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 sub-clinical 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 frequent¹² 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 coma¹⁴ 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 HE² in WD patients may become difficult. Hepatic WD may lead 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 old²³ 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.

Figure 1 Hipomimia in 21-years old WD patient.

- 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 generalized²⁵ (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. consciousness, 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 2 Oromandibular dystonia in 38-years old WD patient.

symptoms is the Global Assessment Scale (GAS) which includes global disability (tier 1: liver, cognition and behavior, motor, osseomuscular) and neurological assessment (tier 2: detailed neuropsychiatric).²⁸

However neither approach includes liver function tests and cannot be used to differentiate HE from neuropsychiatric WD.

PSYCHOPATHOLOGY IN WILSON DISEASE

Typical psychiatric symptoms occur in almost 65% WD patients^{29–31} and include personality disorders, mood disorders, cognitive impairment, psychosis, and less frequently other psychiatric alterations (anorexia, catatonia, substance abuse and others).³² In up to 25% of WD patients psychiatric symptoms may be the initial disease presentation. The most common psychiatric symptoms in patients with WD are personality disorders (46–71%) appearing as abnormal behavior, irritability and/or aggressiveness. The mood disorders presents are the second frequent group of psychiatric symptoms in WD and manifests as depression (30–60% of patients), bipolar affective disorders (18%) with high ratio of suicidal behavior (4–16%). The cognitive disorders occur in about 25% of patients (these data depend on the precision of neuropsychological testing) including e.g. declining school performance in children and in adults mainly executive functions impairment (programming, organizing, and controlling aim-directed behavior). Full clinical picture of dementia is rarely observed, only in advanced disease stage. WD patients usually (apart coexistence of WD and HE) don't present with severe consciousness disturbances (typical for advanced stages of HE).^{28,30,33} The group of WD patients is very heterogeneous; therefore their cognitive-behavioral functioning is highly variable. Furthermore, most paper-pencil cognitive tests may be difficult to perform for patients with motor deficits.

For example, the Number Connection Test A (the test engages visuomotor functions, and response time is measured) was abnormal only in 5 out of 65 Viennese patients with various presentations of WD including some with hand motor dysfunction in (see Figure 3). All patients were on treatment with copper chelators. A more objective tool is brain stem acoustic evoked potentials (see Figure 4). 80% of patients with neurologic WD had a prolonged central conduction time, but only a few patients with hepatic WD.³⁴

Some WD patients suffering from only slight liver dysfunction remain normal in cognitive and psychic functioning, what was confirmed in detailed neuropsychological examinations.^{35–37} The diagnosis of the overt HE is simpler because it relies on the basis of neurological and physical pathological signs. The situation in MHE is far more challenging as the condition in which patients reveal selective, subtle neuropsychological deficits while a

Figure 3 Number Connection Test in patients with Wilson disease.

neurological/physical examination does not disclose any disorders, and a patient often reports no complaints. In such cases systematic neuropsychological evaluation should be comprehensive, and performed by means of particularly sensitive measurement tools that assess different aspects of cognition (attention, perception, language, memory, spatial and constructive abilities, executive function, information processing speed etc.), as well as emotional-affective functioning (depression, anxiety, apathy, sleep disturbances etc.). In overt advanced HE in WD, results of psychological test can be affected even by minimal motor dysfunction, pathological fatigue, apathy, vigilance impairment etc. For this reason, the essential task for an experienced neuropsychologist is a proper choice of tests to minimize influence of confounding variables in measurement of the actual cognitive functioning. It should also be noted that the assessment of cognition during somnolence, confusion, or minimally conscious state is generally unjustified and incorrect, and such states are frequently present (episodically or

Figure 4 Central conduction time in patients with Wilson disease.

persistently) in severe hepatic encephalopathy. As WD patients with the hepatic form of disease, have various types and severity of liver pathology, the results of few neuropsychological group studies which enrolled usually diverse participants are inconsistent.³⁶ Szutkowska-Hoser³⁶ compared 17 WD patients with mild liver dysfunctions without neurological symptoms with a group of healthy individuals matched according to sex, age, education and socio-economic status. All participants were examined by the use of an extensive cognitive test battery assessing attention, learning, arithmetic skills, visual-motor coordination, visual-spatial perception and constructional abilities. Additionally, assuming that any, even slight, neuropsychological deficits may influence patients' everyday functioning researchers examined their subjective quality of life. The study revealed that in early stages of the hepatic form of WD cognitive deficits (if any symptoms occur at all) are selective, very mild and affect primarily visual-motor functions and arithmetic skills, although they do not reduce the quality of life in subjective patients' opinion. Tarter et al³⁸ found in the early stage of nonalcoholic hepatic cirrhosis (among other participants were few WD patients), despite the absence of medical signs of encephalopathy, deficits of flexible cognitive shifting (an executive dysfunction), attention decline and visuomotor impairment.

It is well known from clinical practice that WD patients with liver diseases may disclose different, usually minor emotional-affective impairments (apathy, emotional lability, irritability, mood fluctuation, nervousness etc.). However, a few case reports confirmed that in this population (without evident brain involvement but presence of neurological symptoms) even severe psychiatric states may occur. Sorbello et al³⁷ described the case of a 18 years old WD patient with advanced cirrhosis and normal brain magnetic resonance imaging (MRI) scan developing a full clinical picture of psychosis (with hallucinations, delusions, insomnia and depression). He underwent immediately a liver transplantation. After that, copper metabolism and liver function as well as psychic state became normal. Twelve years after the surgery liver function was still normal, and psychiatric abnormalities were no longer observed. Varghese et al³⁹ described a 19 years old woman listed for liver transplantation for Wilsonian cirrhosis who developed symptoms of mania. Both cases suggest, that severe liver dysfunction in WD patients can cause serious psychiatric illness.

Differences in results of cognitive-behavioral research in hepatic WD are conflicting due to the use of different measurement tools and evaluating selectively incomparable cognitive domains (a complete neuropsychological assessment is very extensive, long-lasting and therefore rarely performed). However, if researchers wanted to establish more adequate neuropsychological profiles at different stages of the HE in WD, they would have to use specially

designed sensitive and comprehensive test battery and provide the monitoring of patients' functioning over time, controlling confounding noncognitive (i.e. even minimal motor or arousal deficits) and independent variables (i.e. current parameters of liver function). The correct psychological measurement should include assessment of various types of attention (vigilance, sustained, selective and divided attention), memory and learning, perception, praxis, construction, information processing speed, working memory, verbal fluency, spatial ability, cognitive flexibility, problem solving, and other executive functions. Cognitive testing should be supplemented by a detailed interview and diagnosis of emotional-behavioral functioning.

In the case of an individual patient, suspected of having HE (especially MHE), the methodological difficulty in psychological assessment is generally due to the lack of detailed measurements of individuals' premorbid cognitive-behavioral functioning, which is highly variable. Therefore, more reliable and conclusive are the results of the large group studies, comparing HE patients with a precisely matched of healthy individuals. However, this type of research suggests only certain psychopathological trends in the population of interest, while every patient requires an individualized approach.

Some patients reporting cognitive complaints do not exhibit real neuropsychological or neurophysiological brain abnormalities even in a comprehensive testing. Their complaints can have multiple origins and may reflect affective or somatic problems, as well as a neurotic personality, which are unrelated to primary cognition dysfunction.³² In individuals with excellent premorbid intelligence and high education, the possible actual decline in some cognitive domains, might be masked by different strategies used by these patients to compensate any deterioration. It has been documented that depression levels assessed in participants by psychiatrists were significantly higher than those in patients' self-rating.³³ This suggests that the evaluation of the psychoaffective functioning contains a variable of subjectivity, especially in patients with somatic dysfunctions. Using self-rated measurement tools assessing cognitive-behavioral functioning in WD patients, a clinician should pay attention to the level of their psychic insight and self-awareness, because some individuals from this population might have diminished control of their own behavior, which is probably related with even minimal prefrontal-subcortical system dysregulation.⁴⁰

DIFFERENTIAL DIAGNOSIS OF HEPATIC ENCEPHALOPATHY AND WILSON DISEASE

HE and WD share many clinical neuropsychiatric signs and symptoms in the milder stages of the disease. Therefore a differentiation of these two disorders based on the clinical symptoms very often it is not possible. The

neuropathological changes in the brain in both disorders are similar with the astroglia proliferation with pathologic astroglia forms (Alzheimer I and II cells) and neuronal degeneration probably due to liver failure with disturbances of brain ammonia metabolism. However, later accumulation of different metals in both disorders (copper in WD, manganese in HE) lead to further neuronal degeneration in basal ganglia with additional cortical and subcortical abnormalities and even brain edema in advanced stages of HE. Further, the WD specific extrapyramidal signs and symptoms and cystic changes in basal ganglia (especially nucleus lentiformis) caused by copper accumulation are not seen in HE. However, in advanced liver disease changes occur in the globus pallidus caused by manganese accumulation.⁴¹ Thus, both in WD and HE structural changes in the basal ganglia may disrupt dopaminergic transmission. In more advanced liver disease the signs and symptoms of HE and WD could further overlap. Additional examinations like electroencephalography (EEG) and brain MRI can help in differential diagnosis. In HE depending for the stage of disease EEG changes are observed (1. theta stage; 2. triphasic waves stage (with high-amplitude ($>70 \mu\text{V}$), positive sharp transients that are preceded and followed by negative waves of relatively lower amplitude); 3. delta stage) which are not present in pure neurological form of WD. In HE, in the

brain MRI hyperintensive changes in T-1 weighted images in both globi pallidi are often observed (probably due to manganese accumulation). In WD such changes are rare (Figure 5) (only when HE is present).⁴² Typical for WD are the hyperintensive changes in T-2 weighted MRI scans located in basal ganglia, thalami and brainstem which can be also seen as well as in brain computed tomography (CT) (Figure 6 a, b and 7 a, b).

Brain metabolites can be analyzed indirectly by magnetic resonance spectroscopy (MRS). Decreased myoinositol (MI), choline (Cho) and increased glutamine and glutamate (Glx) concentrations are used to document cell proliferation, osmotic regulation and/or inflammation in the brain in HE.^{42–44} In contrast in WD and other neurodegenerative disorders the decrease of N-acetyl-aspartate (NAA) is a characteristic marker of neuron damage and depletion (in WD together with decreased Cho and MI).⁴² However, at very early stages of both disorders the picture could quite similar. Finally, it worth to mention that MRS changes observed in HE are reversible and the MRS results normalization were observed after liver transplantation (especially) or pharmacological treatment.⁴⁵

ACQUIRED HEPATOCEREBRAL-DEGENERATION (AHD)

This very rare neurological manifestation of HE was first described 100 years ago by van Woerkem,⁴⁶ 2 years after the description of WD. At this time it was assumed that this syndrome was a different disease entity and was called “acquired hepatocerebral-degeneration”⁴⁷ (AHD, or “non-Wilsonian hepatocerebral-degeneration” or “cirrhosis-associated Parkinsonism”). This syndrome included Parkinsonism, ataxia, oro-facial dyskinesias (mimicking tardive dyskinesia with blepharospasm, dystonia) and cognitive deficits occurring in patients with chronic liver disorders, especially with presence of portosystemic shunting.^{46–48}

AHD was unresponsive to ammonia-lowering therapy.⁴⁸ The pathogenesis of AHD is unknown, but shares many features commonly observed in HE (ie. manganese accumulation in basal ganglia).^{47,48} However, most of the reported AHD patients were not tested with appropriate tests for WD. For example, in a case description from the Mayo clinic the authors argue that WD “... was an unlikely consideration in our patient because of her age (rarely presenting after the third decade) and retained presence of blue-colored iris (copper deposits color the iris brown)”⁴⁹ Today we know that WD may become symptomatic at any age and that the typical Kayser-Fleischer rings may be absent.⁵⁰ The clinical symptoms of AHD are very similar to WD and included extrapyramidal symptoms (Parkinsonism, early postural instability with falls, dystonia, chorea, tremor, myoclonus). Contrary to

Figure 5 The brain magnetic resonance imaging (MRI)—typical picture of HE in 40 years old WD male—increased signal intensity on T-1 weighted images in both globi pallidi (arrow).

Figure 6 The brain neuroimaging of 21-years WD patient; a) brain computed tomography (CT) showing bilateral hypointense lesions in basal ganglia (arrow); b) brain magnetic resonance imaging (MRI) on T-2 weighted images showing increased signal intensity in both putamens (arrow).

Parkinson disease tremor in AHD, WD and HE mostly presents as action tremor (rarely as resting), and the symptoms are bilateral and symmetrical. The presence of chorea, oro-facial dyskinesias, ataxia occurs more frequently in AHD and WD. The response to levodopa treatment (good in Parkinson disease, poor and/or absent in HE and WD patients) and brain MRI could help to distinguish the AHD and WD associated Parkinsonism and Parkinson disease. Finally, 'hepatic myelopathy' is also a particular pattern of HE characterized by severe motor abnormalities exceeding the mental dysfunction. Cases of paraplegia with progressive spasticity and weakness of

lower limbs with hyperreflexia and relatively mild persistent/recurrent mental alterations have been reported, and may reverse with liver transplantation. It should be mentioned that no case of WD with hepatic myelopathy has been published so far, so these presentations should be considered as a specific for HE.^{47,48}

CONCLUSIONS

The diagnosis of overt HE in patients with liver disease is based on well established neurological examination after exclusion of other factors leading to neuropsychiatric

Figure 7 The brain MRI of 30-years women with advanced neurological form of WD on T-2 weighted sequences: a) bilateral hyperintense signal in putamen and thalamus (narrow arrows) and hypointense lesions in globus pallidus (broad arrow). b) hyperintense signal in pons (arrow).

manifestation. Additional examinations which help to differentiate HE are brain MRI and MRS. Diagnosis of minimal hepatic encephalopathy (MHE) is more difficult and may be indistinguishable from neuropsychiatric WD. WD is a complex disorder of liver disease associated with copper induced neuropsychiatric signs. HE and WD in the presence of liver failure could overlap. There is not a single test which can reliably differentiate both conditions. Clinical skills and awareness are required. Every patient with HE due to liver disease of unknown origin should be screened according to WD.

CONFLICTS OF INTEREST

All authors have none to declare.

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