Finally, all recommendations were discussed and approved by all participants.

Once the recommendations were drafted and agreed by the CPG panel another Delphi panel review was conducted, and the recommendations were reviewed. Suggested changes were considered in a revised draft that was subsequently sent for review by the EASL Governing Board and external reviewers.

## Clinical presentation

Symptoms are variable (Box 1) and discussed in detail in the text, the frequency is presented in Table 3 and discussed in the text and age of clinical presentation is discussed in the text.

The most common presentations are liver disease and/or neuropsychiatric disturbances. Pre/asymptomatic patients (no clinical symptoms or minor laboratory abnormalities including slightly increased transaminases) are most often detected by family screening. Herein, the term asymptomatic is used to describe patients without clinical symptoms. However, to be more precise in formulating recommendations, asymptomatic patients without signs of liver involvement or those with signs of liver involvement (increased transaminases) were considered separately.

### Age at onset of symptoms

WD may present symptomatically at any age, although the majority of patients present between the ages of 5 and 35. The youngest recorded case of cirrhosis due to WD was 3 years old[14] but hepatomegaly with increased transaminases has been noted as early as 2 years of age.[15] A small minority (3% to 8%) of patients present beyond the fourth decade, either with hepatic or neurologic disease.[6,8,9] The oldest reported patients were two siblings diagnosed in their eighth decade.[16,17]

**Box 1. Major clinical features of WD.**

**Hepatic**
- Hepatomegaly, splenomegaly
- Steatosis
- Increased AST and/or ALT
- Signs/symptoms of portal hypertension: splenomegaly, esophageal/gastric varices, thrombocytopenia, dilated portal vein, splanchnic collaterals
- Symptoms of decompensated liver disease: ascites, hepatic encephalopathy, jaundice

**Neurological**
- Tremor
- Dysarthria
- Ataxia
- Dystonia
- Parkinsonism
- Dysphagia
- Chorea/athetosis
- Cognitive alterations
- Writing difficulties

**Psychiatric**
- Mood disturbance
- Personality changes
- Depression
- Anxiety
- Psychosis

**Other organ manifestations**
- Kayser-Fleischer-rings, sunflower cataracts
- Renal abnormalities
- Cardiomyopathy
- Pancreatitis
- Skeletal anomalies (*e.g.* arthropathy)

### Physical signs

The clinical hallmark of WD is the Kayser-Fleischer ring, which is present in 95% of patients with and slightly over 50% of those without neurological symptoms[18,19] In children presenting with liver disease, Kayser-Fleischer rings are usually absent.[20] Kayser-Fleischer rings represent deposition of copper in the Desçemet's membrane of the cornea. A slit lamp examination by an experienced ophthalmologist is required for their identification. Optical coherence tomography is a more sensitive method to diagnose Kayser-Fleischer rings.[21] Kayser-Fleischer rings are not entirely specific for WD, since they may be found in patients with chronic cholestatic diseases, including children with neonatal cholestasis. Other ophthalmologic changes are rare, and include sunflower cataracts, which represent deposits of copper in the anterior lens capsule.[22] Signs of liver disease are nonspecific, but WD should be ruled out in any liver disease of unknown origin. Neurologic signs are very variable; they most often consist of tremor, dysarthria, ataxia and/or dystonia.

### Liver disease

Any severity of liver disease may be encountered in patients with WD. WD should be considered with any type of liver abnormality and neurological symptoms. Some neurological patients can have normal liver tests.

Clinically evident liver disease may precede neurologic manifestations by as much as 10 years[8,23] and most patients have some degree of liver disease at presentation. Presenting symptoms can be highly variable, ranging from asymptomatic, which can also be associated with only biochemical abnormalities, to overt cirrhosis with complications. WD may also present as fulminant hepatic failure sometimes associated with a Coombs-negative haemolytic anaemia and/or acute renal failure. It is important to note that WD often presents with only slightly increased transaminases.

#### *Acute liver failure due to Wilson's disease*

We define ALF due to WD as a first and acute presentation of liver disease with liver insufficiency indicated by increased international normalised ratio (INR >2 or when encephalopathy occurs INR >1.5), even in the presence of underlying chronic liver disease. WD should be considered in the differential diagnosis of any young patient presenting with acute hepatitis. Its clinical presentation may be indistinguishable from that of acute viral hepatitis, with jaundice and abdominal discomfort. Once a diagnosis is made, lifelong treatment is necessary. On the other hand, rapid deterioration can occur with fulminant liver failure with encephalopathy and renal failure. Acute liver failure due to WD occurs predominantly in young females (female:male ratio 4:1).[18]