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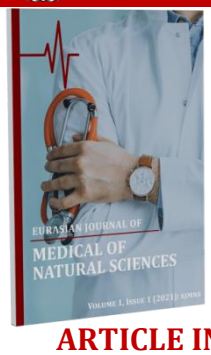

CLINICAL AND MOLECULAR GENETIC DIAGNOSTICS OF WILSON-KONOVALOV DISEASE

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ABSTRACT

Wilson-Konovalov disease, also known as Wilson's disease, is a rare autosomal recessive disorder caused by mutations in the ATP7B gene, leading to copper accumulation in the liver, brain, and other organs. This article explores the clinical and molecular genetic diagnostics of Wilson-Konovalov disease, emphasizing the importance of early detection and genetic testing. Clinical diagnosis is based on characteristic symptoms such as hepatic dysfunction, neurological impairments, and Kayser-Fleischer rings, along with biochemical markers including serum ceruloplasmin and urinary copper excretion. Molecular genetic testing, particularly sequencing of the ATP7B gene, plays a crucial role in confirming the diagnosis, identifying carriers, and facilitating genetic counseling. Advances in next-generation sequencing (NGS) and other molecular techniques have improved diagnostic accuracy, enabling early intervention and personalized treatment strategies. A comprehensive approach combining clinical, biochemical, and genetic analyses is essential for effective diagnosis and management of Wilson-Konovalov disease.

UILSON-KONOVALOV KASALLIGINING KLINIK-MOLEKULAR, HAMDA GENETIK DIAGNOSTIKASI

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ABSTRACT

Uilson-Konovalov kasalligi, shuningdek, Uilson kasalligi sifatida ham tanilgan, ATP7B genidagi mutatsiyalar natijasida kelib chiqqan, jigar, miya va boshqa organlarda mis to'planishiga olib keladigan noyob autosomal retsessiv kasallik. Ushbu maqola Vilson-Konovalov kasalligining klinik va molekulyar genetik diagnostikasini o'rganib, erta aniqlash

Uilson-Konovalov kasalligi, Uilson kasalligi, ATP7B geni, mis almashinuvi, genetik diagnostika, molekulyar diagnostika, keyingi avlod sekvensiyasi, seruloplazmin, Kayser-Fleysher halqasi, jigar disfunktsiyasi, nevrologik simptomlar.

va genetik testning muhimligini ta'kidlaydi. Klinik tashxis jigar disfunktsiyasi, nevrologik buzilishlar va Kayser-Fleischer halqalari kabi xarakterli alomatlarga, shuningdek, sarum seruloplazmin va siydik bilan mis ajralishi kabi biokimyoviy belgilarga asoslanadi. Molekulyar genetik test, xususan, ATP7B genining ketma-ketligi tashxisni tasdiqlashda, tashuvchilarni aniqlashda va genetik maslahatni osonlashtirishda hal qiluvchi rol o'ynaydi. Keyingi avlod sekvensiyasi (NGS) va boshqa molekulyar texnikalardagi yutuqlar diagnostika aniqligini oshirib, erta aralashuv va shaxsiylashtirilgan davolash strategiyalarini yaratish imkonini berdi. Vilson-Konovalov kasalligini samarali tashxislash va davolash uchun klinik, biokimyoviy va genetik tahlillarni birlashtirgan kompleks yondashuv zarur.

Introduction. Wilson-Konovalov disease, commonly known as Wilson's disease (WD), is a rare autosomal recessive disorder of copper metabolism caused by mutations in the ATP7B gene. The disease leads to excessive copper accumulation in various organs, primarily the liver and brain, resulting in progressive hepatic, neurological, and psychiatric manifestations (Bandmann et al., 2015). First described by Samuel Wilson in 1912 and independently studied by Konovalov, the disease remains a significant clinical and genetic challenge due to its variable presentation and the complexity of its diagnosis (Ferenci, 2017). Early detection and timely treatment are crucial to prevent irreversible organ damage and improve patient outcomes.

Wilson's disease is a relatively rare disorder, with an estimated global prevalence of 1 in 30,000 individuals, while the carrier frequency of heterozygous ATP7B mutations is approximately 1 in 90 (Członkowska et al., 2018). The disorder arises due to defects in the ATP7B gene located on chromosome 13q14.3, which encodes a copper-transporting P-type ATPase responsible for incorporating copper into ceruloplasmin and excreting excess copper via bile (Gupta et al., 2018). A failure in this transport mechanism leads to toxic copper accumulation, initially in the liver, followed by systemic distribution affecting the central nervous system and other tissues. The clinical presentation of Wilson's disease varies widely. Hepatic symptoms, such as acute liver failure, chronic hepatitis, and cirrhosis, are common in younger patients, whereas older individuals often exhibit neuropsychiatric manifestations, including dystonia, tremors, dysarthria, personality changes, and cognitive decline (Schilsky, 2017). One of the hallmark clinical signs is the Kayser-Fleischer ring, a copper deposition in the cornea, which is highly indicative of the disease but not always present in hepatic presentations. Given its broad spectrum of symptoms, Wilson's disease is frequently misdiagnosed or diagnosed late, leading to severe complications.

Accurate and timely diagnosis relies on a combination of clinical, biochemical, and molecular genetic approaches. Biochemical markers, including reduced serum ceruloplasmin levels, increased urinary copper excretion, and hepatic copper quantification, provide essential diagnostic clues (Roberts & Schilsky, 2008). However, genetic testing, particularly ATP7B gene

sequencing, has emerged as a definitive diagnostic tool, allowing for early identification of affected individuals, carrier detection, and family screening (Collet et al., 2018). Advances in next-generation sequencing (NGS) have further enhanced the accuracy and efficiency of molecular diagnostics, contributing to better disease management and personalized treatment strategies. This article aims to provide an in-depth review of the clinical and molecular genetic diagnostics of Wilson-Konovalov disease, emphasizing the importance of integrating biochemical and genetic analyses for effective diagnosis and management.

Literature Review. Clinical Diagnosis of Wilson's Disease

The clinical diagnosis of Wilson's disease is often challenging due to its diverse symptomatology and overlap with other hepatic and neurological disorders. According to Członkowska et al. (2018), the Leipzig scoring system, which incorporates clinical, biochemical, and genetic criteria, is widely used for diagnosis. Key diagnostic indicators include hepatic dysfunction (e.g., hepatomegaly, jaundice, cirrhosis), neurological impairment (e.g., tremors, dystonia, dysarthria), psychiatric symptoms (e.g., depression, cognitive decline), and ophthalmologic findings such as the Kayser-Fleischer ring. However, clinical signs alone are insufficient for diagnosis, necessitating further laboratory and genetic investigations.

Biochemical markers play a crucial role in diagnosing Wilson's disease. Serum ceruloplasmin levels are typically low in affected individuals, though normal levels can be observed in certain cases (Roberts & Schilsky, 2008). Elevated urinary copper excretion, particularly after penicillamine challenge, and hepatic copper quantification via liver biopsy remain valuable diagnostic tools (Ferenci, 2017). Recent studies have highlighted the utility of non-invasive imaging techniques, such as MRI, to detect brain abnormalities associated with Wilson's disease, especially in patients with neuropsychiatric symptoms (Zhou et al., 2017).

Molecular Genetic Diagnosis

Genetic testing for Wilson's disease has significantly improved diagnostic accuracy. The ATP7B gene, responsible for copper transport, harbors over 600 known pathogenic mutations, with the most common being H1069Q in European populations and R778L in East Asian populations (Collet et al., 2018). Molecular genetic testing, including Sanger sequencing and targeted next-generation sequencing (NGS), is now widely used for confirming Wilson's disease, particularly in ambiguous cases (Gupta et al., 2018). Early genetic screening of at-risk family members allows for presymptomatic diagnosis and timely intervention, reducing disease burden.

Next-generation sequencing technologies have revolutionized Wilson's disease diagnostics by enabling rapid, cost-effective, and comprehensive ATP7B mutation analysis. A study by Dong et al. (2016) demonstrated that NGS-based approaches can detect both common and rare mutations with high sensitivity, thereby improving diagnostic yield. Whole-exome sequencing (WES) has also been employed in cases with atypical presentations or in patients without identified ATP7B mutations through conventional methods (Bandmann et al., 2015).

Challenges and Future Directions

Despite advances in clinical and molecular diagnostics, challenges remain in diagnosing Wilson's disease accurately and efficiently. Variability in symptom onset, incomplete penetrance of ATP7B mutations, and the presence of modifier genes contribute to diagnostic

uncertainty (Ferenci, 2017). Additionally, access to genetic testing is limited in resource-poor settings, underscoring the need for affordable and widely available diagnostic tools. Future research should focus on refining genetic screening strategies, exploring novel biomarkers, and developing more effective therapies tailored to individual genetic profiles.

In conclusion, a multidisciplinary approach incorporating clinical assessment, biochemical testing, and molecular genetic analysis is essential for the accurate diagnosis and management of Wilson-Konovalov disease. Advances in genetic technologies hold promise for early detection, personalized treatment, and improved patient outcomes.

References:

1. Gerner E.A., Nazarov V.D., Fedorova T.F., Lapin S.V., Pavlova T.A., Novikov S.A., Alekseeva T.M., Emanuel V.L., Panina E.B. Russian Neurological Journal. 2019;(3):10-18.
2. Bayazutdinova G.M., Shchagina O.A., Polyakov A.V. Mutation c.3207C>A of the ATP7B gene is the most common cause of hepatolenticular degeneration in Russia: frequency and cause of distribution. Medical Genetics // 2018. - Vol. 17. No. 4. - P. 25-30.
3. Eremina E.Yu. Wilson-Konovalov disease // Bulletin of modern clinical medicine. - 2011. - Vol. 4. No. 1. P. 38-46.3.
4. Ryzhkova O. P., Kardymon O. L., Prokhorchuk E. B., et al. Guidelines for interpreting data obtained by massively parallel sequencing methods // Medical Genetics. - 2017. - No. 7. - P. 4-17.
5. Sokolov A. A., Dembrovsky V. N., Krasilnikova E. Yu. Provision of medical care and drug provision to patients suffering from life-threatening and chronic progressive rare diseases. Wilson's disease (hepatolenticular degeneration) // Problems of standardization of health care. - 2015. - Vol. 5. - No. 6. - P.30-36
6. Abuduxikuer, K. Wilson disease with hepatic presentation in an eight-month-old boy // World J. Gastroenterol. – 2015. Vol. 1(29). - P. 81-89.
7. Chang I.J., Hahn S.H. The genetics of Wilson disease // Handb Clin Neurol. - 2017. – Vol. 142. - P. 19-34.
8. Chen C., Shen B., Xiao J.J. et al. Currently Clinical Views on Genetics of Wilson's Disease // Chin Med J. – 2015. – P. 128-13.
9. Bandmann, O., Weiss, K. H., & Kaler, S. G. (2015). Wilson's disease and other neurological copper disorders. The Lancet Neurology, 14(1), 103-113.
10. Collet, C., Laplanche, J. L., Page, J., Morel, H., Woimant, F., & Poujois, A. (2018). High-throughput sequencing in Wilson disease: genotype-phenotype correlations and validation of the Leipzig score. Liver International, 38(5), 877-888.
11. Członkowska, A., Litwin, T., Dusek, P., Ferenci, P., Lutsenko, S., Medici, V., ... & Schilsky, M. L. (2018). Wilson disease. Nature Reviews Disease Primers, 4(1), 21.
12. Dong, Y., Ni, W., Chen, W. J., Wan, B., Zhao, G. X., Shi, Z. Q., ... & He, J. (2016). Spectrum and classification of ATP7B variants in a large cohort of Chinese patients with Wilson's disease. Liver International, 36(11), 1639-1646.
13. Ferenci, P. (2017). Diagnosis of Wilson disease. Handbook of Clinical Neurology, 142, 171-180.

14. Gupta, A., Chattopadhyay, I., & Das, S. K. (2018). Molecular pathogenesis of Wilson disease. Journal of Human Genetics, 63(1), 85-90.