


Figure 1: Mean time from first symptom to diagnosis by dominant presenting phenotype, with standard deviation whiskers, in a single Polish referral-centre cohort of adults diagnosed 2008-2023 (p=0.01 hepatic, p=0.03 neurological, p=0.03 psychiatric; cohort mean 22.5 months, SD 27.9), n = 268 [6].

The delay is measurable and it is specific. In 268 adults diagnosed with Wilson disease between 2008 and 2023 at a single Polish referral centre, the mean interval from first symptom to diagnosis was 22.5 months (SD 27.9). Broken down by the dominant symptom at diagnosis, that interval was 18.3 months (SD 23.6, p=0.01) for hepatic presentations, 26.8 months (SD 28.6, p=0.03) for neurological presentations and 65 months (SD 52.3, p=0.03) for psychiatric presentations [6]. Within one cohort, using one set of case definitions, the psychiatric group waited roughly three and a half times as long as the hepatic group.

Other cohorts show the same ordering by a different route. In 163 German patients, the mean interval from first symptom to diagnosis was 25.3 months overall, 44.4 months for neurological and 14.4 months for hepatic presentations (p=0.004), with 22.5% diagnosed only after more than three years and a reported range of 0 to 360 months [7]. Among 179 newly diagnosed Chinese patients, diagnostic errors occurred in 129 (72.1%) and the median delay was one year; all six patients whose first symptom was a mental or psychological abnormality were misdiagnosed, with a mean delay of three years and a range of 0.25 to 9 years [8]. That subgroup is too small to yield a rate, but its direction is consistent. In an Indian tertiary cohort of 307 patients, referring doctors had made a diagnostic error in 192; incorrect labels included

schizophrenia, and treatments received before the correct diagnosis included antipsychotics, electroconvulsive therapy and thalamotomy [9].

Pooling published case reports in which psychiatric symptoms preceded neurological or hepatic involvement gives a mean interval of 864.3 days between the onset of psychiatric symptoms and the diagnosis of Wilson disease; the denominator of pooled reports is not stated [3]. Late-onset disease adds a further layer: among 45 patients in a French national registry diagnosed at a median age of 49 years, the median delay was 20 months in the 20 neurological cases, and 30% of those neurological forms were atypical [10].

What the Published Cases Show

The individual published cases give the delay a shape that the cohort means do not. In every case reviewed here the diagnosis was initially missed, and in every case the event that finally prompted copper studies was the appearance or recognition of a motor sign, not a change in the psychiatric picture.

The longest delay in this series was 19 years. A woman first became severely unwell at 17 with negativism, commanding auditory hallucinations and persecutory delusions, was treated with haloperidol and nortriptyline and later clozapine, and was admitted to eleven different psychiatric wards under shifting diagnoses. Copper studies were sent only when choreoathetoid limb movements, marked intolerance of antipsychotics, thrombocytopenia and mild hyperbilirubinaemia accumulated together; caeruloplasmin was 0.164 g/L and 24-hour urinary copper 240 micrograms. She died following a suicide attempt driven by auditory hallucinations [11]. A 42-year-old man carried a diagnosis of schizoaffective disorder for three years before new resting and action tremor and inability to walk over six to seven months prompted referral from psychiatry to internal medicine, where a Kayser-Fleischer ring,

caeruloplasmin of 17 mg/dL and 24-hour urinary copper of 48.26 micrograms were found; his liver enzymes were normal [12].

Table 1: Published case reports of Wilson disease first presenting as psychiatric illness, showing the interval to diagnosis and the event that prompted copper studies; N = 5 reports [11,12,13,14,15].				
Report, patient	Psychiatric presentation	Years to diagnosis	What prompted testing	Outcome
Elyasi 2017; female, onset age 17	Negativism, commanding hallucinations, persecutory delusions; 11 psychiatric admissions	19	Choreoathetosis, antipsychotic intolerance, thrombocytopenia, hyperbilirubinaemia	Died after suicide attempt driven by hallucinations
Shah and Limbu 2018; male, 42	Disinhibition with sexual content, psychosis, self-neglect; labelled schizoaffective	3	New resting and action tremor, inability to walk over 6-7 months	Zinc sulphate and olanzapine; psychotic symptoms and tremor improved
Buciuc 2025; male, 48	Persecutory delusions, cognitive decline, catatonia	3	Severe dystonia on olanzapine plus abnormal liver function tests	Trintene, zinc and lorazepam; listed for liver transplantation
Doval 2016; male, age not stated	Withdrawal, reduced verbal output, loss of self-care, nocturnal wandering	0.75	Tremulousness, sialorrhoea and bradykinesia a week after risperidone started	Not stated
Chakor and Santhosh 2011; male, 32	Severe psychiatric manifestations requiring admission	Not stated	Tremor present for 5 years; rest and postural tremor and Kayser-Fleischer ring found	Penicillamine and pyridoxine; no neurological worsening, under follow-up

Antipsychotic exposure is a recurring trigger. A 48-year-old man with three years of persecutory delusions and cognitive decline was investigated only after severe dystonia on olanzapine and markedly abnormal liver function tests; consultation-liaison psychiatry recognised catatonia, and a Leipzig score of 6 established the diagnosis in the absence of Kayser-Fleischer rings [13]. A young man treated with risperidone for nine months of

withdrawal, reduced speech and loss of self-care developed tremulousness, sialorrhoea and bradykinesia within about a week of starting the drug; these were initially attributed to the medication, and the authors' stated conclusion is that a proper neurological examination at first referral would have prevented the delay [14]. In a 32-year-old man admitted with severe psychiatric manifestations, the sign that led to testing was tremor that had been present for five years; the authors' lesson is that tremor in any patient with a psychiatric disorder should raise suspicion of Wilson disease [15]. The pattern across these reports is an unusual susceptibility to extrapyramidal effects, attributed to pre-existing basal ganglia copper deposition; it is described qualitatively in the literature and no denominator-based estimate of its frequency exists [16]. Dominant psychiatric manifestations have long been recognised as a diagnostic and therapeutic challenge in specialist series [17], and the difficulties of treating psychiatric symptoms in this disease have been reviewed in detail [16].

Failure Modes of the Individual Diagnostic Tests

Each test on the pathway underperforms in the patient whose only symptoms are psychiatric, and the failures are documented rather than theoretical. Serum caeruloplasmin at the conventional cutoff of 0.20 g/L had a sensitivity of 77.1% to 99% and a specificity of 55.9% to 82.8% across 4,281 subjects in a systematic review [18]. In a Chinese cohort of 1,278 patients with Wilson disease and 1,772 without, the same cutoff gave 99.8% sensitivity but 69.5% specificity, a false-positive rate of 30.5% amounting to 564 false positives; 27.10% of 1,118 patients with non-Wilsonian liver dysfunction and 66.40% (83/125) of those with liver failure fell below it. Moving to the ROC-optimal 0.13 g/L raised specificity to 96.1% at 97.0% sensitivity [19]. Among ATP7B-genotyped subjects, the positive predictive value of a caeruloplasmin below 0.20 g/L was 48.3%, and 40 of 690 healthy subjects with normal ATP7B sequencing had values below that threshold [20].

Tightening the cutoff trades the error the other way: below 0.10 g/L, sensitivity falls to 65.0-78.9% while specificity rises to 96.6-100% [18], and the negative predictive value falls to 91.9% [20]. A caeruloplasmin low enough to be reported as abnormal is therefore a weak positive, and one in the normal range is not a rule-out.

Table 2: Reported performance and stated pitfall of each test on the diagnostic pathway for Wilson disease [18,19,23,22,21,24,10,25].				
Test and threshold	Sensitivity	Specificity	Stated pitfall	Source
Caeruloplasmin <0.20 g/L	77.1-99%	55.9-82.8%	Wide specificity range; acute-phase reactant (N=4,281)	salman2022
Caeruloplasmin <0.20 g/L	99.8%	69.5%	30.5% false positives; 66.4% (83/125) of liver failure falls below	yang2022
Caeruloplasmin <0.10 g/L	65.0-78.9%	96.6-100%	Misses a quarter to a third of true cases	salman2022
24-h urinary copper 40-100 mcg	75.6%	98.3%	Requires a complete collection (N=268)	salman2022
Hepatic copper 4 micromol/g	99.4%	96.1%	Invasive; sampling error in cirrhosis (N=1,150)	salman2022
Kayser-Fleischer ring, slit lamp	35.7% neurological, 9.4% hepatic	Not reported	Absent in 12/45 neurological; present in 27% at diagnosis	ormeci2022, youn2012, fenu2012
Brain MRI, pathognomonic signs	43% (24/55) neurological, 24% of all	Not reported	Normal MRI excludes nothing; normal in all 6 atypical late-onset cases	redziaogrodnik2023, nilles2023
Leipzig score >=4	Not established	Not established	No validated composite performance; a score of 3 leaves it open	ferenci2003

Twenty-four-hour urinary copper at 0.64 to 1.6 micromol per 24 hours has a sensitivity of 75.6% and a specificity of 98.3% in 268 subjects, so roughly a quarter of true cases are missed and the result depends on a complete collection. Hepatic copper performs better, with a sensitivity of 99.4% and a specificity of 96.1% at the conventional 4 micromol per gram dry weight in 1,150 subjects, but it requires a liver biopsy and is subject to

sampling error [18]. The Kayser-Fleischer ring, which anchors two points of the diagnostic score, was present at diagnosis in only 27% of an unselected cohort of 67 patients [21] and was absent in 12 of 45 patients with neurological Wilson disease (26.7%) [22]. Anterior segment optical coherence tomography detected the ring in 71.4% (10/14) of neurological and 21.9% (7/32) of hepatic patients against 35.7% and 9.4% respectively by slit lamp, a significant advantage overall ($p=0.001$) that still leaves most non-neurological patients undetected [23]. Five of six atypical late-onset neurological patients had no ring, and all six had normal T2 and FLAIR brain imaging [10]. Potentially pathognomonic brain magnetic resonance signs were present in 24% of all patients with Wilson disease and 43% (24/55) of those with neurological disease, so a normal scan excludes nothing [24]. The Leipzig score combines these items and sets diagnosis at four points or more, with three leaving the question open [25]; no validated sensitivity or specificity for the composite has been published, so the score inherits the weaknesses of its components rather than correcting them.

The Cost of Arriving Late

Delay matters because the phenotype at which treatment begins governs the risk of deterioration when treatment begins. In a systematic review and meta-analysis of 32 studies and 1,512 patients, early neurological deterioration after starting anti-copper therapy occurred in 217 (14.3%) overall, but in 167 of 763 patients with neurological Wilson disease (21.8%), 5 of 377 with hepatic disease (1.3%) and none of the asymptomatic patients. Of 128 deteriorations with recorded outcome, 31 (24.2%) resolved completely, 35 (27.3%) partially and 51 (39.8%) not at all. D-penicillamine was the drug in use in 153 of the 217 deteriorations (70.5%), trientine in 31 (14.2%) and zinc salts in 15 (6.9%), although the authors caution that this may reflect prescribing frequency rather than differential risk [26]. A multicentre cohort using a strict

three-month definition found worsening in 30 of 115 patients with neurological or mixed presentation (26.1%) and in none of 294 with purely hepatic or asymptomatic presentation, with a second peak beyond twelve months affecting a further 23 of 115 (20%) [27]. In a single cohort of 143 patients, early worsening occurred in 16 (11.1%), only in those who already had neurological signs, and was completely reversible in 53% and partially reversible in 13% [28].

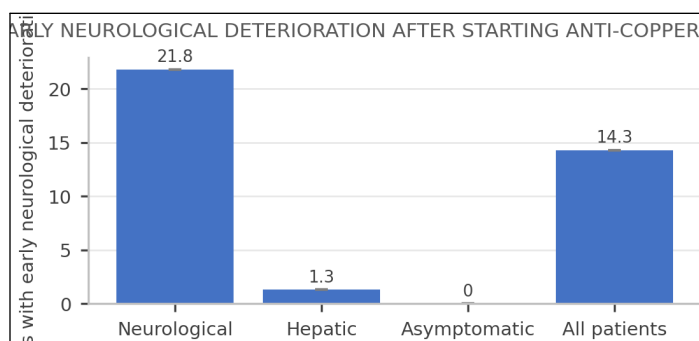


Figure 2: Early neurological deterioration after starting anti-copper therapy by presenting phenotype, as a pooled literature estimate across 32 studies (neurological 167/763, hepatic 5/377, asymptomatic 0, all patients 217/1512), $n = 1,512$ [26].

The mechanism of harm is therefore not the delay itself but what accrues during it. In the 268-patient cohort, delay was associated with subsequent neurological deterioration in univariate analysis ($p=0.02$) but not in logistic regression ($p=0.49$); the independent predictor was the presence of neurological symptoms at diagnosis, with an odds ratio of 38 ($p<0.001$) [6]. A patient found while still psychiatrically isolated carries close to no risk of treatment-induced worsening; the same patient found after motor signs appear carries approximately one chance in five, and if worsening occurs, two chances in five of never recovering.

Treatment outcomes overall are good: 76.1% of one cohort had a stable or improved course after starting treatment [7], 84% of a late-onset neurological group improved [10], and psychiatric symptom prevalence fell from 117 of 218 (53.7%) to 82 of 218 (37.6%) at approximately one year of treatment [4]. No primary study reports outcomes

specifically for the subgroup presenting purely psychiatrically, and that absence should be read as a gap in the literature rather than as reassurance.

Conclusion

For patients whose Wilson disease presents as psychiatric illness alone, a mean delay of 65 months against 26.8 and 18.3 months for neurological and hepatic presentations in the same 268-patient cohort is the most characteristic finding of the group [6]. It is produced by a pathway in which caeruloplasmin is neither sensitive nor specific enough to decide the question, urinary copper misses a quarter of cases, the corneal ring is absent in most patients without established neurological disease, brain imaging is normal in the majority, and the composite score has no validated operating characteristics. The published cases show what closes the gap in practice: a motor sign, often unmasked by an antipsychotic, appearing years after the psychiatric illness began. Because the risk of deterioration on treatment is concentrated almost entirely in patients who already have neurological signs, the interval between psychiatric onset and the first motor sign is the window in which the disease can be treated without that risk. Copper studies in a young patient with an atypical, treatment-resistant or drug-intolerant psychiatric presentation should be ordered before that window closes, and a normal result on any single test should not be allowed to close it.

References

1. Czlonkowska, A., Litwin, T., Dusek, P., Ferenci, P., Lutsenko, S., Medici, V., et al. (2018) Wilson disease. *Nature Reviews Disease Primers*, 4(1): 21.
2. Schilsky, M.L., Roberts, E.A., Bronstein, J.M., Dhawan, A., Hamilton, J.P., Rivard, A.M., et al. (2023) A multidisciplinary approach to the diagnosis and management of Wilson disease: executive summary of the 2022 practice guidance on Wilson disease from the American Association for the Study of Liver Diseases. *Hepatology*, 77(4): 1428-1455.
3. Zimbrea, P.C., Schilsky, M.L. (2014) Psychiatric aspects of Wilson disease: a review. *General Hospital Psychiatry*, 36(1): 53-62.
4. Medici, V., Kebede, N., Stephens, J., Kunjappu, M., Vierling, J.M. (2024) Clinical signs and symptoms of Wilson disease in a real-world cohort of patients in the United States: a medical chart review study. *Frontiers in Gastroenterology*, 2: 1299182.
5. Camarata, M.A., Ala, A., Coskun, A.K., et al. (2023) Major depressive disorder in an international multisite Wilson disease registry. *Journal of the Academy of Consultation-Liaison Psychiatry*, 64(2): 106-117.
6. Antos, A., Niewada, M., Krainski, L., Czlonkowska, A. (2025) Clinical determinants and prognostic impact of delayed diagnosis in Wilson's disease. *Diagnostics*, 15(18): 2358.
7. Merle, U., Schaefer, M., Ferenci, P., Stremmel, W. (2007) Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut*, 56(1): 115-120.
8. Yu, M., Ren, L., Zheng, M., Hong, M., Wei, Z. (2022) Delayed diagnosis of Wilson's disease report from 179 newly diagnosed cases in China. *Frontiers in Neurology*, 13: 884840.
9. Prashanth, L.K., Taly, A.B., Sinha, S., Arunodaya, G.R., Swamy, H.S. (2004) Wilson's disease: diagnostic errors and clinical implications. *Journal of Neurology, Neurosurgery and Psychiatry*, 75(6): 907-909.
10. Nilles, C., Obadia, M.A., Sobesky, R., Dumortier, J., Guillaud, O., Laurencin, C., et al. (2023) Diagnosis and outcomes of late-onset Wilson's disease: a national registry-based study. *Movement Disorders*, 38(2): 321-332.
11. Elyasi, F. (2017) Misidentification of Wilson disease as schizophrenia (1998-2013): case report and review. *Indian Journal of Psychological Medicine*, 39(5): 675-681.
12. Shah, B., Limbu, S. (2018) A case report of misdiagnosis of psychotic symptoms predominant Wilson's disease. *Journal of Neurosciences in Rural Practice*, 9(4): 616-618.

13. Buciu, A.G., Padilla, V., Durand, D., Zelde, E. (2025) Wilson disease hiding in plain sight: a case report of psychosis and catatonia revealing underlying liver dysfunction. Reports, 8(4): 261.
14. Doval, N., Batra, D., Moun, V., Shukla, R. (2016) Misdiagnosis of Wilson's disease in a patient with psychiatric symptoms. Indian Journal of Psychological Medicine, 38(4): 353.
15. Chakor, R.T., Santhosh, N.S. (2011) Severe neuropsychiatric presentation of Wilson's disease. Indian Journal of Psychiatry, 53(2): 170-171.
16. Litwin, T., Dusek, P., Szafranski, T., Dziezyc, K., Czlonkowska, A., Rybakowski, J.K. (2018) Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. Therapeutic Advances in Psychopharmacology, 8(7): 199-211.
17. Srinivas, K., Sinha, S., Taly, A.B., Prashanth, L.K., Arunodaya, G.R., Janardhana Reddy, Y.C., et al. (2008) Dominant psychiatric manifestations in Wilson's disease: a diagnostic and therapeutic challenge. Journal of the Neurological Sciences, 266(1-2): 104-108.
18. Salman, H.M., Amin, M., Syed, J., Sarfraz, Z., Sarfraz, A., Sarfraz, M., et al. (2022) Biochemical testing for the diagnosis of Wilson's disease: a systematic review. Journal of Clinical Laboratory Analysis, 36(2): e24191.
19. Yang, Y., Hao, W., Wei, T., Tang, L., Qian, N., Yang, Y., et al. (2022) Role of serum ceruloplasmin in the diagnosis of Wilson's disease: a large Chinese study. Frontiers in Neurology, 13: 1058642.
20. Mak, C.M., Lam, C.W., Tam, S. (2008) Diagnostic accuracy of serum ceruloplasmin in Wilson disease: determination of sensitivity and specificity by ROC curve analysis among ATP7B-genotyped subjects. Clinical Chemistry, 54(8): 1356-1362.
21. Fenu, M., Liggi, M., Demelia, E., Sorbello, O., Civolani, A., Demelia, L. (2012) Kayser-Fleischer ring in Wilson's disease: a cohort study. European Journal of Internal Medicine, 23(6): e150-e156.
22. Youn, J., Kim, J.S., Kim, H.T., Lee, J.Y., Lee, P.H., Ki, C.S., et al. (2012) Characteristics of neurological Wilson's disease without Kayser-Fleischer ring. Journal of the Neurological Sciences, 323(1-2): 183-186.
23. Ormeci, A.C., Bayraktar, S., Isik, A.O., Cavus, B., Akas, R., Istemiyan, Z., et al. (2022) Is anterior segment OCT superior to slit-lamp biomicroscopic examination for Kayser-Fleischer ring in Wilson's disease? European Review for Medical and Pharmacological Sciences, 26(14): 5178-5185.
24. Redzia-Ogrodnik, B., Czlonkowska, A., Antos, A., Bembenek, J., Kurkowska-Jastrzebska, I., Przybylowski, A., et al. (2023) Pathognomonic neuroradiological signs in Wilson's disease - truth or myth? Parkinsonism and Related Disorders, 107: 105247.
25. Ferenci, P., Caca, K., Loudianos, G., Mieli-Vergani, G., Tanner, S., Sternlieb, I., et al. (2003) Diagnosis and phenotypic classification of Wilson disease. Liver International, 23(3): 139-142.
26. Antos, A., Czlonkowska, A., Smolinski, L., Bembenek, J., Przybylowski, A., Skowronska, M., et al. (2023) Early neurological deterioration in Wilson's disease: a systematic literature review and meta-analysis. Neurological Sciences, 44(10): 3443-3455.
27. Mohr, I., Pfeifferberger, J., Eker, E., Merle, U., Poujois, A., Ala, A., et al. (2023) Neurological worsening in Wilson disease - clinical classification and outcome. Journal of Hepatology, 79(2): 321-328.
28. Litwin, T., Dziezyc, K., Karlinski, M., Chabik, G., Czepiel, W., Czlonkowska, A. (2015) Early neurological worsening in patients with Wilson's disease. Journal of the Neurological Sciences, 355(1-2): 162-167.