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REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Wilson's disease

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SUMMARY
Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism caused by mutations in the *ATP7B* gene, which is located on chromosome 13q14.3. The global genetic prevalence of WD at birth is approximately 13.9–15.4 per 100,000 population. Although WD is a rare condition associated with treatment efficacy, mortality rates in patients with WD (5–6.1%) are higher than healthy controls. Prevalent features of WD include hepatic, neurologic, and psychiatric syndromes, even though various signs and symptoms of the disease have been depicted to this point. If diagnosed and treated at an early stage, WD patients would likely improve and be often largely asymptomatic for the rest of their lives. Prompt diagnosis and lifelong treatment substantially affect outcome.
We aimed to summarize current knowledge about WD epidemiology, genetics, clinical manifestations, diagnostic workup, and current WD management.
Keywords: Wilson's disease; copper; diagnostic algorithms; treatment

INTRODUCTION

Wilson's disease (WD) is a rare, recessively inherited disorder of copper metabolism caused by its pathological accumulation in liver and extrahepatic organs [1]. Accordingly, prevalent features of WD include hepatic, neurologic, and psychiatric syndromes, even though various signs and symptoms of the disease have been depicted to this point. If diagnosed and treated at an early stage, WD patients would likely improve and be often largely asymptomatic for the rest of their lives. Prompt diagnosis and lifelong treatment substantially affect outcome.

We aimed to summarize current knowledge about WD epidemiology, genetics, clinical manifestations, diagnostic workup and current WD management.

WILSON'S DISEASE GENETICS

Wilson's disease is an autosomal recessive inherited disorder of copper metabolism caused by mutations in the *ATP7B* gene, which is located on chromosome 13q14.3. It encodes a copper-transporting P-type ATPase. Mutations in the *ATP7B* gene disrupt the synthesis and function of the *ATP7B* protein, thereby precipitating an impairment in the hepatocellular copper excretion pathway. Until now, 1275 mutations in the *ATP7B* gene have been identified [2]. The missense mutation H1069Q (substitution of histidine with glutamine on the position 1069) in exon 14 is the most common mutation responsible for WD worldwide. About 50–80% of WD patients from Central, Eastern, and Northern Europe carry at least one allele with the H1069Q mutation, with its highest frequency in Poland and Eastern Germany. The H1069Q is the most frequent mutation in Serbian population, found in 38.4–48.9% of analyzed alleles [3, 4].

The approach to identifying pathological mutations in WD focuses on targeting restricted exons known to contain the majority of mutations in one population [2, 3]. This strategy facilitates molecular genetic testing by eliminating the requirement for a protracted and expensive process.

EPIDEMIOLOGY

The global genetic prevalence of WD at birth is approximately 13.9–15.4 per 100,000 population [5]. Additionally, there is a difference in prevalence of WD between epidemiological (1.4 per 100,000) and genetic (13.9 per 100,000) studies. Finally, this disparity may be evidence of underdiagnosis of WD on a population level, or of delayed diagnosis and consequent early deaths [6]. Although WD is a rare condition associated with treatment efficacy, mortality rates in patients with WD (5–6.1%) are higher than healthy controls. Late diagnosis and stopping treatment might lead to a high mortality rate [7].

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CLINICAL PRESENTATION

In addition to the hepatic and neurological manifestations, whose significance is apostrophized through the name of 'hepatolenticular degeneration,' there is plenty of other symptoms and signs that result from the copper accumulation and cell damage in various tissues (Table 1). We will discuss common symptoms of WD in more detail.

Table 1. Clinical manifestations of Wilson's disease

Neurological manifestations	Extrapyramidal manifestations (tremor, parkinsonism, dystonia, chorea, myoclonus, tics)
	Cerebellar manifestations
	Dysarthria
	Dysphagia
	Other features (autonomic dysfunction, seizures, headaches)
Psychiatric manifestations	Personality changes
	Anxiety
	Depression
	Apathy
	Psychotic spectrum
	Mild cognitive impairment/Dementia
Hepatic manifestations	Chronic hepatic failure / cirrhosis
	Acute hepatic failure (including fulminant disease course)
Ocular manifestations	Kayser–Fleischer ring
	Sunflower cataract
	Other features
	nyctalopia, exorpic strabismus, optic neuritis, pallor of the papilla of the optic nerve, loss of accommodation
Other systemic manifestations	Hematologic (hemolytic anemia, thrombocytopenia)
	Myocardial (cardiac hypertrophy, arrhythmias, cardiomyopathy)
	Renal (hematuria, proteinuria, nephrocalcinosis, impairment of renal function)
	Musculoskeletal (osteoporosis, osteomalacia, osteoarthritis)
	Dermatological (hyperpigmentation, acanthocytosis nigricans, bluish discoloration of nails)

Neurological manifestations of Wilson's disease

While all untreated patients will develop neurological manifestations eventually, approximately 40–60% of patients present with neurological symptoms and signs at onset [8]. In patients with predominant neurological form of WD, first symptoms usually occur at around 20 years old, while patients have been described with first symptoms as early as six years old. Lately, special attention is drawn towards late-onset WD, suggesting that classic diagnostic approach should be modified and include testing for WD even for older individuals when high clinical suspicion is present.

Hallmark clinical manifestations of WD stem from basal ganglia involvement. Three major clinical syndromes were identified in patients with neurological symptoms at onset:

a) akinetic-rigid syndrome resembling parkinsonism,
b) generalized dystonic syndrome,
c) "pseudosclerotic" syndrome with predominant cerebellar manifestations.

Tremor is the most common neurological symptom affecting 30–50% of WD patients [9]. While coarse proximal tremor resembling wing-beating is typical for WD, these patients can present with static, kinetic, and intentional tremor. While arms are commonly affected, tremor can affect other body parts as well, mainly head and tongue. Besides tremor at rest, 40% of patients can present with other typical parkinsonian features, including rigidity and bradykinesia [10].

Dystonia (focal, segmental, multifocal, or generalized) is a presenting symptom in up to 69% of patients with neurological symptoms at onset [11]. MRI study showed that putamen was affected in 80% of WD patients with dystonia compared to only 24% in those without dystonia, suggesting its pathophysiological role in dystonia development [12]. Status dystonicus, life-threatening disorder characterized by acute worsening of generalized dystonia, can be induced in some WD patients either by introduction or withdrawal of specific drugs for WD [13, 14].

Cerebellar dysfunction is present in approximately 30% of patients and manifests as cerebellar tremor, appendicular ataxia, and speech and gait disturbances.

Speech disturbances are a pronounced feature of WD and in some case series, such as our own, the most common one, where 90% of patients had speech difficulties prior to treatment initiation [15].

Psychiatric manifestations of Wilson's disease

Most reports show that psychiatric symptoms occur as the earliest manifestation in about 30–40% of patients with WD [16]. The spectrum of these symptoms varies from subtle personality changes to frank psychosis. In our study of already established and treated WD, 72% of them had at least one psychiatric symptom on the neuropsychiatric inventory, while 44% had clinically significant symptoms [17]. Anxiety was the most common and the most severe symptom, followed by depression, apathy, and irritability [17].

Hepatic manifestations of Wilson's disease

Hepatic manifestation varies from subtle structural liver changes, which may be asymptomatic, to more severe presentations such as acute hepatitis, acute liver failure, recurrent jaundice and hemolysis, or cirrhosis [7]. Liver disease is a presenting symptom in about half (40–60%) of WD patients [7]. Usually in children and young adults there is mild to moderate liver disease with mildly elevated liver enzymes, witch if left untreated may progress to chronic liver disease with consequent cirrhosis, portal hypertension, hepatosplenomegaly, coagulopathy, and hypoalbuminemia. Hepatic decompensation may lead to ascites, jaundice, gastrointestinal bleeding due to coagulopathy and esophageal varices and hepatic encephalopathy with hyperammonemia [7]. The most severe form of

hepatic involvement in WD patients is acute liver failure often associated with hemolytic anemia, coagulopathy, encephalopathy, and rapid renal failure. Acute or rapid liver deterioration may occur in those WD patients who stopped treatment [7]. Most severe forms of liver disease may require liver transplantation [7].

Ocular manifestations of Wilson's disease

The most common ophthalmological manifestations of WD are Kayser–Fleischer's (KF) ring and sunflower cataract, but in this disease pathological changes can also be present in the retina, visual pathways, and in the ocular motility [18].

The KF ring is considered a pathognomonic sign of WD, consisting of concentric deposits of copper in Descemet's membrane at the very periphery of both corneas. It occurs in as many as 90.4–100% of people with a neurological form of WD, and somewhat less often (in 50–60% of cases) in those without neurological signs of this disease. This sign is considered not only essential for the diagnosis of WD, but also important for treatment and as a prognostic factor of the disease [7].

Sunflower cataract is a somewhat rarer manifestation of WD, as it occurs in about 2–20% of WD patients [7]. This lens opacification is yellowish in color, located under the lens capsule, with a central disc and radiating leaves that resemble a sunflower flower. It generally does not cause a significant decrease in visual acuity.

Other ophthalmological problems have been described in WD, but mostly sporadically – nyctalopia, exorpic strabismus, optic neuritis, pallor of the papilla of the optic nerve, loss of accommodation [7]. We found that WD patients may have lower intraocular pressure compared to the healthy population [19].

DIAGNOSIS OF WILSON'S DISEASE

Wilson's disease diagnosis is based on a combination of clinical features and laboratory parameters (Table 2) [7]. Multiple clinical, radiographic, and laboratory biomarkers of the WD when combined may facilitate the diagnosis, but the diagnosing process may be challenging because none of these biomarkers is specific to WD [1]. The first two steps should be liver disease laboratory assessment and ophthalmological examination for KF ring, followed by copper metabolism tests. If necessary, liver biopsy should be considered in selected cases. Genetic analysis is necessary for definite WD diagnosis, but still not widely accessible.

1. Laboratory testing should begin with clinical biochemical liver tests, blood counts, and coagulation parameters to assess for liver disease.

2. The KF ring is visible on slit lamp examination or anterior segment optical coherence tomography, rarely by naked eye. Absence of KF ring does not exclude WD diagnosis: it can be found in most cases with neurological form and in approximately half of cases with hepatic form of WD. Similar rings can be found in other chronic hepatic disorders, long lasting cholestasis, and cirrhosis [20, 21].

3. Copper metabolism

a. Serum ceruloplasmin

The normal concentration of ceruloplasmin measured by the enzymatic assay varies among laboratories (with a lower limit 0.15–0.2 g/L) [1]. In WD, ceruloplasmin is usually lower than 0.1 g/L [1]. However, this is typical value for neurologic WD, but it can be normal in about half patients with active liver disease [7, 22]. Modestly subnormal levels of ceruloplasmin (0.14–0.2 g/L) may be detected in heterozygotes [22]. Ceruloplasmin levels are increased in acute inflammation, estrogen supplementation and pregnancy, and decreased in malabsorption syndromes, renal or enteric protein loss, severe liver disease of any etiology and in a distinct genetic disorder – aceruloplasminemia [1].

b. Serum copper

Total serum copper consists of copper incorporated in ceruloplasmin and "free" serum copper which is not incorporated in ceruloplasmin. Total serum copper is usually decreased in proportion to reduced ceruloplasmin levels. Therefore, normal or increased total serum copper in individuals with decreased ceruloplasmin indicate an increase in the concentration of "free" serum copper. In most untreated

Table 2. Routine tests for diagnosis of Wilson's disease (adopted from references [1, 21])

Test	Typical finding	False-negative	False-positive
Serum ceruloplasmin	Decreased by 50% of lower normal limit	• Normal levels in patients with marked hepatic inflammation • Overestimation by immunologic assay • Pregnancy, estrogen therapy	Low levels in patients with malabsorption, malnutrition, aceruloplasminemia and in heterozygotes
24-hour urinary copper	> 100 µg (1.6 µmol) / 24 hours (> 40 µg (0.64 µmol) / 24 hours in children)	Normal Incorrect collection, children without liver disease	Increased: hepatocellular necrosis, cholestasis, contamination
Serum free copper	>100 µg/L (1.6 µmol/L)	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	>250 µg (4 µmol)/g dry weight	Due to regional variation • In patients with active liver disease • In patients with regenerative nodules	Cholestatic syndromes
Kayser–Fleischer rings by slit-lamp examination	Present	Absent • In up to 50% of patients with hepatic Wilson's disease • In most asymptomatic siblings	Other chronic hepatic disorders with long lasting cholestasis and cirrhosis (i.e. primary biliary cirrhosis)

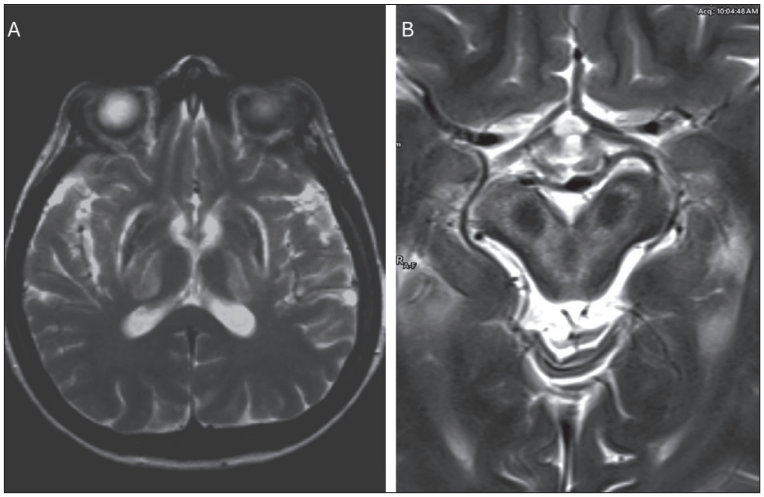

Figure 1. Symmetrical T2W hyperintense lesions of the lateral putamen; heterogeneous lesions of both thalami, hyperintense at the periphery and hypointense centrally; (A) "face of the giant panda sign" of mesencephalon when the substantia nigra and red nucleus are surrounded by a high T2W signal in the tegmentum (B); courtesy of Robert Semnic, MD

patients, "free" serum copper is elevated above 200 μg/L. Measuring serum copper is more important to monitor pharmacotherapy than in the diagnosis of WD [1, 7].

c. Urinary copper

In untreated symptomatic patients urinary copper levels > 100 μg / 24 h (> 1.6 μmol / 24 h) are considered diagnostic for WD. However, up to 23% of patients (mostly children and asymptomatic siblings) may have copper levels less than 100 μg / 24 h at the presentation. Keep in mind that urine copper may be elevated in other hepatic diseases and somewhat elevated in heterozygotes. Incomplete urine collection, copper contamination and renal failure may also affect measuring copper values. The radioactive copper test is available in highly specialized centers and is used if other cooper test or genetic findings are inconclusive [1, 7, 22].

1. Liver biopsy

A liver biopsy is sometimes needed for the differential diagnosis of liver pathology. In terms of the WD diagnosis, liver biopsy is used to measure hepatic parenchymal copper concentration. Hepatic copper > 250 μg (4 μmol)/g dry weight is considered diagnostic for WD [7].

2. Neuroimaging

Brain MRI is very important for WD diagnosis and may be helpful for treatment monitoring [7]. Typical finding is symmetric T2-weighted hyperintense changes in basal ganglia (mainly putamen and caudate nuclei), thalami, midbrain, and pons. In more advanced cases, these abnormalities can be seen in T1-weighted images as hypointense changes [7]. The 'face of the giant panda' in the midbrain is a characteristic sign, but present in up to 20% of cases of neurological WD (Figure 1) [1, 7]. Characteristic brain MRI changes occur in almost all drug-naive neurological WD patients, in 40–75% of hepatic and in 20–30% of presymptomatic WD patients [7], and are always symmetrical [23]. We studied 16 neurologically asymptomatic patients with hepatic form of WD and found that MRI showed brain parenchyma lesions in all untreated, and in 44% of treated patients [24]. In our study, prominent midbrain atrophy was present in patients with WD, with some measures changed regardless of the form of the disease (neurologic *vs.* hepatic). Some of the brain morphometric measures (interpeduncular angle, transverse diameter of the midbrain peduncle, and interpeduncular distance) were useful in differentiating patients from healthy subjects (probability reaching 93%) [25].

Transcranial sonography is a reliable and sensitive tool in detecting basal ganglia abnormalities, including accumulation of copper and other trace metals in WD [26]. We found significantly higher prevalence of hyperechogenicity in lenticular nucleus and substantia nigra in comparison with healthy controls [26].

3. Genetic analysis

The entire *ATP7B* gene sequencing should be performed if the diagnosis is difficult to establish by clinical and biochemical testing. Specific analysis for known mutations is recommended for WD screening in the first-degree relatives of WD proband [22].

WILSON'S DISEASE TREATMENT

The aim of WD treatment is to remove the accumulated copper from tissues and to prevent further copper gain by its increased elimination and/or reduced resorption of dietary copper (Table 3).

1. Dietary copper restriction

Copper is ubiquitous in food and water supplies and a low-copper diet has long been considered important in WD management. However, according to the current recommendations, a low-copper diet is unnecessary although some clinicians suggest avoidance of copper-rich foods such as shellfish, liver, cocoa, nuts, chocolate, mushroom, and dried fruits in first few months of treatment [27].

2. Chelation therapy

Chelating agents mobilize intracellular copper into the circulation and enhance its urinary excretion [28]. The most used chelating agents are penicillamine and trientine.

• Penicillamine

Penicillamine is a thiol with a sulfhydryl group that binds copper and facilities its excretion into urine. In

Table 3. Dosing, adverse effects and treatment monitoring for current Wilson's disease treatment (adapted according to references [27, 29])

Treatment	Symptomatic adults	Adults with severe neurological symptoms*	Maintenance dose (typically after 2 years)	Children	Adverse effects	Target for urinary copper excretion (typically after 9–12 months)
Penicillamine	start with 250 mg/day, increase dose weekly up to 1000–1500 mg/day in two divided doses	start with 125 mg/day, slowly increasing by 125 mg per 1–2 weeks, up to 1000–1500 mg/day in two divided doses	750 mg–1000 mg/day	125 mg/day slow increase by 125–250 mg per week to 20 mg/kg/day in two divided doses	early: • hypersensitivity reactions (fever and rash), proteinuria, bone marrow suppression (thrombocytopenia and neutropenia), • neurological worsening late: • lupus-like syndrome, Goodpastures syndrome, elastosis perforans serpiginosa, cutis laxa, poor wound healing	approximately 200–500 µg / 24h (3–8 µmol/24h)
Trientine	800–1600 mg/day for trientine dihydrochloride (Cufence); 450–975 mg/day for trientine tetrahydrochloride (Cuprior) in two divided doses	start with 150–200 mg/day, slowly titration by 150–200 mg per 1–2 weeks up to 800–1600 mg/day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses.	800–1600 mg/day for trientine dihydrochloride (Cufence) or 450–975 mg/day for trientine tetrahydrochloride (Cuprior) in two doses	150–200 mg/day, slowly increasing by 150–200 mg/week to 400–1000 mg/day for trientine dihydrochloride (Cufence) or 225–600 mg/day for trientine tetrahydrochloride (Cuprior) in two divided doses	Early • urticaria or other rashes, arthralgia, myalgia, proteinuria, hematuria, sideroblastic anemia • neurological worsening	approximately 150–500 µg / 24 h (2.4–8 µmol / 24 h)
Zinc	150 mg/day of elemental zinc** divided in 2–3 doses	150 mg/day in 2–3 divided doses	150 mg/day in 2–3 divided doses	25 mg / day in patient < 6 years; 75 mg / day mg divided in three doses in patients aged 6–16 years or < 50 kg; 150/day mg divided in three doses in patient > 16 years or > 50 kg	early nausea, abdominal pain, gastritis, and paradoxical neurological worsening	< 100 µg / 24 h (< 1.6 µmol / 24 h)

*Generalized dystonia, oromandibular dystonia with dysphagia;
**Doses are for elemental zinc; therefore, true dose of zinc salt may differ and should be calculated

recommended doses of 1–2 g per day it initially leads to up to 9 mg of cupriuresis per day. Typically, by the end of 12–18 months after treatment introduction, penicillamine-induced copper excretion decreases following decrement of tissue accumulated copper [27]. According to the recommendations of recent therapeutic guidelines and our own experience, penicillamine is recommended for use in symptomatic patients during the initial intensive phase of treatment and later as maintenance therapy [15, 27, 29, 30]. It could also be recommended in presymptomatic patients. Women with WD should be made aware of the importance of continuing therapy during pregnancy, as stopping treatment may be associated with clinical deterioration [27]. However, breastfeeding should be avoided because penicillamine is excreted in breast milk and may interfere with the infant's copper metabolism [27]. In symptomatic adults, recommended penicillamine dose is 1–1.5 g per day (the dose in children is 20 mg/kg/day) [27, 29]. Given that most adverse effects are dose-dependent, the general rule is to start low and go slow, aiming to reach the initial target dose in 6–8 weeks. We usually start with 125–250 mg per day with dose increments of 125 mg per week in adults presenting with neurological symptoms.

Although it is not necessary, we usually admit patient to the hospital to initiate treatment because careful monitoring for adverse effects is essential, including neurological follow-up, full blood count, liver function tests and renal profile every week during the first month of treatment initiation. Then, in outpatient settings, we advise monitoring the mentioned parameters once a month during the first six months of therapy. After establishing sustainable clinical improvement, which is estimated to require about two years of continuous use of chelators, the dose may be reduced to 500–750 mg per day to prevent disease progression. According to The Wilson's Disease Support Group UK, 24-hour urinary copper output while continuing medications (on treatment) should be 3–8 µmol / 24 h (200–500 µg / 24 h) with chelating agents [27].

On the basis that high doses of penicillamine may disrupt pyridoxine metabolism, prophylactic supplementation

with 50 mg once a day is usually advised [2, 7, 30]. D-penicillamine should be taken twice a day on an empty stomach, preferably fasting 3–4 hours before and 2–4 hours after the dose.

Up to 30% of WD patients with neurological symptoms at presentation may develop paradoxical neurological worsening after penicillamine treatment introduction. It may occur within the first six months after treatment initiation [31]. Sometimes deterioration is irreversible or even fatal [14].

• Trientine

The four amino groups of trientine form a stable ring complex with copper and facilitate cupriuresis. The efficacy of trientine and penicillamine regarding urinary copper excretion is similar. Trientine is a life-saving treatment option in patients in whom penicillamine had to be discontinued due to adverse events or in patients who have increased risk of adverse effects (i.e. history of autoimmune diseases, severe thrombocytopenia, or renal disease and allergy to penicillin) [1, 27]. Trientine could be used as a first-line therapy in the initial intensive and the later maintenance phase of treatment in both symptomatic and asymptomatic WD patients; it is safe to use during pregnancy but should be avoided during breastfeeding [27].

• Zinc salts

Zinc salts reduce intestinal absorption of copper. Zinc salts given orally are absorbed by the intestinal cells, in which they increase production of metallothionein, cysteine-rich protein that can bind various metal ions [29]. Subsequently, metallothionein-bound copper is eliminated by feces when the enterocytes are shed in the intestinal lumen during physiological intestinal cell turnover [27, 29]. According to a recent guidance, zinc is recommended as maintenance therapy in symptomatic patients once symptoms have regressed following treatment with oral copper chelators and as the first-line therapy in asymptomatic patients [27]. Zinc is administered as sulfate, acetate, or gluconate salts. The recommended dose is 150 mg of elemental zinc in adults, or 75 mg in children, in two or three divided doses per day. Food interferes with zinc absorption – therefore, it should not be given at mealtimes. Zinc can be safely used during pregnancy [27, 29].

LONG TERM OUTCOME

Patients with WD who are timely diagnosed and compliant to de-coppering treatment have favorable disease outcome. The treatment adherence is a single most important determinant of a good long-term disease prognosis [7, 15]. However, despite overall good response to de-coppering treatment, a significant proportion of patients feature residual neurological symptoms [32, 33]. In our patients with neurological form of WD who had good therapy adherence, presence of dystonia at the disease onset was a predictor of residual disability, in line with other studies suggesting that dystonia is a poor indicator of both short- and long-term outcome [15, 33]. The extent to which the diagnostic and treatment delay negatively affects prognosis varies among studies [15, 34]. A four-fold increased mortality rate compared to the general population was reported with cumulative mortality over 10 years of 9.3% in WD compared to the mortality rate of 2.4% in reference healthy individuals [35]. Principal causes of death in WD include long diagnostic delay, non-compliance to the therapy, and the development of malignancies [36]. In our cohort of 142 patients, the most frequent causes of death were liver failure due to cirrhosis in 16.6% and hemorrhage due to esophageal varices in 13.3% of patients, while a surprisingly high rate of suicide (13.3%) was observed, with mortality rate due to suicide being 1.7 times higher compared to the age-matched Serbian population [37].

Both mental and general health were among the Quality of Life (QoL) dimensions mostly affected in WD [38]. QoL is poor in patients who experienced a long delay in treatment and generally worse in patients with neurological form of the disease than in patients with hepatic form [39]. Psychiatric symptoms (in particular depression) were identified as a significant determinant of poor QoL in WD [39, 40]. A lack of standardized QoL assessment scale and more studies with larger sample sizes represent an unmet need in addressing QoL in WD [37, 38].

CONCLUSION

WD is a treatable neurovisceral disorder not to be missed. There are numerous clinical, biochemical, and imaging biomarkers which, combined, facilitate a timely diagnosis of WD. Prompt therapy aimed to reduce copper overload should be immediate, if possible, even in asymptomatic individuals. Early treatment is connected to favorable outcome, it could prevent further progression of symptoms, may reduce present symptoms and significantly influence patients' quality of life.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: Marina Svetel has received speaking honoraria from Makpharm, Salveo, Unihem and Pharmaswiss. Nikola Kresojević received speaking honoraria from Makpharm, Salveo, Remedica, and travel grants from Vemax Pharma, Salveo, Goodwill Pharma. Aleksandra Tomić has received speaking honoraria from Makpharm, Unihem, and travel grant from Medtronic. Milica Ječmenica Lukić and Vladana Marković received speaking honoraria from Makpharm. Nataša Dragašević and Igor Petrović received speaking honoraria from Makpharm and Salveo. Iva Stanković, Tatjana Pekmezović, Ivana Novaković, Marija Božić, Marko Svetel, and Jelena Vitković have nothing to report.

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Вилсонова болест

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САЖЕТАК

Вилсонова болест (ВБ) је аутозомно рецесивни наследни поремећај метаболизма бакра узрокован мутацијама у гену *ATP7B*, који се налази на хромозому *13q14.3*. Глобална генетска преваленција ВБ при рођењу је приближно 13,9–15,4 на 100.000 становника. Иако је у питању ретка болест за коју постоји ефикасна терапија, стопе морталитета код болесника са ВБ (5–6,1%) веће су од здравих контрола. Доминантне карактеристике ВБ укључују хепатичне, неуролошке и психијатријске синдроме, а поред њих су описани бројни други симптоми и знаци. Ако би се дијагноза поставила и лечење започело у раној фази, стање болесника са ВБ би се вероватно побољшало и болесници би често били углавном без симптома до краја живота. Правовремена дијагноза и доживотно лечење значајно утичу на исход.

Циљ нам је био да сумирамо тренутна знања о епидемиологији ВБ, генетици, клиничким манифестацијама, дијагностичкој обради и тренутном управљању ВБ.

Кључне речи: Вилсонова болест; бакар; дијагностички алгоритам; лечење