Encephalopathy in Wilson Disease: Copper Toxicity or Liver Failure?

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Hepatic encephalopathy (HE) is a complex syndrome of neurological and psychiatric signs and symptoms that is caused by portosystemic venous shunting with or without liver disease irrespective of its etiology. The most common presentation of Wilson disease (WD) is liver disease and is frequently associated with a wide spectrum of neurological and psychiatric symptoms. The genetic defect in WD leads to copper accumulation in the liver and later in other organs including the brain. In a patient presenting with Wilsonian cirrhosis neuropsychiatric symptoms may be caused either by the metabolic consequences of liver failure or by copper toxicity. Thus, in clinical practice a precise diagnosis is a great challenge. Contrary to HE in neurological WD consciousness, is very rarely disturbed and pyramidal signs, myoclonus dominate. Asterixis and many other clinical symptoms may be present in both disease conditions and are quite similar. However details of neurological assessment as well as additional examinations could help in differential diagnosis. (J Clin Exp Hepatol 2015;5:S88–S95)

Hepatic encephalopathy (HE) is brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma. This definition[1–3] is based on the concept that encephalopathies are 'diffuse disturbances of brain function[4] and that the adjective 'hepatic' implies a causal connection to liver insufficiency and/or perihepatic vascular shunting.[5]

HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations.[6] In its lowest expression[7,8] HE subtly diminish only some cognitive abilities revealed by very sensitive psychometric neuropsychological tests oriented towards complex subsystem of attention, working memory, psychomotor speed and some forms of visuospatial ability, as well as electrophysiological and other functional brain measures[9,10] Since the condition affects only isolated components of cognitive functioning, which may not be impaired to the same degree, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) suggests the use of at least two tests depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to serve as a comparator.[11] Disturbances of the sleep–wake cycle with daytime somnolence are frequent[12] whereas reversal of the sleep–wake cycle is less consistently seen.[6,13]

In non-comatose patients with HE, motor system abnormalities such as hypertonia, hyperreflexia, and a positive Babinski sign can be seen. In contrast, deep tendon reflexes may diminish and even disappear in coma[14] although pyramidal signs can still be seen. Rarely, transient focal neurological deficits can occur.[15] Seizures are very rarely reported in HE.[16–18] Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, parkinsonian-like tremor, and dyskinesia with diminished voluntary movements are common findings; in contrast, the presence of involuntary movements similar to tics or chorea occur rarely.[14,17,19] Asterixis or "flapping tremor" is often present in the early-middle stages of HE that precede stupor or coma, and is in actuality not a tremor, but a negative myoclonus consisting of loss of postural tone.

Wilson Disease (WD) is an autosomal recessive disorder of copper metabolism with pathological copper accumulation in many organs with damage of affected tissue (mainly liver and brain).[20–22] WD is caused by mutation in the *ATP7B* gene located on chromosome 13 which encodes a copper transporting transmembrane protein, mostly expressed in liver, and involved in copper transport in trans-Golgi network in hepatocytes. Since WD is a primary liver disease which may present as "acute" liver failure or decompensated chronic liver disease, defining

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Abbreviations: AHD: acquired hepatocerebral-degeneration; Cho: choline; EEG: electroencephalography; Glx: glutamine and glutamate; HE: hepatic encephalopathy; MHE: minimal hepatic encephalopathy; MRI: magnetic resonance imaging; MRS: magnet resonance spectroscopy; MI: myoinositol; NAA: N-acetyl-aspartate; WD: Wilson disease
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the type of HE[2] in WD patients may become difficult. Hepatic WD may leading to the typical metabolic encephalopathy usually named HE. On the other hand, WD may lead to neurologic symptoms which can also occur in liver failure.

This review discusses the neurological and psychiatric signs of WD and its differentiation from HE.

NEUROLOGICAL MANIFESTATION OF WILSON DISEASE

Almost 40–50% of WD patients present with neurological symptoms.[20,22].The first neurological symptoms appear usually at the age between 20- and 30-years, however the youngest patient in whom neurological symptoms occurred was 6 years old[23] and the oldest was 72 years old.[24]

Different classifications of neurological presentation of WD are used, but most often are based on the dominant neurological signs:

1) Tremor is the most frequent neurological symptom occurring in almost 80% of WD patients. It could be a resting, intentional, and/or postural tremors, often with a "wing-beating" tremor.
2) Akinetic-rigidity (parkinsonian-like) symptoms are the second frequent neurologic symptoms in of WD and include hypomimia (Figure 1), drooling, micrographia, bradykinesia which occur in almost 40% of WD patients with neurological presentations.
3) ataxia
4) dystonia is the most severe neurologic presentation of WD, and occurs in almost 10–30% of patients presenting as focal (risus sardonicus, oro-facial dystonia, limb dystonia), segmental (trunk dystonia) or even generalized[25] (Figure 2)

However in many cases it is very difficult to classify the patient's neurological symptoms due to mixed presentations. Severity of neurological impairment may be scored using Unified Wilson's disease Rating Score (UWDRS) which consist 3 parts including: 1. conciousness, 2. changes in activities of daily life and 3. the results of the clinical neurological examination.[26,27] Contrary to HE, disturbed consciousness, pyramidal signs, myoclonus and/or asterixis in neurological cases of WD are very rarely observed. Another possibility to quantify the

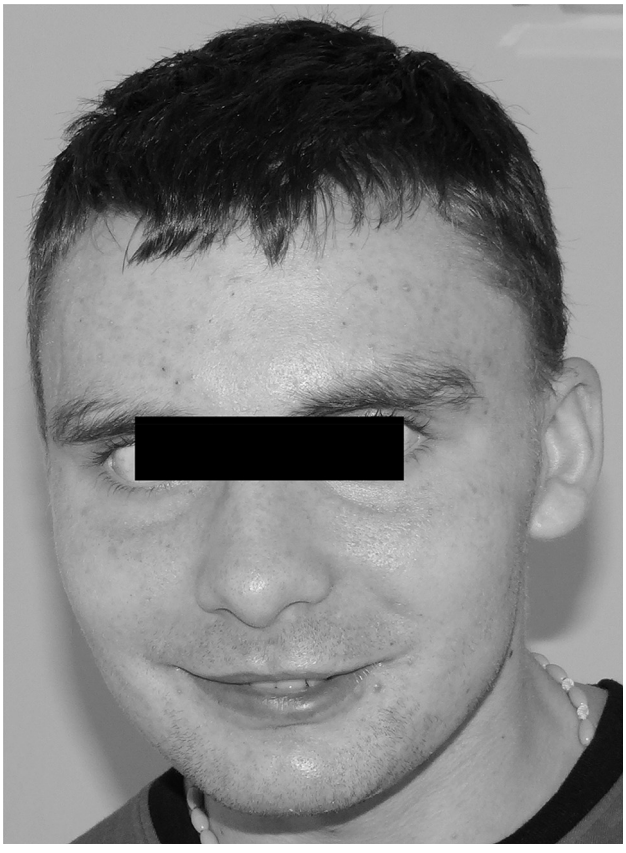

Figure 1 Hipomimia in 21-years old WD patient.

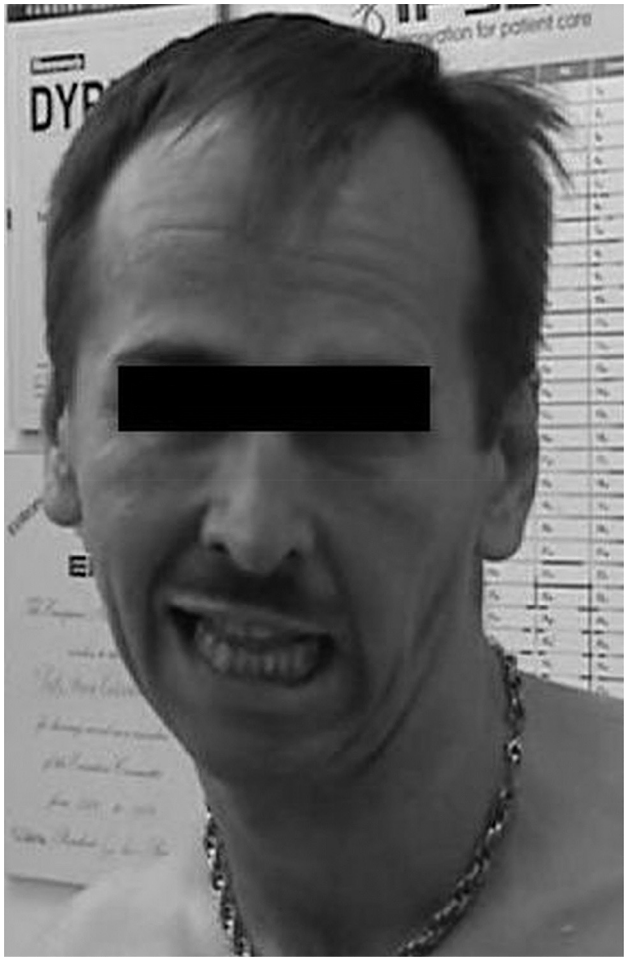

Figure 2 Oromandibular dystonia in 38-years old WD patient.