New Methods of Testing and Brain Imaging in Hepatic Encephalopathy: A Review

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KEYWORDS

• Hepatic encephalopathy • Ammonia • Psychometric testing • Stroop app
• Brain imaging • Magnetic resonance spectroscopy • Single-photon emission CT
• PET

KEY POINTS

- Hepatic encephalopathy (HE) is a clinical diagnosis requiring the exclusion of other causes of altered cerebral function.
- Diagnosis requires the presence of decompensated cirrhosis, acute liver failure, acute-on-chronic liver failure, or portosystemic shunting without cirrhosis.
- Psychometric tests are useful in the diagnosis of covert HE (CHE) but can be expensive and time consuming.
- Serum ammonia measurement is not routinely recommended for diagnosis.
- Functional brain imaging plays an important role in the diagnosis and understanding the pathogenesis of HE.

INTRODUCTION

HE comprises a spectrum of neuropsychiatric manifestations that can occur in patients with cirrhosis, acute liver failure, acute-on-chronic liver failure, or major portosystemic shunting without intrinsic liver disease.[1] It is characterized by disturbances in cognitive and motor function that can manifest as a change in personality, altered mood, diminished intellectual capacity, abnormal muscle tone, and tremor, among other symptoms in chronic liver disease.[2] The manifestations of this entity in acute liver failure can include abrupt-onset delirium, seizures, and coma as a result of cerebral

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edema, increased intracranial pressure, and eventually brain herniation as a terminal event.[3,4] Early symptoms of HE might be subtle in nature and require psychometric testing to be identified.[5] Clinically obvious psychomotor derangements may occur later on as the disease progresses. Hence, it is imperative to identify these subtle manifestations to facilitate early diagnosis.[5] A diagnosis of HE is mainly clinical and usually made by the exclusion of other causes of brain or spinal cord dysfunction and proved by response to available therapy.[5] Certain imaging characteristics, such as basal ganglia hyperintensity on T1-weighted MRIs, are present in patients with end-stage liver disease, pointing toward the diagnosis, but are not pathognomic for HE.[6] Functional brain imaging is valuable and has provided important information into the understanding of the pathophysiology of HE but an optimal, clinically relevant and easily accessible test remains elusive.[7]

DIAGNOSING HEPATIC ENCEPHALOPATHY

To suspect a diagnosis of HE, as the term implies, a clinician has to first identify the presence of cirrhosis, acute liver failure, or portosystemic shunts without intrinsic liver disease. Testing should include methods for diagnosing CHE and overt HE.[5] Early symptoms include cognitive deficits in attention, visual perception, visuospatial construction, motor speed, and accuracy.[8] The subtle nature of these deficits can require psychometric testing for diagnosis. Clinically obvious symptoms and signs occur later on as the disease is advancing but a diagnosis can be made only after exclusion of other causes of cerebral dysfunction.[5] Additional diagnostic approaches include biochemical analysis to determine serum ammonia levels, brain imaging, electroencephalogram (EEG), lumbar puncture (LP), and other new methods of functional brain imaging, like magnetic resonance spectroscopy (MRS), PET, and single-photon emission computed tomography (SPECT).[5]

PSYCHOMETRIC TESTS

Hamster and colleagues[9] paved the way for further standardization in testing methods for CHE; 96 cirrhotic patients and 163 healthy age-matched controls were subjected to more than 30 different psychometric tests to assess cognitive domains ranging from premorbid intelligence levels to verbal abilities to visuomotor function and to coordination. It was published that the line tracing test, pegboard, aiming and steadiness of motor performance scale, and digit symbol test could effectively differentiate cirrhotic and noncirrhotic patients. CHE patients show abnormalities, particularly in areas of attention (loss of vigilance and disorientation), executive functions (problem solving, planning, and judgment), visuospatial coordination, and psychomotor speed (reaction times).[10] Underlying many of these deficits is an impaired response inhibition.[11] Psychometric testing strategies focus on defining abnormalities related to these domains using neuropsychological or neurophysiologic tests.[11] An overall brief description of available psychometric tests and their practical application in diagnosis of CHE are depicted in **Table 1**.

The drawbacks of applying psychometric tests in CHE patients include time and effort added to outpatient visits, lack of standardization, reliance on psychological expertise to administer and interpret results, the expensive and copyrighted testing procedures involved in the application of these tests, and potential reimbursement issues.[12]

STROOP APPLICATION

The Stroop smartphone application (app), which was developed by Bajaj and colleagues,[13] is a short and recently validated test to screen and diagnose patients