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UPDATE OF EXPERT RECOMMENDATIONS ON WILSON'S DISEASE MANAGEMENT

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Wilson's disease is a rare autosomal recessive hereditary disorder of copper metabolism characterized by excessive copper build up in tissues, including brain and liver. The genetic defect localized at the 13q14 – q21 locus affects the gene for copper transporting protein ATP7B in the liver. This defect can be caused by deletions, insertions or missense mutations, leading to disruption of the copper incorporation into ceruloplasmin and the excretion of excess copper into bile. The disease is characterized by liver damage, neuropsychiatric symptoms, musculoskeletal, hematological and renal clinical signs, the presence of Kayser-Fleischer rings as well as many other possible symptoms, with their manifestation depending on the timeliness of diagnosis, stage and form of the disease, and therapeutic interventions.

Organizations investigating the problems of Wilson's disease regularly issue new recommendations as knowledge about the disease expands. Innovative diagnostic and therapeutic procedures are put into practice, and views on the course of the disease features change. The general updates of the latest international recommendations described in this article for their early introduction into practical healthcare relate to diagnostic algorithms, indications and the choice of timing and methods of drug treatment in various groups of patients with Wilson's disease, including a more complete review of neuropsychiatric care, as well as the possible tools for therapy monitoring.

Key words: Wilson's disease, ceruloplasmin, ATP7B, serum copper, Wilson's disease therapy.

There are currently 5 international guidelines for Wilson's disease (WD): American Association for the Study of Liver Diseases, 2022 (AASLD) [7], European Association for the Study of the Liver, 2012, update scheduled for 2023 (EASL) [3], British Association for the Study of the Liver, 2022 (BASL) [2], European Society for Paediatric Gastroenterology, Hepatology and Nutrition, 2018 (ESPGHAN) [16], Protocole National de Diagnostic et de Soins, 2022 (PNDS) [6, 11, 12, 15, 16] The main goal of WD communities is regular high-quality updates of existing recommendations in all areas of management for WD patients based on incoming scientific data and observations.

The diagnostics section of AASLD 2022 [14] focuses on the psychiatric manifestation associated with WD, which can mask as a bipolar, depressive or psychotic disorder, personality changes, cognitive difficulties and sleep disorders [12]. Thus, any patient with a neurological or mental disorder with unexplained liver disease can be examined for possible WD.

Pediatric recommendations have common features and differences, too. But all recommendations indicate the need for a WD examination for all chil-

dren with liver disease or unexplained hemolytic anemia and children of 5 years and older with unexplained neuropsychiatric symptoms.

Comparison of BASL (2022) [15] and ESPGHAN (2018) [16] recommendations demonstrate differences in the age limit for the examination. According to BASL, all children with liver diseases or children from 5 year and older with neurological symptoms are subject to examination [15], while ESPGHAN suggests conducting studies in children with liver diseases only from 1 year and older and in any teenagers with neurological signs [16].

The diagnostic evaluation for WD, agreed upon at a consensus meeting, according to ESPGHAN is presented in Table 1 and is carried out in 3 stages [16].

Leipzig Score is recommended by EASL [6] and ESPGHAN [16] as a standardized and valid method for estimating the probability of WD based on a weighted score of diagnostic criteria. This proposed diagnostic score for WD is interpreted as follows: ≥ 4 – WD diagnosis is likely; 2 to 3 – WD diagnosis is probable, but more investigations are needed; 0 to 1 – WD diagnosis is unlikely.

Организация и экономика здравоохранения

Table 1 – Diagnostic evaluation for Wilson's disease [16]

Leipzig Score	-1	0	1	2	4
Kayser-Fleischer rings		absent		present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		absent		present	
Coombs negative haemolytic anaemia + high serum copper		absent	present		
Urinary copper (in the absence of acute hepatitis)		normal	1-2 x ULN	>2 x upper limit of normal (ULN), or normal but >5 x ULN 1 day after challenge with 2 x 0.5 g D-penicillamine	
Liver copper quantitative	normal		< 5 x ULN (<250 µg/g)	>5 x ULN (>250 µg/g)	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		absent	present		
Serum ceruloplasmin (nephelometric assay)		> 0.2 g/l	0.1-0.2 g/l	< 0.1 g/l	
Disease-causing mutations detected		none	1		2

The stages of the study are recommended according to the three-level testing of indicators:

1. Clinical evaluation for hepatosplenomegaly, ascites, Kayser-Fleischer (KF) rings; liver tests: alanine aminotransferase (ALT)/ aspartate aminotransferase (AST), bilirubin, international normalized ratio (INR), alkaline phosphatase (ALP); biochemical tests for copper metabolism, serum ceruloplasmin (Cp), 24-hour urine copper excretion (UCE);

2. Molecular testing (common mutations, genome-wide sequencing);

3. Copper in the liver (if molecular testing fails or is unavailable).

An algorithm for WD diagnostic approach in a patient with unexplained liver disease is shown in Figure 1. The initial testing consists of Cp, UCE, and a slit lamp ophthalmoscopy [12].

Proposed diagnostic methods for WD have common features as well as some differences:

1. Serum ceruloplasmin: all clinical recommendations are in agreement that it cannot be used alone to make WD diagnosis.

Suggestive cutoffs: ≤ 0.2 g/L [6, 16], < 5 mg/dL [14], < 0.1 g/L [15], ≤ 0.14 g/L [11]

2. UCE: variable cutoff in asymptomatic and symptomatic children:

(> 0.64 µmol/24 h and > 1.6 µmol/24 h) [6]

(> 0.65 (µmol/24 h and $> 1,6$ µmol/24 h) [16]

($>$ and 0.6 µmol/24 h and $> 1.6/$ µmol/24 h) [15, 11]

3. Liver biopsy [6, 11, 12, 15, 16]: all guidelines confirm it may help with the WD diagnosis when other noninvasive tests are inconclusive.

4. Brain MRI [6, 11]: indicated for all patients with suspected WD with neurological or psychiatric manifestations and for all patients starting therapy.

5. Genetic testing: should be performed for all patients with suspected WD [11, 14, 15]

PNDS [11] recommends determining the relative exchangeable copper to total copper in blood serum (REC). REC is an excellent diagnostic biomarker with sensitivity and specificity close to 100% for the diagnosis of WD when its value exceeds 18.5%. REC helps to distinguish between Wilson's hepatopathy and hepatopathy of other genesis (non-alcoholic fatty liver disease (NASH), autoimmune, infectious hepatopathies). In addition, REC can become an important contribution to family screening, allowing to differentiate heterozygous carriers or healthy subjects with no variants from patients with WD if REC exceeds 15%.

According to experts, the accuracy of laboratory data may suffer due to known factors influencing serum Cp (estrogen level, inflammation) or incom-

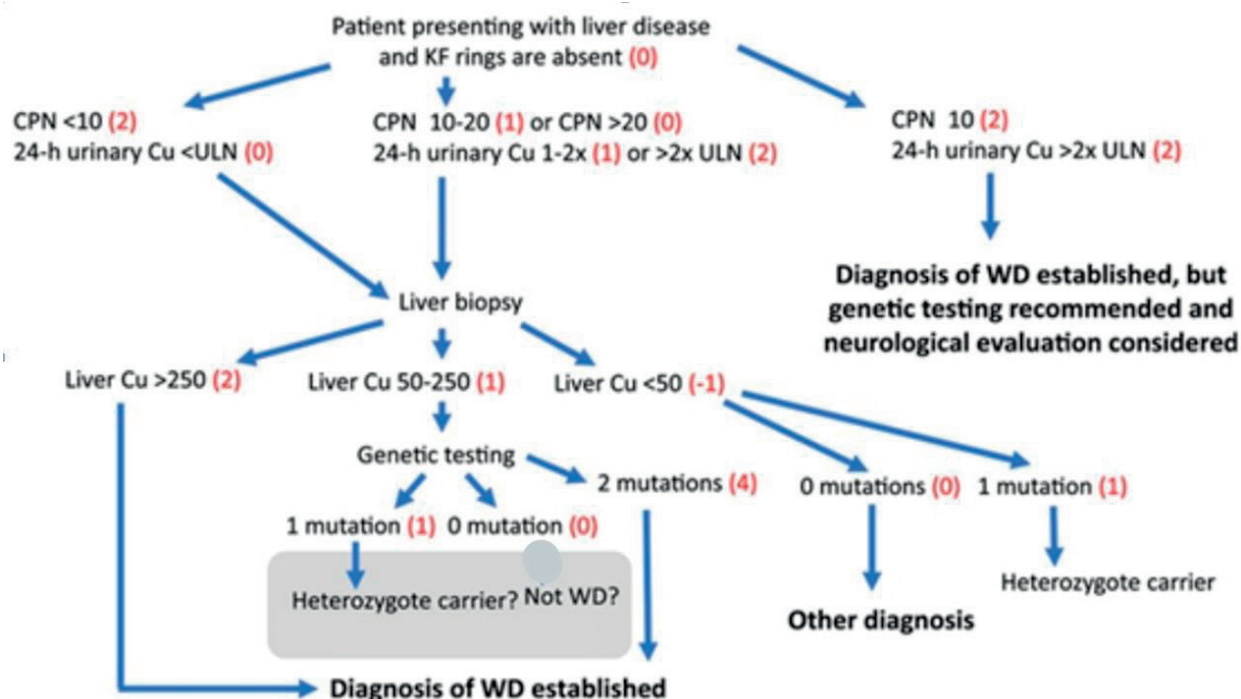


Figure 1 – Amplified Algorithmic Approach согласно AASLD 2022 [12]; CPN – ceruloplasmin

plete collection or contamination of 24-hour urine sample. When studying liver copper, the size of the biopsy sample and the storage conditions of the material can affect the results. Another important factor leading to misinterpretation of the results may be the competence of the staff and the completeness of the genetic analysis.

To reduce the analysis results inaccuracies the following actions are recommended: executing clinical recommendations for other diseases associated with low serum Cp levels, confirming the technical adequacy of the test material, checking creatinine levels, repeating the analysis, checking the report and/or discussing it with a pathologist, reviewing protocols, genetic counseling to confirm trans (not cis) mutations [11].

PNDS 2022 [11] recommends an assessment of brain involvement in all newly diagnosed patients, whether they are children, adolescents or adults, including a consultation with a neurologist and brain MRI. While EASL [6], BASL [15], AASLD [14] consider an MRI only for patients with suspected WD with psychiatric or neurological abnormalities detected during a neurological examination.

When diagnosing WD, according to all recommendations, it is necessary to conduct a family screening of the patient's relatives. First of all, brothers and sisters should be checked, followed by parents to detect transposition mutations and exclude cases of pseudodominance. The determination of serum Cp, ICE, REC, liver enzymes and

molecular biological search for familial mutations of the ATP7B gene by Sanger sequencing of the exons is carried out among the family members.

The screening of uncles, aunts and cousins of the patient is carried out based on the high frequency of heterozygous carriers – 1/31 individuals, which contributes to the timely and effective treatment of those identified.

The question of medical treatment for the genetically pre-symptomatic patients with 2 pathogenic variants of the ATP7B gene and a normal copper profile remains open. There is no consensus on the treatment of this category of patients. Careful monitoring is necessary, for example, a 6-month clinical and biological observation to decide on the adequate timing of treatment.

Updated recommendations for treatment start depend on the patient's symptoms and the presence of organ damage.

The phases of the disease in the absence of treatment include asymptomatic increase in serum enzymes with accompanying liver inflammation, then subsequent manifestations of nonspecific symptoms of liver disease with the eventual development of neuropsychiatric symptoms and ensuing cirrhosis. The terminal stage of liver failure manifests with characteristic symptoms of portal hypertension and its complications (ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma or cholangiocarcinoma). Death occurs in 3-5% of patients with acute liver failure (ALF) [12]

Организация и экономика здравоохранения

Table 2 – Recommendations for WD therapy for adults

Society, Year Published	Recommended Initial Therapy	Recommended Therapy for Maintenance and Asymptomatic Patients
AASLD, 2022 [14]	Chelator ± zinc	Chelator or zinc
EASL, 2012 [6]	Chelator	Chelator or zinc
Common Features Among Guidelines [6, 12, 14] 1. Use of chelating agents for the initial decoppering phase 2. Dose reduction of chelating agents or zinc during maintenance therapy 3. Cautious initiation with high dose chelators in neurologic WD due to risk for paradoxical worsening		

Following these stages, asymptomatic patients without signs of organ damage may be treated with either a lower maintenance dose of a chelating agent or with zinc initially. However, treatment can be ineffective with any drugs and at any phase, which should lead to a revision of pharmacotherapy [14].

The drug therapy recommended for symptomatic and asymptomatic adult patients with WD is presented in Table 2.

The drug therapy recommended for symptomatic and asymptomatic patients with WD in pediatric practice is presented in Table 3.

Some promising emerging therapies that may address these limitations are in development: [12, 15]

1. Bis-choline tetrathiomolybdate: phase 3, once-daily oral agent [12]

2. Gene therapy: phase 1 or 2 [12]

Treatment Monitoring at the initial stage, according to all recommendations, involves a general blood test, a kidney profile tests, liver function tests, a urine test strip and the main indicators of copper balance: UCE and non-ceruloplasmin-bound serum copper (NCC) [6, 11, 14, 15, 16]

According to BASL [15] and ESPGHAN [16], the frequency of monitoring is recommended as "close monitoring" in the first few months: 1 week after treatment, then every 2 weeks for 3 months, every 1-3 months until remission and every 3-6 months thereafter. AASLD [14] and EASL [6] recommend scheduled monitoring at least twice a year.

Summary of recommendations for therapeutic monitoring is presented in Table 4.

Development of more accurate methods of monitoring for WD is an open challenge because the target range for UCE is variable, which explains the need for a new test to determine the exchangeable copper in blood.

Beyond that, emphasis on the estimated NCC ($NCC = \text{total serum Cu } (\mu\text{g/dL}) - C_p \text{ (mg/dL)} \times 3.15$) was recently reduced [12]. A new strategy for the determination of serum copper using anion exchange high-performance liquid chromatography in combination with inductively coupled plasma mass spectrometry HPLC-ICP-MSM emerged. Thus, the "exchangeable" copper fraction could become an alternative clinical biomarker of WD by

Table 3 – Recommendations for WD therapy for children

First Line for Asymptomatic Children	First Line for Symptomatic Children	Low Copper Diet Recommended in All Guidance
EASL [6]/ESPGHAN [16]: Chelators (D-penicillamine (DPA), trientine*) or zinc salts Zinc salts AASLD[14]: DPA or lower-dose trientine than initial therapy, zinc BASL [15]: DPA NOT recommended for asymptomatic *or* symptomatic patients Zinc salts (evidence, 3)	EASL [6]: DPA, trientine, zinc salts in neurological patients ESPGHAN [16]: Chelators, zinc salts (maintenance) AASLD [14] /BASL [15] DPA or trientine Zinc salts (maintenance)	Particularly within the first year of treatment, in conjunction with medical therapy ESPGHAN [16] and BASL [15]: Dietary Cu restrictions based on initial response to treatment, normalization of liver function tests, and considering quality of life (QOL)

* Trientine can be used in patients who are intolerant to DPA or at increased risk for adverse effects

Table 4 – WD treatment monitoring maintenance

Society, Year	Treatment	UCE, $\mu\text{mol/d}$	UCE, 48 h Off Treatment	NCC
AASLD, 2022 [14]	DPA/trientine Zinc salts	3-8 / 2.4-8 < 1.6	0.2-0.6 $\mu\text{mol/d}$ Yearly assessment	Normalization as a secondary treatment target, < 2.4 $\mu\text{mol/L}$ (BASL) [15]
BASL, 2021 [15]	DPA/trientine Zinc salts (NEW)	3-8 0.5-1.2		
EASL, 2012 [6]	DPA/trientine Zinc salts	3-8 < 1.6		
ESPGHAN, 2018 [16]	DPA/trientine Zinc salts	3-8 0.5-1.2		

more precise determination of NCC, as shown in Figure 2. [15].

UCE is a recommended method of monitoring copper balance as it is an objective indicator that changes according to the phase of the disease: the phase of active chelation and maintenance phase.

Another common monitoring method in all guidelines is the control of exchangeable copper in combination with UCE with the recommendation of direct dosage during follow-up until achieving

normal range (from 0.62 to 1.15 $\mu\text{mol/L}$). Elevated exchangeable copper must be a sign of poor adherence to treatment [11].

It is necessary to emphasize the importance of monitoring and compliance with the recommendations. The issues of nonadherence to the treatment, rescue therapy and assessment of the need for liver transplantation (LT) are as relevant as possible, thus, making the role of lifelong treatment and constant monitoring extremely important

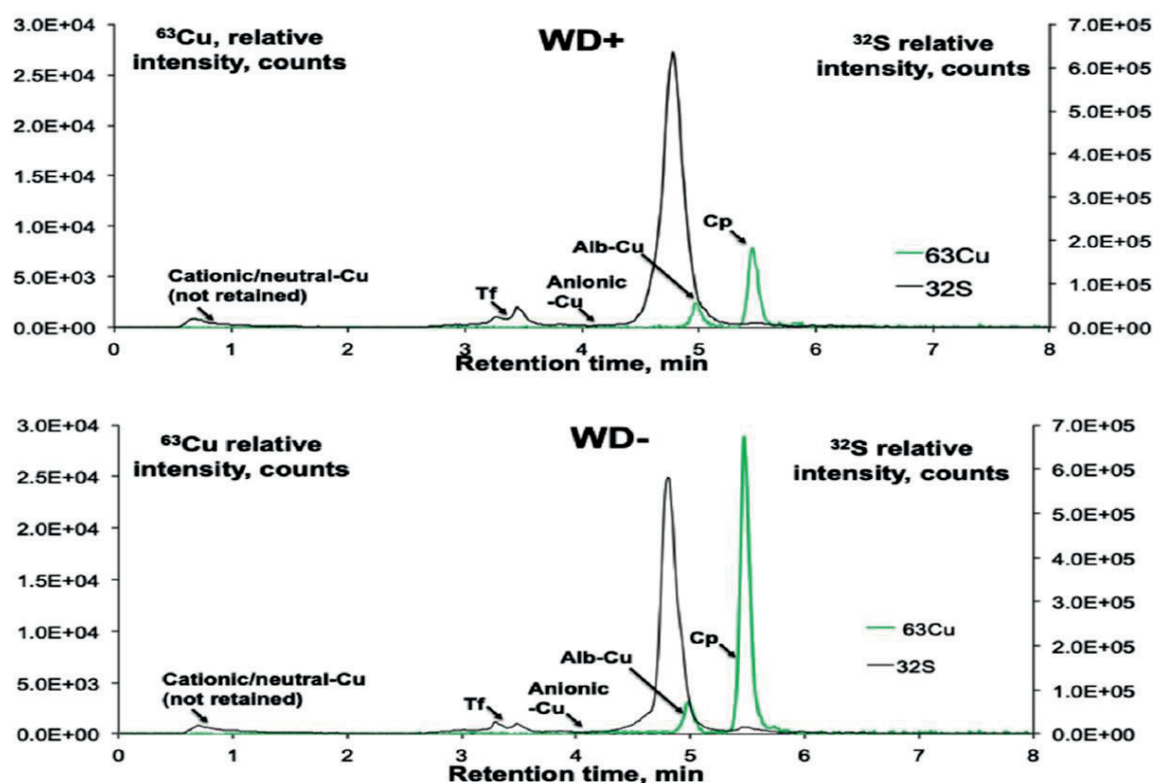


Figure 2 – Typical SAX-ICP-MS-MS chromatograms for real serum samples using the optimized conditions to illustrate the retention times and peak identification: WD+, not treated with EDTA, Wilson’s disease positive (diagnosis confirmed); WD-, not treated with EDTA, Wilson’s disease negative. Abbreviations: Alb – albumin; Cp – ceruloplasmin; Tf – transferrin [17]

[6, 15]. For example, changes in copper metabolism parameters may precede treatment failure. Also, while easily detected through tests, missed non-compliance with the treatment regimen in patients can lead to decompensation of liver cirrhosis or neurological deterioration.

LT is recommended for acute liver failure or decompensated cirrhosis if other treatment is ineffective [6, 14]. Wilson Index for prognosis, which includes evaluation of serum bilirubin, aspartate aminotransferase, INR, WBC count and albumin, equal to or more than 11 points is associated with a high probability of death without liver transplantation and, thus, is a direct indication for it.

Therapy of psychiatric symptoms for a long time remained the most important problem of WD management due to the poor quality of diagnosis and treatment, and in symptomatic patients the most important issue concentrated on the development of new methods of therapy and diagnostic search.

Previous WD recommendations recognized the possibility that psychiatric symptoms may be present in patients earlier than any other symptoms [6]. Currently the emphasis was made on preventing incorrect or late diagnosis of the psychiatric form of WD, which should be excluded in any teenager with unexplained cognitive, mental or motor disorders [6, 16].

Updated recommendations for the management of psychiatric form of WD include PNDS, which notes that for patients living with WD interdisciplinary assistance is required, including various specialists: neurologists, hepatologists, pediatricians, psychiatrists, paramedical specialists (speech therapists, psychologists, physiotherapists, neuropsychologists) [11].

Simultaneously, BASL [15] indicates the improvement of diagnosis when, regardless of the initial clinical presentation, a family history of liver diseases or neurological diseases should cause suspicion of WD. Its recommendations of the therapeutic approach are focused on the inclusion of a psychiatrist in a multidisciplinary team for selected complex patients and caution in the use of psychopharmacotherapy in patients with liver cirrhosis [15].

AASLD 2022 [14] clearly acknowledges the psychiatric manifestation of WD allocating a separate psychiatric form of WD. Psychiatric symptoms are claimed to possibly occur with or without hepatic or neurological symptoms. For instance, the presence of ≥ 1 psychiatric problem is really common in WD and up to 40% of patients met the criteria of ≥ 3 mental symptoms at the time of diagnosis; however, purely mental manifestations are commonly associated with delayed diagnosis [14].

Psychiatric examination is recommended in the early stages of WD. The possibility of using psychi-

atric screening tools with subsequent referral to an official consultation should be considered for effective diagnosis.

Removal of pathological copper deposits during treatment usually leads to an improvement in psychiatric symptoms in WD [19].

Several case reports tell about psychotropic drugs used in WD [14, 19]. Being careful is recommended when using neuroleptics due to the risk of developing extrapyramidal symptoms in mild form of the disease; clozapine due to the risk of agranulocytosis [8, 10]. Lithium is preferable for symptoms of bipolar disorder due to its excretion exclusively through the kidneys, however constant monitoring of its content in blood is still needed [14].

Currently, the key issues in the ESPGHAN guidelines for WD are:

1. Limited consensus on neurological and psychiatric manifestations;
2. Focus on other liver-related problems;
3. A wide range of multi-system phenotypic manifestations with age overlap;
4. Insufficient quantity or absence of RCT on WD;
5. Focus on a series of cases and consensus of experts;
6. Data for the pediatric population extrapolated from a series of adult cases [16].

General updates in the WD recommendations, according to experts, enhance and complement the main sections of diagnosis, therapy and neuropsychiatric management. The full versions of the recommendations pay attention to many aspects of improving the quality of patient care: updated diagnostic algorithms (reduced emphasis on estimated NCC, introduction of REC, expanded genetic testing) and advanced understanding of the pathogenesis of WD. Adjustments and additions have been made to the sections of medical treatment and nutritional requirements too. The updated recommendations also cover the issues of symptomatic and asymptomatic WD, prognosis based on the new WD index, treatment failures and patient adherence, family planning and pregnancy. Considerable emphasis is placed on neuropsychiatric involvement with a more comprehensive review of the spectrum of psychiatric diagnostics. An important recognition of the fact that psychiatric symptoms can occur at any time during the progression of the disease, and therefore the guidance on the neurological form of WD and its psychopharmacotherapy has been improved.

CONCLUSION

The key points of the WD recommendations presented below contribute a significant amount of new information for the clinical practitioner's work in

order to timely diagnose and competently monitor patients with WD.

1. Mainly, diagnostic algorithms have been updated; new tools for effective treatment monitoring as well as a more comprehensive interdisciplinary approach to neuropsychiatric disorders occurring at any time during WD have been introduced.

2. All recommendations agree that any patient with unexplained liver disease associated with a neurological or mental disorder should be examined for WD. French guidelines further suggest systematic brain assessment in all newly diagnosed WD patients.

3. The AASLD 2022 offers an advanced algorithmic approach to WD with a greater emphasis on genetic testing and neurological evaluation. The treatment adequacy is judged first by clinical and biochemical improvement, then by subsequent stability, and finally by measuring 24-hour urine copper excretion, which, along with the assessment of clinical signs (for example, neurological symptoms, Kayser-Fleischer rings) and laboratory tests, is critical for treatment monitoring.

4. The estimated concentration of copper not bound with ceruloplasmin (NCC) has decreased importance according to the AASLD 2022 guideline due to its measurement limitations and low correlation with clinical manifestations of WD. However, the need to improve methods for measuring NCC is still emphasized.

5. Another essay proposed for the evaluation of NCC is the exchangeable copper in serum, which has been emphasized in the French recommendations. Although this has not yet been confirmed worldwide, the measurement of exchangeable copper may allow to identify poor adherence to treatment.

6. Lifelong treatment is recommended for WD patients. The AASLD 2022 emphasizes that the initiation of treatment depends on whether the patient has symptoms or not, and whether organ damage is present. Asymptomatic patients without signs of organ damage can be treated initially with either a lower maintenance dose of a chelating agent or zinc.

Conflict of interests. The authors have no conflicts of interest to declare.

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ОБНОВЛЕНИЯ ЭКСПЕРТНЫХ РЕКОМЕНДАЦИЙ ПО МЕНЕДЖМЕНТУ БОЛЕЗНИ УИЛЬСОНА

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Болезнь Уилсона – редкое аутосомно-рецессивное наследственное нарушение метаболизма меди, характеризующееся избыточным отложением меди в тканях, в том числе головного мозга и печени. Генетический дефект, локализованный в локусе 13q14 – q21, оказывает влияние на ген белка АТР7В, транспортирующего медь в печени, с формированием дефектов по типу делеций, вставок или миссенс-мутаций, что нарушает включение меди в церулоплазмин и выведение избытка меди в желчь. Заболевание характеризуется поражением печени, нейропсихиатрическими симптомами, скелетно-мышечными, гематологическими, почечными проявлениями, формированием колец Кайзера-Флейшера и множеством других симптомов в зависимости от своевременности диагностики, стадии, формы течения и терапевтического вмешательства. Организации, исследующие проблемы Болезни Уилсона, регулярно выпускают рекомендации по мере расширения знаний о заболевании и внедрения в практику новых диагностических и лечебных процедур, изменении взглядов на особенности течения болезни. Описанные в статье общие обновления последних международных рекомендаций касаются диагностических алгоритмов, показаний и выбора сроков и методов медикаментозного лечения у пациентов различных групп с Болезнью Уилсона, определения и возможных инструментов мониторинга терапии, включая более полный обзор нейропсихиатрической помощи, с целью раннего внедрения новых данных в практическое здравоохранение.

Ключевые слова: болезнь Уилсона, церулоплазмин, АТР7В, медь сыворотки, терапия болезнь Уилсона.

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УИЛСОН АУРУЫН БАСҚАРУ БОЙЫНША САРАПТАМАЛЫҚ ҰСЫНЫСТАРДЫ ЖАҢАРТУ

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Уилсон ауруы – бұл сирек кездесетін аутосомды-рецессивті тұқым қуалайтын мыс метаболизмінің бұзылуы, ол тіндерде, соның ішінде ми мен бауырда мыстың артық жиналуымен сипатталады. 13q14 – q21 локусында локализацияланған генетикалық ақау бауырдағы *atp7b* мысын тасымалдайтын генге әсер етеді, ол жою, кірістіру немесе миссенс мутация түріне сәйкес ақауларды қалыптастырады, бұл мыстың церулоплазминге қосылуын және артық мыстың өтке шығарылуын бұзады. Ауру бауырдың зақымдануымен, нейропсихиатриялық белгілермен, тірек-қимыл аппаратының, гематологиялық, бүйрек көріністерімен, Кайзер-Флейшнер сақиналарының пайда болуымен және диагностиканың уақтылығына, сатысына, курс формасына және терапевтік араласуға байланысты көптеген басқа белгілермен сипатталады. Уилсон ауруы проблемаларын зерттейтін ұйымдар ауру туралы білімнің кеңеюіне және тәжірибеге жаңа диагностикалық және емдік процедураларды енгізуге, ауру ағымының ерекшеліктеріне көзқарастың өзгеруіне байланысты үнемі ұсыныстар шығарады. Мақалада сипатталған соңғы халықаралық ұсыныстардың жалпы жаңартулары диагностикалық алгоритмдерге, көрсеткіштерге және Уилсон ауруы бар әртүрлі топтағы емделушілерде дәрі-дәрмекпен емдеу мерзімдері мен әдістерін таңдауға, терапияны анықтаудың және ықтимал бақылау құралдарына, соның ішінде практикалық денсаулық сақтау саласына жаңа деректерді ерте енгізу мақсатында нейропсихиатриялық көмекке толық шолу жасауға қатысты.

Кілт сөздер: Уилсон ауруы, церулоплазмин, АТР7В, мыс сарысуы, Уилсон ауруы терапиясы.