Expanding the Spectrum of Hepatic Encephalopathy

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Key Concepts

• The spectrum of hepatic encephalopathy or SONIC (spectrum of neuro-cognitive impairment in cirrhosis) starts well before any clinical signs and symptoms appear
• Minimal or covert hepatic encephalopathy is epidemic in cirrhosis and can affect patients and caregivers in medical, psychological and socio-economic terms
• Driving ability may be hampered in minimal/covert hepatic encephalopathy and measures to improve insight into this are essential
• Treatment strategies for hepatic encephalopathy include those aimed at the gut or at systemic ammonia scavenging or both but treatments for covert/minimal hepatic encephalopathy are not standard of care
• Controversies abound in this field of HE regarding the appropriate testing and treatments for minimal/covert HE and legal issues regarding driving

Summary

The burden of hepatic encephalopathy (HE) continues to increase and with the longer lifespan of cirrhotic patients, the expanding spectrum of HE beyond simple clinical confusion and disorientation have increased in importance. Covert and minimal HE are terms used to define poor cognitive function in cirrhotics who otherwise appear normal on physical examination. These patients however are impaired on daily activities including driving and work, have a poor quality of life, increased progression to overt HE and impaired socio-economic status. Driving impairment has been shown on simulation, on-road testing and a higher number of driving errors. Despite this, however, at this time there are no medico-legal concerns regarding minimal/covert HE but should be centered around patients with overt HE currently on therapy. Testing for covert HE is usually not possible during the clinic visit and may require collaboration with a trained professional/assistant. Additionally, tests should only be administered to patients after adequate screening to exclude other causes of neuro-cognitive dysfunction. Treatments for this expanded spectrum of HE are similar to that for overt HE with lactulose, rifaximin and probiotics being the most studied therapies. Studies have shown improvement in quality of life and cognition but more trials with endpoints of overt HE prevention are needed. Currently treatments for minimal/covert HE can be offered on a case-by-case basis. The spectrum of HE extends beyond patients admitted with confusion and therefore requires additional effort to diagnose. However, given the negative impact of minimal/covert HE on cirrhotics and their caregivers, it is highly relevant to identify these patients for prognostication, counseling and potential therapy.
Burden of Hepatic Encephalopathy and Expanding the Spectrum

The burden of hepatic encephalopathy (HE), as evidenced by hospitalizations and total cost, is relentlessly rising. In addition to the medical and financial costs, HE also places a significant burden on caregivers and society. While the above costs are easy to estimate since they represent the burden of overt or clinically diagnosable HE, there is a much higher burden if the entire Spectrum of Neuro-Cognitive Impairment in Cirrhosis (SONIC) is considered. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities seen in patients with liver disease after exclusion of other known brain diseases. This definition therefore includes an entire sub-stratum of HE that cannot be diagnosed and has the potential to worsen the prognosis of patients, caregivers and society. Expanding the spectrum of HE therefore, requires a deeper understanding of the whole range of neuro-cognitive impairments, that can in turn help in accurate prognostication and treatment.

Nomenclature and Gradation of Hepatic Encephalopathy

HE can be divided according to the underlying cause or by severity.

Division According to the Underlying Cause

Type A: Acute liver failure-associated, Type B: associated with Bypass i.e. porto-systemic shunting without liver problems and Type C: associated with Cirrhosis. This discussion will concentrate on Type C only.

Division According to the Severity of HE

The severity assessment of HE is important since most treatment decisions are guided by this evaluation. The broad categories are patients with clinically diagnosable or “overt HE” and those without clinically diagnosable HE. Minimal HE is defined as impaired cognition on specialized tests in cirrhotic patients without obvious clinical signs and symptoms of the disease while overt HE is defined as patients with obvious clinical signs and symptoms of HE. While the West-haven criteria have been traditionally used to diagnose the severity of HE, stage 0 and 1 are not amenable to multi-center scientific studies, while stages 2 through 4 have a relatively high inter-rater reliability (Table 1).

Therefore, the term “COVERT HE” was introduced by the consensus statement of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) in 2011 which included minimal HE and grade 1 of the West-Haven criteria for ease of multi-center studies (Table 2, Figure 1). Therefore patients with asterixis or mental status changes including disorientation have overt HE. For the remainder of this document, minimal/covert HE will be used to signify impaired cognitive performance in a patient without disorientation or asterixis.

Characteristics of Minimal/Covert HE-Associated Impairment

Patients with minimal/covert HE have difficulties in several daily activities because their cognitive domains are negatively impacted. Specifically the ability to remember things quickly (working memory), reaction time and psychomotor speed (needed to react quickly), visuo-motor coordination (need to drive, draw, design, work in blue-collar jobs), oMinimal hepatic encephalopathy (MHE) is the most prevalent cognitive complication that is epidemic in cirrhosis. Patients with MHE have difficulties in several cognitive domains including psychomotor speed, reaction time, visuo-motor coordination and inhibitory control.

Importance of the Expanded Spectrum of HE

Minimal/covert HE can affect from 30-84% of patients tested but most studies report this diagnosis in the range of 35-55% of cirrhotic patients. This represents an epidemic cognitive dysfunction in patients with cirrhosis. The knowledge of this expanded spectrum is essential because

Table 1: West-Haven Criteria Illustrating the Subjectivity of Stages 0 and 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
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<tbody>
<tr>
<td>0</td>
<td>No abnormalities detected</td>
</tr>
<tr>
<td>I</td>
<td>Trivial lack of awareness, Euphoria or anxiety</td>
</tr>
<tr>
<td>II</td>
<td>Shortened attention span, Impairment of addition or subtraction</td>
</tr>
<tr>
<td>III</td>
<td>Lethargy or apathy, Disorientation for time</td>
</tr>
<tr>
<td>IV</td>
<td>Obvious personality change, Inappropriate behaviour</td>
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Table 2: Expanding the Spectrum of HE according to ISHEN criteria

<table>
<thead>
<tr>
<th>Mental status</th>
<th>Unimpaired</th>
<th>Covert HE</th>
<th>Overt HE</th>
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<tbody>
<tr>
<td>Performance on specialized tests</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Not needed but will be abnormal if tested</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Absent</td>
<td>Absent</td>
<td>Present unless patient is in coma</td>
</tr>
</tbody>
</table>
minimal/covert HE affects the patients and their family from a medical, psychological and socio-economic standpoint. Studies across several countries and using cirrhosis-specific or general questionnaires have mostly concluded that minimal/covert HE adversely impact health-related quality of life (HRQOL). This impact ranges from domains as diverse as physical pain, eating, movement and work which can prevent patients from reaching their full potential as productive members of society. There is also increasing evidence that treating minimal/covert HE can improve HRQOL. Patients with minimal/covert HE also have a significantly higher incidence of development of overt HE compared to those without minimal/covert HE. This knowledge is important because this aids in counseling of patients and caregivers as to the specific symptoms of overt HE. At this time, there is evidence from open-label single center studies that minimal/covert HE treatment can prevent overt HE development but this is not standard of care at this time. Therefore the diagnosis of minimal/covert HE can aid prognostication. Cognitive dysfunction in cirrhosis can be directly linked with employment especially in blue-collar workers since those cognitive domains are disproportionately affected in minimal/covert HE. This cognitive dysfunction can also affect income and socio-economic status, which has also been confirmed in multi-center evaluations. An especially important aspect of daily life affected by minimal/covert HE is driving which will be discussed below.

Driving Impairment in Minimal/Covert HE

Cognitive impairments in minimal/covert HE can definitely affect driving, in which these domains are used constantly and need to be updated minute by minute. Driving a car is one of the most accomplished and one of the most dangerous tasks that we perform in our daily life and medical impairments do have an important role to play in determining driving capability. Driving in patients with minimal/covert HE has been a focus of testing for several years including tests performed on (A) Simulators (B) On-road driving tests and (C) analysis of actual driving offenses. Simulator studies have shown that minimal/covert HE patients have difficulty with car crashes, problems navigating and a predisposition to fatigue-related accidents and offenses on the simulator. On-road driving tests, by and large, have demonstrated that patients with MHE are worse drivers than those without minimal/covert HE and a significant proportion of them were considered to be “unsafe” drivers. Translation of these studies into the real world shows that patients with minimal/covert HE have a high likelihood of actual car crashes and driving offenses both retrospectively and prospectively.

There is also evidence that patients with cirrhosis have a significantly higher likelihood of death compared to non-cirrhotic patients and that patients with minimal/covert HE often have poor insight into their driving skills. Therefore this situation becomes even more important to handle.
The important thing to remember is that not everyone with minimal/covert HE is a bad driver and that poor driving outcomes, such as accidents can also happen to good drivers under adverse circumstances\textsuperscript{21}. A corollary of this condition is dementia in which although experts agree that the clinical dementia rating scale can predict increased risk of collisions, there is no one single test that was accurate enough to predict future crashes\textsuperscript{22}. This remains the case with minimal/covert HE as well. However, increasing awareness of this is important and there is improvement into the insight into driving impairment after poor performance on driving simulation\textsuperscript{23}. It is also important to counsel patients to use GPS if possible and avoid driving for long-distances and potentially at night. As far as therapy is concerned a randomized, double-blind, placebo-controlled trial has shown that rifaximin therapy can improve driving simulator performance compared to placebo\textsuperscript{24}. A cost-effectiveness analysis shows that rapid minimal/covert HE detection and potential treatment of lactulose may be cost-effective compared to rifaximin, but there is no current treatment recommendation for minimal/covert HE \textsuperscript{25}.

What is Our Legal Liability and Responsibility?

From a legal perspective, doctors or clinicians are not trained in assessing fitness to drive and are not officers of the state agency charged with determining fitness to drive. However, we must act in the best interests of the patient and society, while following the applicable local laws. As members of society with special knowledge of known causes of driver impairment, physicians can educate the public and legislatures and advocate for changes in driving-related legislation\textsuperscript{21}.

Since the diagnosis of minimal/covert HE is not uniform and there is little evidence about the natural history of this disease, minimal/covert HE per se should not be considered a reason for concluding that patient is a bad driver. A more pressing concern is patients with overt HE who are now controlled on medication. Those patients are more likely to experience a recurrence and therefore those patients are those in whom clinicians can face liability. Therefore in our population, those with prior overt HE should be those in whom driving should be restricted.

What should a physician do when faced with a potentially impaired driver? They must follow the

<table>
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<th>Table 3: Methods for minimal/covert HE detection</th>
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<tr>
<td>Method</td>
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<td>---------------------------------------------</td>
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<tr>
<td>Formal psychological Assessment</td>
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<tr>
<td>Neuro/psycho-physiologic tests (EEG, Evoked potentials, Critical Flicker Frequency)</td>
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<tr>
<td>Paper-pencil tests (Block design tests, PHES)</td>
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<tr>
<td>Computerized tests (Inhibitory control test, Scan, CDRS, Continuous RT)</td>
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CDRS: cognitive drug research system, ICT: inhibitory control test, PHES: psychometric hepatic encephalopathy score

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<th>Table 4: Checklist Pertaining to Covert HE testing (the answer to most questions should be yes before proceeding to testing)\textsuperscript{26}</th>
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<tr>
<td><strong>Pre-testing Checklist</strong></td>
</tr>
<tr>
<td>Patients who are at risk for accidents or job-related mistakes, have cognitive complaints or poor quality of life</td>
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<tr>
<td>No current overt HE (alert, oriented, MMSE &gt;25)</td>
</tr>
<tr>
<td>Not on psycho-active drugs (chronic anti-depressants are acceptable)</td>
</tr>
<tr>
<td>No uncontrolled neuro-psychiatric disorders</td>
</tr>
<tr>
<td>Patient is able to comprehend cognitive test procedures</td>
</tr>
<tr>
<td>Adequate vision (corrected with spectacles), hearing and motor strength to perform tasks</td>
</tr>
<tr>
<td>Counseled patient and relatives regarding potential results</td>
</tr>
<tr>
<td><strong>Testing Techniques and Environment</strong></td>
</tr>
<tr>
<td>Quiet environment with relaxed patients</td>
</tr>
<tr>
<td>Using techniques with locally available normative values</td>
</tr>
<tr>
<td>Trained examiner using tests with scripts or protocols</td>
</tr>
<tr>
<td><strong>Post-Testing Questions</strong></td>
</tr>
<tr>
<td>Counseled patient and relatives regarding results and performance</td>
</tr>
<tr>
<td>Offered treatment trial if requested</td>
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</tbody>
</table>

MMSE (mini-mental status exam >25) cut-off has been used in select prior HE studies to demonstrate absence of disorientation.
applicable local laws on mandatory reporting; inform the patient and their family of the potential impairment; and where possible, recommend a fitness-to-drive evaluation by a driving instructor trained in detecting driving impairment. However, the state drivers licensing agency has the ultimate authority to determine fitness to drive. A state-wise breakdown of reporting duties within the US is available at www.ama-assn.org/resources/doc/public.../older-drivers-chapter8.pdf

**Diagnosis of Minimal/Covert HE**

There is ample evidence suggesting minimal/covert HE can impact patients and their caregivers’ lives, however there is a large array of tests that have been used to diagnose this condition. These testing strategies fall into three large categories with differing advantages and disadvantages (table 3):

1. Paper-pencil psychometric tests
2. Computerized tests
3. Neuro-physiological tests

These testing strategies evaluate several domains of cognition including inhibitory control, working memory, psychomotor speed, reaction time and visuo-motor coordination. *Most tests are not within the scope of administration within a regular clinic practice. Therefore it is appropriate to involve a health-care professional such as a psychologist to formally diagnose minimal/covert HE during an encounter separate from that of the clinician’s visit*. A high-sensitivity short test, such as the Stroop App, could be used in clinic by a nurse or medical assistant to exclude those who are unlikely to minimal/covert HE so that the ultimately referred patients are likely to be impaired; however it needs to be validated in other centers.

However, before these tests are administered, a checklist to evaluate the appropriate patient population for minimal/covert HE testing is important (Table 4). This is important because these tests are sensitive, not specific. According to the ISHEN guidelines, for individual centers or for proof-of-concept studies, testing strategies that the team is experienced with and have population norms are sufficient to diagnose minimal/covert HE. However for multi-center studies, it is recommended that patients at least have impairment on two types of testing strategies (computerized, paper-pencil or neuro-physiological) to ensure comparability between centers.

![Flowchart for Covert HE testing](image-url)
Management of Minimal/Covert HE

It is critical to have a plan ready for potential treatment before initiating the testing process. If the patient performs normally on cognitive tests, then repeat testing should be considered in 6 months (figure 2). If minimal/covert HE is diagnosed, then it is important to discuss treatment options with patients and caregivers. Currently there is NO standard of care to treat minimal/covert HE. This is largely because studies are not uniform in their diagnostic criteria, length of drug, are often open-label, potentially biased studies and outcomes studied are rarely beyond the cognitive test improvements that were used to diagnose minimal/covert HE.

However, despite there being no standard of care, treatment can be offered to patients on a case-by-case basis. The first step however, is to evaluate whether the patient believes they have a problem. This is important because if they are still in the "pre-contemplation stage" then any offers of therapy will not be accepted since minimal/covert HE patients have never been confused or disoriented. Therefore a sizable proportion may believe that they do not have an issue due to poor insight. This poor insight was improved by subjecting patients to driving simulation in a study. However, the treatment not being standard of care, clinicians are not liable for not offering treatment at this time.

Evidence Pertaining to Medical Treatment in Minimal/Covert HE

Treatments that have been regularly studied using randomized trials are similar to those used for overt HE i.e., predominantly those that affect the gut milieu to potentially reduce nitrogenous and other products. Agents that have been studied for this condition are lactulose, rifaximin and probiotics for the most part. There have been few randomized, placebo-controlled, double-blind studies in this field. As shown in Table 5, minimal/covert HE studies have shown some benefits to patients beyond simply improving cognition. However a large fraction of those studies that have reduced overt HE and improved HRQOL have been open-label studies which strongly raises the potential for bias. Probiotic studies are even more difficult to interpret since the type of organisms and duration of treatment are different. Rifaximin therapy, while effective, may be expensive in certain countries.

Therefore medical treatment for minimal/covert HE should be offered on a case-by-case basis to patients who are willing to undergo a treatment trial over 4-6 weeks to evaluate response. This treatment strategy could be restricted to those patients who have difficulties in employment, daily function, who have poor HRQOL or those with specific cognitive complaints.

Conclusions

Expanding the spectrum of hepatic encephalopathy is essential in understanding the entire spread of disease that can affect our patients and their families even before disorientation and confusion sets up. This insight is crucial in enhancing diagnostic, prognostic and treatment strategies in patients with cirrhosis across the spectrum of neuro-cognitive impairment in cirrhosis (SONIC).

References

New Treatments in Liver Disease


