Editorial Commentary

Wilson's disease: practical information for general physicians

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Wilson's disease is an autosomal-recessive disorder with an *ATP7B* mutation that causes a functional failure of the copper-transporting protein ATP7B (1,2). As a result, unbound copper in the blood increases, and due to copper accumulation, multiple organs show various symptoms, e.g., Kayser-Fleischer rings, acute liver failure, liver cirrhosis, liver cancer, dysarthria, tremors, character changes, renal disorders, rheumatological symptoms, endocrinopathy, heart failure, and arrhythmias (3,4). This disease afflicts approximately 1 in 40,000 people, with approximately 1 carrier for every 100 people, and early diagnosis is difficult. The peak onset is approximately at the age of 10–11 years; however, the age of onset can vary widely from 3 to 50 years (1).

Ideally, after the diagnosis, patients with Wilson's disease must be supported by a multidisciplinary team consisting of general physicians, hepatologists, neurologists, and rehabilitation professionals. However, as the clinical presentations vary, differential diagnosis from other common diseases is difficult in the primary care center, and the diagnosis is frequently delayed. Therefore, general physicians must be familiar with the clinical manifestations, diagnostic workup, initial management, and timing to refer to a specialist. Several clinical practice guidelines have been available for specialists (5-8); however, considering that non-experts will initially diagnose the cases, the practical guide for general physicians to diagnose Wilson's disease and points for the initial management, long-term follow-up, and family screening was an unmet need. In this issue of *The Lancet Gastroenterology and Hepatology*, Shribman *et al*. presented a practical guide for non-experts to investigate and manage Wilson's disease (9). They focused on the clinical presentation, diagnostic workup, initial management, and longer-term management, considering the update in the actual clinical practice, e.g., easier access to genetic tests, liver imaging, neuroimaging, and transient elastography for the liver. The guidance also included recommendations for earlier consultation with a specialist center for Wilson's disease to introduce the initial treatment smoothly.

Regarding the clinical presentation, the identification of the combination of liver injury, neurological symptoms, psychiatric symptoms, hematological disorders, renal injury, and rheumatological symptoms, family history of liver disease and neurological disorder, and Kayser-Fleischer rings at the bedside is important. Further assessments with routine investigations of the complete blood count, serum biochemical analyses of liver function, coagulation profiles, and serum ceruloplasmin followed by wider screening tests of 24-h urine collection and slit-lamp examination are necessary.

At this stage, the presence of Kayser-Fleischer rings, serum ceruloplasmin <0.20 g/L, and urinary copper output >40 μg in 24 h could lead to the diagnosis of Wilson's disease (9,10), and disease suspicion should be taken

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seriously and referred to experienced specialists for further examinations and treatment initiation (9).

More assessments are conducted for cases suspected of Wilson's disease. These assessments are conducted for diagnosis, assessment of the disease severity, and staging of liver disease and involve serum copper concentration, genetic testing, liver imaging, transient elastography for measuring liver stiffness, neuroimaging, liver biopsy, etc. (3,4,7-10). Recently, non-invasive methods for diagnosing and follow-up of liver diseases are developing rapidly (8), and among them, ultrasonography is a useful, and important examination for general physicians. Hepatic steatosis and cirrhotic changes can be detected, which is also useful when screening for liver tumors in a longer-term follow-up. Non-invasive liver stiffness measurement by transient elastography is useful to detect liver fibrosis and follow the time-dependent changes of its staging.

For the initial management, chelation therapy using D-penicillamine (DPA) or trientine, which mobilizes intracellular copper into the circulation and enhances the urinary excretion of copper, is the primary treatment (5-7). DPA is a dimethylated cysteine and a key copper chelator, which promotes the excretion of excess copper into the urine (3,5). It effectively improves copper deposition in the liver and prevents the progression of liver failure (5). A careful follow-up of response to chelation therapy and adverse events is needed. For example, DPA may increase copper deposition in the brain; therefore, the effect of DPA on neurological symptoms is questionable (11). The paradoxical worsening of neurological or psychiatric symptoms is seen in 11–30% of cases for the first 6 months after treatment initiation (9). Although distinguishing from disease progression is difficult, general physicians must understand this phenomenon and refer to specialists when necessary. In addition to chelation therapy, dietary copper restriction is important. Generally, avoidance of eating chocolates, nuts, liver, shellfish, and mushrooms for at least the first year of treatment is recommended. When acute liver failure occurs, early referral to the hepatologists is essential as liver transplantation is indicated (9).

The physicians managing the long-term care of patients with Wilson's disease must be aware of the occurrence of malignant diseases such as hepatocellular carcinoma (HCC) in a fibrotic liver. A previous study reported that among 45 cases of HCC with Wilson's disease, 41 were complicated with liver cirrhosis (11). In addition, Ohkoshi-Yamada *et al.* reported that even under DPA treatment for 36 years, the remaining copper deposition in the liver may cause fatty liver change, cirrhosis, and HCC (12). Therefore, DPA is considered useful to prevent HCC occurence; however, long-term follow-up is essential for this disease. A recent basic study reported the contribution of copper and cuproptosis-related genes on regulating HCC development by targeting tumor immune microenvironments and immune checkpoint genes (13). The result suggests that the recently developed systemic treatment for HCC using immune checkpoint inhibitors and tyrosine kinase inhibitors (14,15) could be effective for these tumors.

In conclusion, this guidance, which was developed by the British Association for the Study of the Liver and supported by the British Society of Gastroenterology and Association of British Neurologists, provides clear practical information for general physicians in primary care settings to investigate cases with suspicion of Wilson's disease, consult with specialists, and initially manage the disease under their guidance. Physicians must know that diagnostic delays can be life-threatening and lead to irreversible neurological disorders; therefore, early recognition, diagnosis, referral to specialists, treatment initiation, and long-term follow-up in a multidisciplinary setting is important.

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