REVIEW ARTICLE

Wilson's Disease: A Review

Amie Vidyani*, Fauziah Diayu Retnaningtyas, Ulfa Kholili, Titong Sugihartono, Iswan Abbas Nusi, Poernomo Boedi Setiawan, Ummi Maimunah, Budi Widodo, Husin Thamrin Muhammad Miftahussurur, Herry Purbayu

Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Wilson's disease is a disease that results from a genetic disorder that causes copper accumulation. Wilson's disease has presented challenges for physicians during the last century, but it can be diagnosed and treated over time. Diagnosing Wilson's disease is challenging for doctors because of its wide range of clinical manifestations and complexity. Studies that can help diagnose Wilson's disease include a 24-hour copper urine examination and neurological tests, such as a CT scan or MRI, and liver function tests. There is also a scoring system to help medical personnel diagnose this disease. Correct diagnosis and adequate therapy can be provided, such as penicillamine, trientine, zinc, and, most rarely, liver transplantation. It is also necessary to monitor the side effects of treatment and its effectiveness of treatment. When receiving therapy, Wilson's disease has a better prognosis than if it is not treated.

Keywords: Diagnoses, Manifestation, Prognosis, Therapy, Wilson's disease

Correspondence: Amie Vidyani
E-mail: amie.vidyani@fk.unair.ac.id

Article history: •Received 7 June 2022 •Revised 13 September 2022 •Accepted 7 November 2022 •Published 31 January 2023

INTRODUCTION

Wilson's disease is a hereditary copper transport disorder characterized by ATP7B copper-binding protein dysfunction (Hedera, 2017). The incidence of this disease is 1 in 30,000 individuals (Chaudhry, 2022). This disease can affect all ages, from young to old, especially ages 5 to 35 (EASL, 2012). This disease's clinical symptoms vary widely, from hepatic to neurological symptoms, so the disease is complicated to identify. Therapeutic determinations in this disease must also be considered carefully because there are differences in treatment in patients with hepatic and neurological symptoms (Członkowska et al., 2018). Wilson's disease is an autosomal recessive hereditary condition characterized by copper accumulation in the cornea, eyes, liver, and brain (Bagilkar, 2016). This disease is also called hepatolenticular degeneration. This disease is caused by a mutation of the ATP7B gene on chromosome 13, this chromosome encoding the copper transport P-type ATPase (ATP7B) in the trans-Golgi tissue of hepatocytes (Członkowskaet al., 2018). The function of ATP7B is to transfer intracellular copper to the bile and regulate the synthesis of ceruloplasmin (Brewer et al., 2015). This disease is classified as very rare and progressive. It can cause liver disease, central nervous disorders, and death if not treated. The incidence of developing Wilson's disease is 1 in 30,000 individuals. Therefore, this review will discuss Wilson's disease, starting from the pathogenesis, clinical manifestations, diagnosis to therapy of this disease.

PATHOGENESIS

Copper is an essential trace element and a necessary component of many proteins in the human body (Dong and Wu, 2012). Adult humans contain about 100 mg of copper. This metal balance is influenced by gastrointestinal absorption and bile excretion. Although the required intake of copper is about 0.9 mg per day, the average diet provides approximately 2–5 mg per day. Since biliary excretion is the primary route of copper elimination, the liver plays a crucial role in copper metabolism by controlling biliary copper excretion (Patil et al., 2013). Copper is readily absorbed in the stomach and duodenum before entering the liver's portal circulation. Copper enters ceruloplasmin and binds to albumin and amino acids like histidine.

The liver is the main organ of copper homeostasis. This organ regulates the storage and excretion of copper (Mazi et al., 2020). Copper balance regulation is determined by biliary copper excretion, where the amount expelled in bile equals the size of the hepatic copper pool. Hepatocytes are the principal location of copper absorption and buildup in the liver. Hepatocytes regulate copper-to-bile excretion based on intracellular copper concentrations. The study found that the liver will neutralize copper consumed quickly, and within 24 hours, 10% of the amount given will appear in the plasma and be fed into ceruloplasmin (EASL, 2012).

Excess copper in the blood can damage mitochondria and cause cell oxidative damage (Brewer et al., 2015). In Wilson's disease, copper homeostasis fails, causing copper to circulate in the blood and accumulate in human organs such as the liver, brain, kidneys, and cornea. Mutations cause this homeostasis failure in the ATP7B gene on chromosome 13 (Yuan et al., 2020). The ATP7B gene regulates the excretion of copper into bile and combines copper with apoceruloplasmin to form ceruloplasmin. Ceruloplasmin is an α2-globulin protein synthesized in hepatocytes and binds to 6 copper ions. This form is a functional form of copper storage in the bloodstream (Ramos et al., 2016).

Available at https://e-journal.unair.ac.id/CIMRJ ; DOI: 10.20473/cimrj.v4i1.36428

Ceruloplasmin is then released into the bloodstream to capture copper and enter it into the plasma. Thus, 90% of the copper is in the plasma. Copper has no effect on the rate of synthesis or secretion of ceruloplasmin, but inability to integrate these metals results in the rapid degradation of plasma apoproteins. Mutations in the ATP7B gene cause a decrease in the formation of ceruloplasmin, thereby increasing levels of free copper in the blood (Linder, 2016). Free copper in the blood will accumulate in human organs such as the brain, liver, cornea, and red blood cells.

CLINICAL MANIFESTATIONS

Wilson's disease's clinical manifestations are extensive and knowledge sharing about clinical presentation of the disease is very important. For acute symptoms, patients may present with liver failure, hemolysis, or both, and chronic symptoms may present with liver disease, neurological disease, or both (Shribman et al., 2019). Because the manifestations of Wilson's disease are vast, symptoms differ according to the organ affected.

Patients with Wilson's disease may show signs of fulminant liver failure, including coagulopathy and encephalopathy, hemolytic anemia with a negative Coomb test, renal failure, and increased blood and urine copper concentrations (Nagral et al., 2019). Usually, patients present with cirrhosis of the liver or present with signs of massive necrosis with connective tissue that will lead to cirrhosis. Serum alkaline phosphatase (ALP) concentrations are usually decreased, and if the ratio of ALP (IU/L) to bilirubin (mg/dL) is less than 2, it can be diagnosed as Wilsonian fulminant hepatitis (Mainardi et al., 2019). Clinical signs of Wilson's disease may resemble those of chronic hepatitis; therefore, screening for Wilson's disease is essential in such patients (Bandmann et al., 2015; EASL, 2012). Some patients may appear with symptoms resembling hepatic cirrhosis, including ascites, spider naevi, splenomegaly, and portal hypertension, and a minor number of patients may present with decompensated hepatic cirrhosis (Mansour and McPherson, 2018). Consequently, young patients present with or without symptoms of chronic liver disease. Cirrhosis, which is not clear, should be screened for Wilson's disease.

Next are neurological symptoms. The neurological manifestations of Wilson's disease usually appear as early as 20 to 50 years of age. Neurological manifestations occur in 40-50% of patients with Wilson's disease. Neurological symptoms can be classified into a) akinetic-rigid syndrome resembling Parkinson's disease, b) pseudosclerosis dominated by tremors, c) ataxia, and d) dystonic syndrome (Greenland and Barker, 2018). Symptoms such as changes in behavior, deterioration in the school or work environment, and the inability to perform activities that require eye-hand coordination can appear before neurologic characteristics appear (Tomasz et al., 2018). Other symptoms are tremors, lack of motor coordination, drooling, dysarthria, dystonia, spasms, migraines, headaches, and insomnia, although seizures are common. Wilson's disease's seizure types can vary from grand mal, simple partial, complex, and periodic myoclonus (EASL, 2012; Rasib et al., 2021). Patients with Wilson's disease may also find personality disorders, such as depression, anxiety, and psychosis. These neurologic symptoms arise from damage to the basal ganglia, pons, medulla, thalamus, cerebellum, and subcortical brain areas. CT or MRI scans reveal extensive brain lesions, cortical atrophy, and changes in the white matter. Cognitive impairment in Wilson's disease is usually accompanied by neurological deficits and often without association with cortical abnormalities or hepatic encephalopathy because, in these diseases, pathological changes in the basal ganglia are the leading cause of cognitive deficits. Dystonia can also occur in Wilson's disease, this disorder causing strange postures. Dystonia in the facial muscles and mandibula will cause a stiff face with an open mouth, known as a vacuous smile (Kalita et al., 2015).

Wilson's disease also presents clinical manifestations in the form of eye symptoms. The eye has Kayser-Fleischer rings and Sunburst or sunflower cataracts. Both of these symptoms are reversible with treatment or after a liver transplant. Kayser-Fleischer rings usually appear on the edges of the cornea. This occurs due to copper buildup in the Descemet's layer on the inner surface of the cornea (Pandey et al., 2019). The first buildup at the top usually occurs. This ring is golden brown. Although this ring can be seen with the naked eye, it is still necessary to check with a slit lamp to confirm this ring's presence. The appearance of the Kayser-Fleischer ring indicates copper accumulation in the brain. This ring occurs in 30-50% of patients with hepatic or presymptomatic symptoms; therefore, this ring's absence does not exclude Wilson's disease. On the other hand, this ring can be found in up to 95% of patients with neurological symptoms. The presence of a Kayser-Fleischer ring and a low level of ceruloplasmin (<0.2 g/L) is sufficient to confirm a diagnosis of Wilson's disease (Kathawala and Hirschfield, 2017). However, if this ring is not found, low ceruloplasmin levels do not always confirm Wilson's disease diagnosis. This situation can appear in autoimmune hepatitis, celiac disease, familial aceruloplasminemia, and advanced liver disease. Sunburst or sunflower cataracts can only be seen using a slit lamp. This cataract does not affect vision, unlike other types of cataracts. This cataract occurs due to copper buildup in the lens. It is a greenish disc in the anterior capsule with a spike-like shape. The clinical manifestation of Wilson's disease varies considerably. However, liver disease and cirrhosis, neuropsychiatric disorders, Kayser-Fleischer rings in Desçemet's corneal membrane, and acute hemolysis episodes associated with acute liver failure are the most prominent characteristics (Stremmel et al., 2019).

DIAGNOSIS

Diagnosis of Wilson's disease is challenging to establish, the symptoms of Wilson's disease are often non-specific, and the association with different organs makes the diagnosis difficult. The diagnosis is more accessible when the patient presents neurologic symptoms, K-F rings, and low ceruloplasmin concentrations. Typically, the presence of a K-F ring and a ceruloplasmin concentration of less than 100 mg/L suffices for a diagnosis (Liu et al., 2017). However, K-F rings were found frequently in patients with neurologic symptoms and only in half in patients with hepatic symptoms (Langwińska-Wośko et al., 2016). This clinical manifestation is often overlooked on physical examination, especially in patients who have black corneas. Low ceruloplasmin levels cannot be used as a reference because several conditions cause ceruloplasmin to decrease, such as hepatic insufficiency due to advanced liver disease (Martínez-Morillo and Bauca, 2022).

Low serum copper levels, increased liver transaminase enzymes, aminoaciduria, and hemolytic anemia are laboratory findings that support the diagnosis of Wilson's disease (Bandmann et al., 2015, Kaler, 2013). Analysis of copper excretion for 24 hours in the urine is an easy

and essential test to perform. If the 24-hour urine copper excretion is over 100 g, it is indicative of Wilson's disease in the absence of cholestasis of the liver. The upper limit of normal interlaboratory urinary copper excretion is 40 µg per 24 hours. This limit depends on the level of sensitivity. The inspection also requires a particular copper-free container made of polyethylene and disposable (Dong and Wu, 2021). Because it is challenging to diagnose Wilson's disease, in 2001, Ferensi and her friends proposed to use a scoring system. This scoring collected biochemical, clinical, and genetic data from each patient and was given a quantitative scoring. This scoring system is now included in the Clinical Guidelines for Wilson's Disease issued by the European Association for the Study of the Liver (EASL). This scoring system is called the Leipzig score (EASL, 2012). Ceruloplasmin is the blood's primary copper carrier. Normal levels of ceruloplasmin ranges between 0.15 and 0.2 g/L (Ferenci, 2017). Wilson's disease is typically below 0.1 g/L, particularly in patients with neurological symptoms, but can be abnormally low in approximately 50% of patients with active Wilson's liver disease. Although Wilson's disease is a disease of copper overload, serum total copper levels in patients are usually low due to decreased levels of ceruloplasmin in the blood (Patil et al., 2013). Normal or elevated serum copper levels coupled by a decline in ceruloplasmin levels indicate an increase in the concentration of copper in the blood that is not bound to ceruloplasmin (copper that is not bound to ceruloplasmin or called free copper).

A 24-hour urine copper examination is helpful for the diagnosis and monitoring of Wilson's disease (Hedera, 2017). A 24-hour urine copper test reveals the quantity of free copper in the circulation of untreated patients. Patients suffering from renal failure cannot undergo this examination. Wilson's disease can be diagnosed if the 24-hour urinary copper excretion level is higher than 1.6 mol/24 hr in untreated patients (Merle and Weiskirchen, 2016). Problems in measuring 24-hour copper excretion include insufficient urine collection and copper contamination of the collection apparatus (this becomes less problematic with the appearance of single-use containers) (EASL, 2012). It might be challenging to interpret 24-hour urine copper excretion due to overlapping findings with other kinds of liver disease (e.g., autoimmune hepatitis, active chronic liver disease, or cholestasis, particularly during acute liver failure origin) (Schroeder et al., 2021). Problems that arise in measuring 24-hour urine copper excretion, such as non-sticky urine collection and contamination of the urine collection container, make this examination difficult. The interpretation can overlap with other diseases such as autoimmune hepatitis, active chronic liver disease, cholestasis, and acute liver failure, whatever the cause (Robson et al., 2020). Copper buildup in the liver is a characteristic of Wilson's disease. This examination can only be done with a liver biopsy. This examination is not routinely carried out in Indonesia.

TREATMENT

The first step is to determine the degree of the disease using the Nazer prognostic index. Patients with a score of <7 can be treated medically. A score of 7-9 requires a clinical assessment of whether sufficient medical or liver transplantation is sufficient. A score >9 should be considered as liver transplantation. Therapy for Wilson's disease is lifelong because copper accumulation in the body cannot be achieved only with a low-copper diet (Aggrawal and Bhatt, 2018). There are 2 phases: the acute phase, the copper reduction, and the maintenance phase. The therapy used is a copper chelator, zinc, or both. Copper chelators work by binding copper directly in blood and tissues and excreting it, whereas zinc inhibits copper absorption in the intestine. Copper chelator, D-penicillamine, is the first therapy of choice, but it has toxicities and side effects that increase neurological symptoms. Trientine is a better chelator agent than penicillamine because it has fewer side effects but the same effectiveness (Stremmel and Weiskirchen, 2021).

Penicillamine use should be accompanied by pyridoxine administration because pyridoxine deficiency caused by penicillamine will worsen neurological symptoms (Rodriguez-Castro et al., 2015). The recommended dose for penicillamine is 750-1500 mg per day in divided doses 2-4 times, and pyridoxine doses are 25 mg per day. Penicillamine is best given 1 hour before or 2 hours after eating because the absorption is down to 50% when given with food. Zinc administration is the therapy of choice in patients with hepatic/cirrhosis symptoms without decompensation/neurological symptoms (Haftu et al., 2020). Zinc can also be given to presymptomatic patients. Zinc causes a negative balance by reducing copper absorption in the intestine (Maares and Haase, 2020). The recommended dose is 50 mg elemental zinc three times a day, each dose at least 1 hour after consuming food and beverages other than water, and should be separated from penicillamine/trientine. Trientine works by increasing the excretion of copper into the urine, much like penicillamine. The recommended dose is 900-2700 mg/day in 2 or 3 divided doses.

One way to control copper in the body is a diet low in copper. Patients should avoidfoods high in copper, such as chocolate, nuts, liver, mushrooms, shellfish, and the use of copper cookware (Radhika et al., 2016). Administration of copper chelators such as penicillamine and trientine must be monitored for toxicity in bone marrow suppression and proteinuria (Hedera, 2019). Complete blood count, UL, and standard biochemical profile were performed regularly (Poujois and Woimant, 2018). The effect of the copper chelator can be monitored using the free serum copper level per 24 hours. Free copper levels were calculated by reducing total serum copper with ceruloplasmin copper. The norm is 1.6-2.4 µm/L (10-15 µg/dL). The serum copper level should be below 3.9 µg/L (<25 µg/dL) with therapy. Side effects of zinc are nausea or epigastric pain, which occurs in only 10% of patients (Plum et al., 2010). The use of zinc is classified as safe, so it does not require monitoring toxicity through urinalysis or serum levels.

PROGNOSIS

The untreated Wilson's disease can be fatal. Most of the patients will experience death from liver disease and complications of neurological symptoms. Due to Wilson's disease, medical therapy is generally ineffective in acute liver disorders (Kathawala and Hirschfield, 2017). Patients with neurological symptoms who do not fully improve usually will develop sequelae and, in some cases, worsen at the start of therapy. The Nazer prognostic score can be used to determine prognosis, but generally, the prognosis depends on the degree of liver and neurologic damage and the level of medication adherence (Stankiewicz et al., 2021).

CONCLUSION

Wilson's disease is genetic and causes excess copper accumulation in the liver and/or brain. Mutations cause this disease in the ATP7B gene on chromosome 13. Mutations in the ATP7B gene cause a decrease in the formation of ceruloplasmin, thereby increasing free copper levels in the blood. Diagnosing Wilson's disease is challenging for healthcare professionals because of its wide range of clinical manifestations and complexity. Tests to help diagnose Wilson's disease include a 24-hour copper urine test, neurological tests such as a CT or MRI scan, and liver function tests.

Adequate therapy, such as penicillamine, trientine, zinc, and liver transplantation, can be given. Administration of medical therapy must be accompanied by complete blood counts, standard biochemical profiles, and urinalysis to monitor the side effects of treatment and its effectiveness of treatment. Wilson's disease can have a better prognosis with therapy than if it is not treated.

ACKNOWLEDGEMENT

The author thanks the Faculty of Medicine, Universitas Airlangga and Dr. Soetomo General Academic Hospital.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

FUNDING DISCLOSURE

This research was self funded.

AUTHOR CONTRIBUTION

All author have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

REFERENCES

Aggarwal A, Bhatt M 2018. Advances in treatment of Wilson disease. Tremor and Other Hyperkinetic Movements 8:525. DOI: 10.7916/D841881D.

Bagilkar VV. 2016. Wilson's disease. Asian J Nurs Educ Res 6(4):533-537. DOI:10.5958/2349-2996.2016.00099.9.

Bandmann O, Weiss KH, Kaler SG. 2015. Wilson ' s disease and other neurological copper disorders. Lancet Neurol 14(1):103-113. DOI:10.1016/S1474-4422(14)70190-5.

Brewer GJ, Dennis L. 2015. Wilson's Disease. In: Kasper AS, Fauci SL, L Longo (eds). Harrisons's Principles of Internal Medicine, 19th ed. New York: McGraw-Hill, p 2519.

Chaudhry HS AA. 2022. Wilson Disease. In: StatPearls [Internet]. StatPearls Publishing 2022.

Członkowska A, Litwin T, Dusek P, et al. 2018. Wilson disease. Nat Rev Dis Primers 4(1):21. DOI:10.1038/s41572-018-0018-3.

Dong Q-Y, Wu Z-Y. 2012. Advance in the pathogenesis and treatment of Wilson disease. Transl Neurodegener 1(1):1-8. DOI:10.1186/2047-9158-1-23.

Dong Y, Wu ZY. 2021. Challenges and suggestions for precise diagnosis and treatment of Wilson's disease. World J Pediatr 17(6):561-565. DOI:10.1007/s12519-021-00475-4.

EASL 2012. EASL clinical practice guidelines: Wilson's disease. J Hepatol 56(3):671-685. DOI: 10.1016/j.jhep.2011.11.007.

Ferenci P. 2017. Diagnosis of Wilson disease. Handb Clin Neurol 142:171-180. DOI: 10.1016/B978-0-444-63625-6.00014-8.

Greenland JC, Barker RA. 2018. The differential diagnosis of Parkinson's disease. Exon Publ 2018:109-128.

Haftu H, Mustefa M, Gebrehiwot T. 2020. Zinc monotherapy as an alternative treatment option for decompensated liver disease due to Wilson disease?. Case Report Hepatol 2020. https://doi.org/10.1155/2020/1275940.

Hedera P. 2017. Update on the clinical management of Wilson's disease. Appl Clin Genet 10:9.

Hedera P. 2019. Clinical management of Wilson disease. Ann Transl Med 7(S2):S66-S66. DOI:10.21037/atm.2019.03.18.

Kaler SG. Inborn errors of copper metabolism. Handb Clin Neurol. 2013;113:1745-1754. DOI:10.1016/B978-0-444-59565-2.00045-9.

Kalita J, Ranjan A, Misra UK. 2015. Oromandibular Dystonia in Wilson's Disease. Mov Disord Clin Pract 2(3):253-259.

Kathawala M, Hirschfield GM. 2017. Insights into the management of Wilson's disease. Therap Adv Gastroenterol 10(11):889-905.

Langwińska-Wośko E, Litwin T, Dzieżyc K, Członkowska A. 2016. The sunflower cataract in Wilson's disease: pathognomonic sign or rare finding? Acta Neurol Belg 116(3):325-328. DOI:10.1007/s13760-015-0566-1.

Linder MC. 2016. Ceruloplasmin and other copper binding components of blood plasma and their functions: An update. Metallomics 8(9):887-905. DOI:10.1039/c6mt00103c.

Liu J, Luan J, Zhou X, Cui Y, Han J. 2017. Epidemiology, diagnosis, and treatment of Wilson's disease. Intractable Rare Dis Res 6(4):249-255. DOI:10.5582/irdr.2017.01057.

Maares M, Haase H. 2020. A guide to human zinc absorption: general overview and recent advances of in vitro intestinal models. Nutrients 12(3):762.

Mainardi V, Rando AEK, Valverde M, et al. 2019. Acute liver failure due to Wilson disease: Eight years of the national liver transplant program in Uruguay. Ann Hepatol 18(1):187-192. DOI:10.5604/01.3001.0012.7911.

Mansour D, McPherson S. 2018. Management of decompensated cirrhosis. Clin Med (Northfield Il) 18(Suppl 2):s60.

Martínez-Morillo E, Bauça JM. Biochemical diagnosis of Wilson's disease: An update. Adv Lab Med. 2022;3(2):103-113. DOI:10.1515/almed-2022-0020.

Mazi TA, Shibata NM, Medici V. 2020. Lipid and energy metabolism in Wilson disease. Liver Res 4(1):5-14. DOI:10.1016/j.livres.2020.02.002.

Merle U, Weiskirchen R. 2016. Wilson'S disease: an inherited, silent, copper intoxication disease. Cit EMJ Neurol 4(1):74-83.

Nagral A, Sarma MS, Matthai J, et al. 2019. Wilson's disease: clinical practice guidelines of the Indian national association for study of the liver, the Indian society of pediatric gastroenterology, hepatology and nutrition, and the move-

ment disorders society of India. J Clin Exp Hepatol 9(1):74-98.

Pandey N, John S. 2019. Kayser-Fleischer Ring. In: StatPearls [Internet]. StatPearls Publishing.

Patil M, Sheth KA, Krishnamurthy AC, Devarbhavi H. 2013. A review and current perspective on Wilson disease. J Clin Exp Hepatol 3(4):321-336.

Plum LM, Rink L, Haase H. 2010. The essential toxin: impact of zinc on human health. Int J Environ Res Public Health 7(4):1342-1365.

Poujois A, Woimant F. 2018. Wilson's disease: A 2017 update. Clin Res Hepatol Gastroenterol 42(6):512-520. DOI:10.1016/j.clinre.2018.03.007.

Radhika P, Gvvs KB, Anbarasu K, et al. 2016. Low copper containing diet for Wilson disease patients 4(3):147-149.

Ramos D, Mar D, Ishida M, et al. 2016. Mechanism of copper uptake from blood plasma ceruloplasmin by mammalian cells. PLoS One 11(3):e0149516.

Rasib AR, Jabarkhil AA, Sediqi MF, Mansoor AI, Asady A. 2021. Wilson's disease presenting with generalized tonic-clonic seizure and cerebellar dysfunction. Int Med Case Rep J. 14:529-532. DOI:10.2147/IMCRJ.S320639.

Robson AF, Lockett P, Tetlow L, Chaloner C. 2020. Evaluation of 24-h urine containers for urine copper measurement by inductively coupled plasma mass spectrometry. Ann Clin Biochem 57(3):246-248. DOI:10.1177/0004563220915949.

Rodriguez-Castro KI, Hevia-Urrutia FJ, Sturniolo GC. 2015. Wilson's disease: A review of what we have learned. World J Hepatol 7(29):2859-2870. DOI:10.4254/wjh.v7.i29.2859.

Schroeder SM, Matsukuma KE, Medici V. 2021. Wilson disease and the differential diagnosis of its hepatic manifestations: a narrative review of clinical, laboratory, and liver histological features. Ann Transl Med 9(17):1394-1394. DOI:10.21037/atm-21-2264.

Shribman S, Warner TT, Dooley JS. 2019. Clinical presentations of Wilson disease. Ann Transl Med 7(Suppl 2).

Stankiewicz R, Patkowski W, Zieniewicz K. 2021. Diagnostic dilemma and treatment outcome in acute liver failure due to Wilson's disease. Ann Transplant 26:1-6. DOI:10.12659/AOT.930146.

Stremmel W, Merle U, Weiskirchen R. 2019. Clinical features of Wilson disease. Ann Transl Med 7(S2):S61-S61. DOI:10.21037/atm.2019.01.20.

Stremmel W, Weiskirchen R. 2021. Therapeutic strategies in Wilson disease: pathophysiology and mode of action. Ann Transl Med 9(8):732-732. DOI:10.21037/atm-20-3090.

Yuan X-Z, Yang R-M, Wang X-P. 2020. Management Perspective of Wilson's Disease: Early Diagnosis and Individualized Therapy. Curr Neuropharmacol 19(4):465-485. DOI:10.2174/1570159x18666200429233517.

Mallhi TH, Khan AH, Adnan AS, Tanveer N, Aftab RA. 2021. Expanded Dengue Syndrome. Springer Nature Singapore. https://doi.org/10.1007/978-981-15-7337-8.