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EASL-ERN Clinical Practice Guidelines on Wilson's disease☆

European Association for the Study of the Liver*

Summary

Wilson's disease is an autosomal recessive disorder of copper metabolism which affects the liver, brain and other organs. Diagnosis is based on: clinical features; biochemical tests, including plasma ceruloplasmin concentration, 24-h urinary copper excretion, copper content in the liver; and molecular analysis. Leipzig score and additionally relative exchangeable copper determination are recommended for diagnosis. Pharmacological therapy comprises chelating agents (penicillamine, trientine) and zinc salts, while only chelators are recommended for significant liver disease. Monitoring is based on clinical symptoms, liver tests and copper metabolism (urinary copper excretion, exchangeable copper) to detect poor compliance and over/under-treatment. Acute liver failure is challenging as making a diagnosis is difficult and pharmacological therapy may not be sufficient to save life. Liver transplantation has a well-defined role in Wilsonian acute hepatic failure but may also be considered in neurological disease.

Introduction

Wilson's disease (WD) is an autosomal recessive genetic disorder of copper metabolism which leads to toxic accumulation of copper in the liver, nervous system and other organs.[1,2] Disease-causing mutations on both alleles of *ATP7B* result in WD, in which defective biliary excretion of copper and the absence of holoceruloplasmin complex (five molecules of copper bound to ceruloplasmin) lead to copper accumulation in body organs.[3] Heterozygotes have no disease symptoms. Increased levels of non-protein-bound toxic copper within the hepatocytes lead to hepatitis and cell death, with subsequent release of copper into the circulation. Since the maturation process of ceruloplasmin requires functional intact ATPase 7B, decreased mature ceruloplasmin is secreted into the circulation due to decreased or absent ATPase 7B activity in hepatocytes.[2,4]

The original prevalence estimates for WD of 1:30,000-1:50,000 from 1984 still appear valid according to the recent systematic literature review, at least for the United States, Europe, and Asia.[5] More than 2,700 distinct variants have been described in the *ATP7B* gene, from which over 800 have a confirmed role in disease pathogenesis.[1,2]

Clinical presentation can vary widely, but the key features of WD are liver involvement that can lead to cirrhosis, neurological and psychiatric signs and symptoms, Kayser-Fleischer rings in Desçemet's membrane of the cornea, and acute episodes of haemolysis often in association with acute liver failure (ALF). WD may present at any age, in young children as well as in elderly.[6–8]

The age at presentation, as well as the distribution of presenting symptoms, often depend on the main focus of the institution which collected the data (paediatrics, hepatology, neurology) as well as the region where the data were obtained, except for big national registries. Whether the different genotype distribution has an impact on the phenotypic presentation is unknown. However, the preponderance of typical *ATP7B* mutations varies among different populations. The H1069Q variant is typical for patients with Central- or Eastern European background,[9–11] while R778L (exon 8) occurs mostly in Eastern Asia[12] and C271X (exon 2) in India.[13]

Methods

The European Association for the Study of the Liver (EASL) and ERN-Rare Liver invited a panel of experts to develop clinical practice guidelines (CPGs) aimed at providing recommendations, based on the best available evidence, for the diagnosis and management of WD for hepatologists, neurologists, general physicians, paediatricians, specialists in training and other healthcare professionals who provide care for this patient population.

P.S. was invited to chair the CPG and a further 11 panellists (including one Governing Board representative [E.T.]) were then selected to comprise the remainder of the CPG panel. The process undertaken is summarised in Fig. 1. The panel initially agreed on the most relevant topics to be addressed in the guideline. The CPG panel drafted 24 clinically relevant ques-

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Clinical Practice Guideline Panel: Chair: Piotr Socha; Secretary to the Chair: Wojciech Jańczyk, Alberto Zanetto. Panel members: Patrizia Burra, Anna Czlonkowska, Dominique Debray, Peter Ferenci†, Uta Merle, Emanuele Nicastro, Aurelia Poujois, Hartmut Schmidt. EASL Governing Board Representative: Emmanuel Tsochatzis.

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