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The Treatment of Patients With Hepatic Encephalopathy: Review of the Latest Data from EASL 2010

A Review of Selected Presentations
From the 45th Annual Meeting of the
European Association for the Study of the Liver
April 14–18, 2010
Vienna, Austria

With commentary by
Kevin D. Mullen, MD
Professor of Medicine
Case Western Reserve University
Director, Gastroenterology Fellowship Program
Department of Gastroenterology
MetroHealth Medical Center
Cleveland, Ohio

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with hepatic encephalopathy (HE).

Statement of Need/Program Overview: An abundance of new information has recently come to light in the treatment of patients with HE regarding quality of life (QOL), pharmacokinetic data, ammonium reduction, etc. and a distinct educational need exists in the gastroenterology and hepatology community for an updated understanding of the latest treatment strategies. The abstract review monograph will present the most current data emerging within this therapeutic area.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Outline challenges in the detection and treatment of various stages of HE.
2. Describe the significance of using rifaximin to reduce risk of HE-related hospitalization and breakthrough HE.
3. Review the latest information from the EASL 2010 on the use of targeted agents as treatment options for HE.
4. Describe QOL, pharmacokinetic, and ammonia reduction data in patients with HE.

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Recent Advances in the Diagnosis and Treatment of Hepatic Encephalopathy

A Review of Selected Presentations from the 45th Annual Meeting of the European Association for the Study of the Liver
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15 Rifaximin Treatment Improved Quality of Life in Patients with Hepatic Encephalopathy: Results of a Large, Randomized, Placebo-Controlled Trial[1]

A Sanyal, N Bass, K Mullen, F Poordad, A Shaw, K Merchant, E Bortey, WP Forbes, S Huang

Rifaximin, a broad-spectrum, gut-selective, minimally absorbed oral antibiotic, has demonstrated efficacy in the treatment of acute hepatic encephalopathy (HE) and more recently in the prevention of overt HE recurrence.[2] In the randomized phase III RFHE3001 trial conducted over a 6-month period, rifaximin (550 mg twice daily) reduced the risk of breakthrough overt HE by 57.9% compared with placebo (hazard ratio, 0.421; 95% confidence interval [CI], 0.276–0.641; $P<.0001$) in patients with cirrhosis and a history of recurrent (2 or more episodes) overt episodic HE. Rifaximin also reduced the number of hospitalizations due to HE. Lactulose, a nonabsorbable sugar that prevents the absorption of gut-derived ammonia, was used by more than 90% of patients at baseline and during the 6-month trial.

In this analysis of RFHE3001, Sanyal and colleagues evaluated the effect of rifaximin and breakthrough HE on patient-reported health-related quality of life, using the validated and disease-specific Chronic Liver Disease Questionnaire (CLDQ). The CLDQ includes 29 items in 6 domains: abdominal symptoms, systemic symptoms, emotional function, fatigue, activity, and worry. Individual domains are ranked on a 7 point scale, with 1 being most severe and 7 being least severe. Higher scores indicate a better quality of life. CLDQ overall score and individual domain scores were subjected to longitudinal analysis; calculated area under the curve was normalized by exposure time (time-weighted average [TWA]) for each patient. Since fatigue subdomain scores were found to be highly correlated with disease severity, it was chosen as a key secondary endpoint. Rifaximin treatment led to significantly higher mean TWA score for fatigue versus that for placebo (3.2 vs 2.5, $P=.0087$) and for the overall CLDQ score (3.7 vs 2.9, $P=.0093$). Mean TWA scores were also significantly higher for the other 5 domains with rifaximin treatment compared with placebo (Table 1).

The investigators found that rifaximin safety was comparable to placebo with an 80% and 79.9% incidence of adverse events in each treatment group, respectively. The most commonly reported events (occurring in ≥12% of patients in either treatment group) included peripheral edema (15.0% vs 8.2%), nausea (14.3% vs 13.2%), dizziness (12.9% vs 8.2%), fatigue (12.1% vs 11.3%), and diarrhea (10.7% vs 13.2%), for rifaximin and placebo, respectively. A total of 20 patients, 9 patients in the rifaximin group and 11 patients in the placebo group, died during the trial; disease progression was the primary reason for most of the deaths.

The results of this analysis indicate that rifaximin significantly improves the quality of life for patients with hepatic cirrhosis and recurrent, overt HE.

Table 1. Mean Time-Weighted Average Scores for Each Domain and the Overall CLDQ

	Rifaximin (n=140)	Placebo (n=159)	*P*-value
Overall	3.7	2.9	.0093
Abdominal symptoms	4.1	3.3	.0090
Emotional function	3.9	3.0	.0065
Systemic symptoms	3.9	3.2	.0160
Activity	3.7	2.8	.0022
Worry	3.5	2.8	.0436
Fatigue	3.2	2.5	.0087

149 Persistent Deficit in Learning of Response Inhibition Following Onset of Overt Hepatic Encephalopathy in Cirrhosis[3]

J Bajaj, DM Heuman, C Schubert, DP Gibson, JB Wade, A Topaz, D Bell, RT Stravitz, RK Sterling, AJ Sanyal

Episodes of overt HE lead to acute mental status changes that are usually reversible. However, for some patients, chronic neurologic damage may occur. To determine if cognitive function deteriorates after overt HE, Bajaj and colleagues evaluated the psychometric performance of patients with or without prior overt HE in 2 trials. The first was a cross-sectional analysis of 226 patients in which the mean age was 57 years, 75% of participants being male, and 69% having a hepatic C virus (HCV) infection; the model for end-stage liver disease (MELD) was 9, with overt (n=52), minimal (n=120), and no minimal HE (n=54). The second was a prospective study of 59 patients with liver cirrhosis and no prior episodes of overt HE, who later developed overt HE (n=15; mean age, 54 years; male, 80%; HCV infection, 80%) or who did not develop overt HE (n=44; mean age, 55 years; male, 73%; HCV infection, 74%). Psychometric performance was evaluated by a psychometric battery, including number connection test A+B, digit symbol test, and block design test. These tests were given in conjunction with an inhibitor control test (ICT) where high lures indicate poor response inhibition. Since ICT has identical halves, the ability to learn response inhibition was studied by measuring the improvement (or reduction) in lures between the first and second ICT halves (ΔL1–2). All overt HE patients were adherent to lactulose treatment and had a normal mental status as determined by a mini-mental score greater than 25.

In the cross-sectional analysis, the study authors found that patients with overt HE and minimal HE performed the worst on all psychometric measures compared with patients who had no minimal HE (P<.0001). In addition, the ability to learn response inhibition was preserved in patients with no minimal HE (ΔL1-2, 1.7) and minimal HE (ΔL1-2, 1.9), but was lost in patients with overt HE (ΔL1-2, 0.2; P=.003).

Patients who developed overt HE in the prospective trial were tested for psychometric performance 36±25 days after the HE episode and retested 4±2 months apart, whereas patients who did not develop overt HE were retested 4±3 months apart. In both patient groups, the psychometric battery tests remained similar to baseline values. However, loss of learning was found for patients who developed overt HE. Following an episode of overt HE, overall lure response worsened (12 vs 18, P=.0001) and the ability to learn response inhibition (ΔL1-2) declined from 3.0 before the overt HE episode to 0.3 after the episode (P=.001). Prior to an overt HE episode, 14 of the 15 patients had a ΔL1-2 of 1 or greater, compared with only 2 patients after an overt HE episode. Learning remained intact for those patients who did not have an overt HE episode during follow-up.

The ability to learn response inhibition, as demonstrated by the change in ICT between the first and second halves, is lost in patients following an episode of overt HE, even though these patients adhere to lactulose treatment. The authors believe that because ICT has identical halves, it offers a sensitive measure to detect chronic neurologic damage in patients with overt HE.

150 Severity of Chronic Cognitive Impairment in Cirrhosis Increases with Number of Episodes of Overt Hepatic Encephalopathy[4]

J Bajaj, C Schubert, AJ Sanyal, D Bell, L Pisney, DM Heuman

HE is associated with neuronal and astrocyte injury in patients with cirrhosis. While acute HE episodes are often reversible, recurrent acute HE episodes may lead to chronic neurologic damage. In this cross-sectional study, Bajaj and colleagues determined if recurrent acute episodes of HE lead to progressive chronic cognitive damage, as determined by psychometric performance measures after overt HE onset. The investigators included 50 patients who had at least 1 prior HE episode, who were in clinical remission with lactulose or rifaximin, and who had normal mental status (mini-mental exam score >25). Mean duration of follow-up was 13±12 months and patients had a median of 2 HE episodes

Table 2. Mean Psychometric Test Scores

	Mean scores (SEM)
NCT-A, seconds	48 (22)
NCT-B, seconds	149 (87)
DST	41 (13)
BDT	26 (15)
ICT Lures	15 (9)
ICT Targets, % correct	89 (12)

Table 3. Correlation between Psychometric Performance and the Number of Overt HE Episodes, Hospitalizations, and Duration Between the First HE Episode and Testing

	Number of HE Episodes		Number of Hospitalizations for HE		Duration Between First HE Episode and Testing	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value	Correlation coefficient	*P* value
NCT-B	0.35	.047	0.35	.05	–	–
DST	-0.46	.009	0.46	.009	-0.36	.04
ICT Lures	-0.50	.002	-0.59	.0001	0.48	.007
ICT Targets	-0.43	.009	-0.44	.015	–	–

(range, 1–13) requiring at least 1 hospitalization (range, 1–7). Infection (n=18) was the predominant reason for the first hospitalization, followed by transjugular intrahepatic portosystemic shunt (TIPS; n=10), medication (n=7), and spontaneous reasons for the remaining patients.

All patients underwent a psychomotor test battery including number connection test (NCT) A+B, digit symbol test (DST), block design test (BDT), and ICT (lures and targets). Poor cognitive performance is indicated by high ICT lure and NCT scores and low DST, BDT, and ICT target scores. All patients had highly abnormal test scores after HE onset (Table 2). Worse psychometric performance was highly correlated with the number of HE episodes, the number of HE hospitalizations, and the duration between the first HE episode to testing (Table 3).

In patients with cirrhosis, deficits in working memory, psychomotor speed, attention and response inhibition worsen with the number and severity of overt HE episodes. The study investigators conclude that these deficits likely resulted from chronic neurologic injury due to the metabolic perturbations that led to HE that was slow to reverse.

161 THDP-17 Inhibits the Glutaminase Activity in Caco-2 Cell Cultures[5]

MM Diaz-Herrero, JA del Campo, P Carbonero, M Jover, J Vega Perez, F Iglesias Guerra, I Periñán, JD Bautista, M Romero Gómez

Hyperammonemia plays a key role in the pathogenesis of HE. Ammonia that reaches the brain is thought to be neurotoxic.[6] Two likely sources of ammonia production include: 1) the breakdown of urea by intestinal bacteria, and 2) glutaminase activity in gut enterocytes that is increased in patients with liver cirrhosis and correlates with minimal HE.[7] Thus, inhibition of glutaminase activity in gut enterocytes is a potential target for therapeutic intervention in patients with cirrhosis and HE. The study investigators have previously demonstrated in vitro inhibition of glutaminase activity by the compound THDP-17.[5] The aim of the current study was to assess the ability of THDP-17 to inhibit K-type glutaminase activity in colon carcinoma cell (Caco-2) cultures. Caco-2 cells were cultured using standard growth conditions at a density of 50,000 cells per well in 12-well plates. Culture medium contained 2 mM of L-glutamine. Glutaminase activity was assayed using a protocol previously described by Heini and colleagues.[8]

Following 48 hours of treatment with 100 mM THDP-17, 42% of the initial glutaminase activity in Caco-2 cells was inhibited.[5] This is in comparison with the 48% inhibition of Caco-2 cell glutaminase activity found after 48 hours of treatment with 100 mM 6-diazo-5-oxo-norleucina, a known inhibitor of glutaminase.

Given the inhibitory activity of THDP-17 in Caco-2 cells and its ability to cross cell and mitochondrial membranes, investigators found that THDP-17 offers a potential new therapeutic option for patients with hepatic encephalopathy.

185 Minimal Hepatic Encephalopathy (MHE): Simplified Diagnosis and Relationships with the Development of Overt Hepatic Encephalopathy (OHE)[9]

C Pasquale, L Ridola, I Pentassuglio, S Nardelli, M Trezza, C Marzano, O Riggio

Patients with liver cirrhosis can have cognitive deficits, or minimal HE, that may reduce their quality of life and ability to operate a motorized vehicle. Importantly,

patients with minimal HE are at a heightened risk for developing overt HE. In clinical practice, however, these patients are often overlooked, due to a lack of a simple and standardized technique to help identify patients with minimal HE. The Psychometric Hepatic Encephalopathy Score (PHES) is currently considered the gold standard for assessing minimal HE in patients with cirrhosis. The following 5 tests are included in the PHES, the DST, trail making test A and B, serial dotting test (SDT), and line tracing test (LTT). The goal of the current study was to simplify the PHES and determine if a correlation exists between PHES or simplified PHES (sPHES) and the development of HE.

Of the 79 patients (male, 62%; mean age, 60±13 years; Child-Pugh Classification A/B, 81%; Model for end-stage liver disease score, 14±6) with liver cirrhosis who were studied, 45 patients were diagnosed with minimal HE by PHES. Psychometric test outcomes were expressed as z-scores of an Italian population standardized for age and education. Backward logistic regression analysis was used to simplify PHES. This involved incorporating the z-scores of the 5 tests in PHES at the first step of the logistic regression and then eliminating variables in a stepwise fashion, such that removal did not impair the regression. This resulted in a simplified model that contained 3 tests: DST, SDT, and LTT. This simplified model was not significantly different than a model containing all 5 tests in its ability to identify patients with minimal HE. For both models, PHES and sPHES, the rate of patients correctly classified as having minimal HE was 94%.

In total, 20 patients developed overt HE during follow-up. The probability of developing overt HE was significantly higher in patients with minimal HE compared with those who did not have minimal HE (PHES, *P*=.012 and sPHES, *P*=.019). According to Cox's analysis, development of overt HE during follow-up was independently associated with Child-Pugh class, MELD score, the presence of large porto-systemic shunt and PHES (simplified, relative risk=3.17; *P*=.04; or not simplified, relative risk=3.75; *P*=.03).

In summary, the study authors found that a simplified psychometric measure including DST, SDT, and LTT was equally able to identify patients with minimal HE as the whole PHES, which also includes trail making test A and B. Both PHES and the simplified PHES correlated with development of overt HE and were found to be independent factors for the occurrence of overt HE. Given these results, further validation of the simplified PHES in an independent group of patients is warranted.

189 Mild Hepatic Encephalopathy (HE) Assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is Highly Prevalent in Ambulatory Patients with Cirrhosis

C Randolph, J Bajaj, MY Sheikh, R Vemuru, G Morelli, LA Balart, M Chojkier, MS Harris, JD Bornstein, K Mullen

While patients with mild (or minimal) HE typically have no outward symptoms of HE, they often have mild cognitive and psychomotor deficits that can reduce their quality of life and increase their risk for negative outcomes such as job loss and motor vehicle accidents. The prevalence of mild HE in patients with cirrhosis ranges from 30–84%.[10-15] The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommends that detection of mild HE be assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This recommendation is based on the finding that RBANS correlates with quality of life issues, including impaired daily functioning and job loss, and has well-established population norms. In this analysis, Randolph and colleagues used RBANS to qualify subjects for the ASTUTE trial, a phase 2b study designed to test the efficacy of AST-120 (spherical absorbent carbon) in the treatment of patients with mild HE.[16]

A total of 206 subjects who met the specified inclusion criteria (cirrhosis, age 18–70 years, MELD ≤25, no TIPS or surgical shunt, no overt HE within 3 months, no use of lactulose, rifaximin or neomycin within 7 days) were screened by RBANS for participation in the randomized trial. Screened patients were mostly male (61%) with a mean age of 55.4 years. Hepatitis C infection was the most common underlying liver disease. More than half (56%) of the patients screened scored below the 10th percentile on the RBANS total scale, after adjusting for age and education and were eligible for randomization in the ASTUTE trial. Qualifying RBANS scores were similar among education levels: 54% of college attendees, 57% of high school graduates, and 59% of high school dropouts qualified.

The results of this analysis indicate that mild HE is highly prevalent among patients with well-compensated cirrhosis and is not predicted by age, education, MELD score, or indicators of portal hypertension.

195 Rifaximin Decreases Venous Ammonia Concentrations and Time-Weighted Average Ammonia Concentrations Correlate with Overt Hepatic Encephalopathy (HE) as Assessed by Conn Score in a 6-Month Study[17]

A Sanyal, N Bass, F Poordad, MY Sheikh, K Mullen, S Sigal, T Frederick, R Brown Jr., B Bhandari, S Sedghi, K Merchant, S Huang, A Shaw, E Bortey, WP Forbes

Elevated blood ammonia concentrations play a key role in the pathogenesis of overt HE and are quantitatively associated with central nervous system effects. Thus, ammonia levels may be a useful marker for severity of overt HE. Treatments for HE, such as lactulose and probiotics, aim to lower intestinal ammonia production and absorption. In the multinational, double-blind, randomized phase III trial RFHE3001, rifaximin (n=140) reduced the risk of breakthrough overt HE over a 6-month period by 57.9% compared with placebo (n=159) in patients with cirrhosis (MELD ≤25) and a history of recurrent (≥2 HE episodes as indicated by a Conn score ≥2 within past 6 months), overt episodic HE.[2]

Two objectives were sought in this subanalysis of RFHE3001 presented by Sanyal and colleagues. First, the effect of rifaximin treatment on concentrations of venous ammonia was determined. Second, the correlation between venous ammonia concentrations and breakthrough HE was assessed by Conn score (scale 0–4, with more severe impairment indicated by a higher score) which is currently recommended by the Working Party on Hepatic Encephalopathy for the assessment of overt HE in clinical trials.[2,18,17] Venous ammonia concentrations were measured at baseline and during treatment on days 24, 84, and 168. Ammonia concentrations were expressed using TWA (area under the curve for ammonia concentrations over time normalized by exposure time).

Of the 299 patients randomized in RFHE3001, 104 patients (35%) experienced breakthrough HE defined as an increase in Conn score to 2 or greater or an increase in Conn score to 1 and an asterixis grade increase by 1 unit if the baseline Conn score was equal to 0.2. Overall, 194 patients remained in remission. Rifaximin treatment significantly decreased venous ammonia concentrations compared with placebo (-5.7 mg/dL vs -0.3 mg/dL, respectively; *P*=.0391). Patients with breakthrough HE had significantly higher venous ammonia concentrations (mean TWA, 102.4 mmol/L) compared with those patients who remained in remission (85.4 mmol/L; *P*=.0079). A significant and positive correlation was found between mean venous ammonia TWA and breakthrough HE (Spearman correlation coefficient of 0.22, *P*=.0005). The ability of venous ammonia concentrations to predict breakthrough HE was found to be good as determined by a Receiver Operating Characteristic curve analysis, 0.64 (95% CI, 0.57–0.72).

In conclusion, rifaximin was found to significantly decrease venous ammonia concentrations and protect against breakthrough episodes of overt HE. Given the ability of TWA of venous ammonia concentrations to independently predict breakthrough HE, the study investigators asserted that the Conn score is a reliable and clinically relevant measure of breakthrough HE episodes.

202 A Case Control Study of IMPACT: A Brief and Effective Web-Based Neuropsychological Assessment Battery to Diagnose Minimal Hepatic Encephalopathy (MHE)[19]

M Tsushima, W Tsushima, V Tsushima, N Lim, E Madrigal, C Jackson, M Mendler

Efforts are currently aimed to find a simplified psychometric performance test battery for the diagnosis of minimal HE in patients with cirrhosis. ImPACT (Immediate Post-concussion Assessment and Cognitive Testing) is a short, user-friendly, internet-based neuropsychological test battery that includes 6 modules resulting in 4 composite scores: verbal memory, visual memory, visual motor speed, and reaction time. In this case control study, the authors compared the ability of ImPACT with traditional testing (paper-and-pencil tests [PPT]), which included number connection A and B tests and DSTs to evaluate patients at risk for minimal HE versus a control cohort of healthy volunteers.

Included in this study were 90 patients (mean age, 54.3 years; male, 69%) with cirrhosis (MELD, 10.39±3.42) and no evidence of overt HE, and 131 age-, gender-, and education-matched controls that were free of liver disease and otherwise healthy. Patients and controls were compared on traditional PPT and the 4 ImPACT composite scores. Participants were excluded from the study if they were currently using treatments applicable to overt HE or sedatives, narcotics, or antidepressants. A positive PPT score was defined by a score 2 standard deviations below the normative mean on 1 or less PPT. A patient was determined to have a positive ImPACT score if their score was 2 standard deviations from the control mean.

Table 4. ImPACT Composite Scores in Patients vs Controls

	Patients	Controls	*P* value
Verbal memory	78.9	71.4	<.001
Visual motor speed	26.5	22.7	<.001
Reaction time	0.89	1.00	<.01

Table 5. ImPACT Composite Scores in Positive PPT vs Negative PPT Patients

	Positive PPT	Negative PPT	*P* value
Verbal memory	58.1	74.2	<.05
Visual motor speed	16.8	24.0	<.05
Reaction time	1.24	0.95	<.05

Among the 90 patients at risk for minimal HE, 16 had a positive PPT, and 25 had a positive ImPACT score. Compared with controls, patients had worse scores on 3 of 4 ImPACT composite scores (Table 4). Patients who had a positive PPT also performed worse on ImPACT compared with patients who had a negative PPT (P<.05; Table 5). PPT and ImPACT scores were significantly correlated. The ImPACT visual motor speed composite score had the highest correlation: number connection test A (r=-0.46), number connection test B (r=-0.54), and the DST (r=0.70).

Based on these data, the study authors concluded that ImPACT is a simple and effective tool for the evaluation of psychometric performance and offers a potentially new standard for diagnosing minimal HE.

513 Double-Blinded Crossover Trial Analyzing the Usefulness of Rifaximin in the Treatment of Minimal Hepatic Encephalopathy (MHE): An Interim Analysis[20,19]

L Grande, M Jover, M Fobelo, B Figueruela, MJ Jiménez, E Hoyas, I Camacho, A Pérez, M Maraver, R Aparcero, JA Del Campo, A Fernández-Palacín, C Almeia, E Suárez, M Romero-Gómez

Because rifaximin is minimally absorbed, it has been thought to be more conducive for long-term use compared with other antibiotics that are readily absorbed and associated with significant side effects.[2,19] In this double-blinded crossover trial conducted by Grande and colleagues in Spain, 17 patients with liver cirrhosis and minimal HE were randomized to receive rifaximin (1,200 mg/day, two 200-mg tablets given every 8 hours) or placebo for 4 weeks. After a 4-week washout period, patients who initially received rifaximin were given placebo, and those initially given placebo were given rifaximin, again for 4 weeks.

Results of the interim analysis of this study demonstrated that in the first phase of the study, rifaximin treatment significantly improved the area under the curve of glutamine oral challenge compared with placebo (-52.3±53 mg/mL/hr vs -5.62±10.56 mg/mL/hr, respectively; P=.045). No statistical difference was found in the glutamine oral challenge between treatment groups in the second phase of the study. However, the Psychometric Hepatic Encephalopathy Score (PHES) improved with rifaximin treatment in the second phase of the study compared with placebo (2±1.75 vs -1±1.15, respectively, P=.05).

At this time, rifaximin treatment appears superior to placebo in reducing intestinal ammonia production and improving PHES in patients with cirrhosis and minimal HE. Final results of this study are anticipated.

536 Saccadic Latency as an Objective and Quantitative Marker of Hepatic Encephalopathy[21]

M Schranz, F Krismer, J Roos, I Graziadel, S Mechtcheriakow, W Vogel, RH Carpenter, H Zoller

Neuropsychiatric impairment in patients with HE is highly variable and its clinical staging subjective. Thus, there is a need for a simple quantitative clinical marker for assessing HE severity. Impairment of smooth pursuit eye movements (SPEM, conjugate movements used to track the smooth trajectory of small dots) has been previously documented in patients with HE and found to correlate with severity of HE.[22] To date, eye movement response times, or saccadic latencies, which are under higher brain control than SPEM, have not been studied and may offer a more objective and quantitative marker of HE.

In the current study, Schranz and colleagues determined the association between saccadic latency and established tests for HE (porto-systemic encephalopathy test, critical flicker frequency, MELD score, and ammonia concentration) in patients with cirrhosis (n=71) and controls after liver transplantation (n=31).[21] Patients with cirrhosis had significantly longer saccadic latencies

compared with controls after liver transplantation (278 ms vs 244 ms, respectively; *P*<.001). Moreover, median saccadic latencies were prolonged for both groups compared with an age-matched control group (175 ms). Saccadic latency correlated with measures of established HE tests including porto-systemic encephalopathy test, critical flicker frequency, and MELD score. The prevalence of early saccades was also significantly correlated with partial pressure of ammonia. Saccadic latency did not correlate with blood urea and sodium concentration, indicating that this measure is not influenced by kidney function.

The study investigators contend that measure of saccadic latency in patients with cirrhosis represents an objective and quantitative marker for HE that can be easily and quickly administered by untrained hospital personnel.

810 Prior Hepatic Encephalopathy and Alcohol Etiology Determine Cognitive Function After Liver Transplantation[23]

R Garcia-Martinez, C Jacas, J Alonso, V Vargas, M Simon-Talero, J Cordoba

For some patients, cognitive function will improve, but may not normalize after liver transplantation. A number of factors can influence how well cognitive function improves, including prior HE and alcoholism. The objective of this prospective trial was to evaluate cognitive function in patients after liver transplant and determine how prior HE and alcoholism influence outcome.

Neuropsychologic tests were performed within 2 months prior to liver transplant in 63 consecutive patients. Liver transplant was successful in 52 patients (11 with prior HE only, 24 alcoholics, 13 with both conditions, and 4 with no HE or alcohol abuse), and these patients were reassessed for cognitive function 11 months after liver transplant. T-values were used to describe neuropsychologic measures. A T-value of 50 represents the mean in a normal, unimpaired, population. One standard deviation below the mean represents a T-value of 40, and 2 standard deviations below the mean gives a T-value of 30, and so on.

Prior to liver transplantation the majority of neuropsychologic function domains were impaired. Memory, attention, and motor function—the domains that characterize minimal HE—were predominantly affected. After liver transplant, global cognitive function improved (Figure 1), but did not return to normal for those patients with prior HE, cirrhosis due to alcohol use, or both.

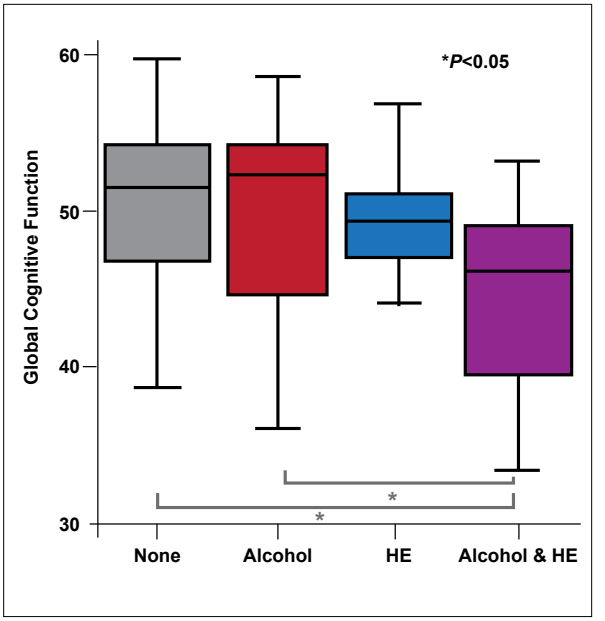

Figure 1. Global cognitive function.

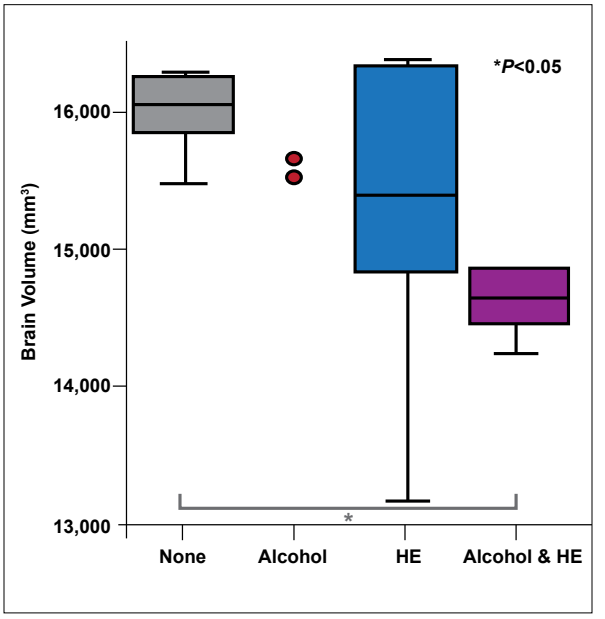

Figure 2. MRI measurement of brain volume.

Moreover, patients with both conditions exhibited brain atrophy according to magnetic resonance imaging (MRI) after liver transplant (Figure 2).

Improvement in cognitive function after liver transplantation depends on prior HE and alcohol use. The

investigators found that having both conditions appears to cause loss of brain tissue and irreversible brain damage. They suggested that optimal management of HE prior to liver transplant may help improve cognitive function after transplant. The results of this trial may also influence how patients are prioritized for liver transplant.

References

1. Sanyal A, Bass N, Mullen K, et al. Rifaximin treatment improved quality of life in patients with hepatic encephalopathy: results of a large, randomized, placebo-controlled trial. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 15.
2. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010; 362: 1071-1081.
3. Bajaj J, Heuman DM, Schubert C, et al. Persistent deficity in learning of response inhibition following onset of overt hepatic encephalopathy in cirrhosis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 149.
4. Bajaj J, Schubert C, Sanyal AJ, Bell D, Pisney L, Heuman DM. Severity of chronic cognitive impairment in cirrhosis increases with number of episodes of overt hepatic encephalopathy. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 150.
5. Diaz-Herrero MM, del Campo JA, Carbonero P, et al. THDP-17 inhibits the glutaminase activity in Caco-2 cell cultures. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 161.
6. Romero-Gomez M. Pharmacotherapy of hepatic encephalopathy in cirrhosis. *Expert Opin Pharmacother.* 2010; 11: 1317-1327.
7. Romero-Gomez M, Ramos-Guerrero R, Grande L, et al. Intestinal glutaminase activity is increased in liver cirrhosis and correlates with minimal hepatic encephalopathy. *J Hepatol.* 2004; 41: 49-54.
8. Heini HG, Gebhardt R, Brecht A, Mecke D. Purification and characterization of rat liver glutaminase. *Eur J Biochem.* 1987; 162: 541-546.
9. Pasquale C, Ridola L, Pentassuglio I, et al. Minimal hepatic encephalopathy (MHE): Simplified diagnosis and relationships with the development of overt hepatic encephalopathy (OHE). Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 185.
10. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J Gastroenterol Hepatol.* 2001; 16: 531-535.
11. Groeneweg M, Quero JC, De B, I, et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology.* 1998; 28: 45-49.
12. Hartmann IJ, Groeneweg M, Quero JC, et al. The prognostic significance of subclinical hepatic encephalopathy. *Am J Gastroenterol.* 2000; 95: 2029-2034.
13. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology.* 2002; 35: 357-366.
14. Quero JC, Schalm SW. Subclinical hepatic encephalopathy. *Semin Liver Dis.* 1996; 16: 321-328.
15. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol.* 2001; 96: 2718-2723.
16. Randolph C, Bajaj J, Sheikh MY, et al. Mild hepatic encephalopathy (HE) assessed by the Repeatable Battery for the Assessment Neuropscyological Status (RBANS) is highly prevalent in ambulatory patients with cirrhosis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 189.
17. Sanyal A, Bass N, Poordad F, et al. Rifaximin decreases venous ammonia concentrations and time-weighted average ammonia concentrations correlate with overt hepatic encephalopathy (HE) as assessed by Conn Score in a 6-months study. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 195.
18. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002; 35: 716-721.
19. Tsushima M, Tsushima W, Tsushima V, et al. A case control study of IMPACT: a brief and effective web-based neuropsychological assessment battery to diagnose minimal hepatic encephalopathy (MHE). Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 202.
20. Grande L, Jover M, Fobelo M, et al. Double-blind crossover trial analyzing the usefulness of rifaximin in the treatment of minimal hepatic encephalopathy (MHE): an interim analysis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 513.
21. Schranz M, Krismer F, Roos J, et al. Saccadic latency as an objective and quantitative marker of hepatic encephalopathy. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 536.
22. Montagnese S, Gordon HM, Jackson C, et al. Disruption of smooth pursuit eye movements in cirrhosis: relationship to hepatic encephalopathy and its treatment. *Hepatology.* 2005; 42: 772-781.
23. Garcia-Martinez R, Jacas C, Alonso J, Vargas V, Simon-Talero M, Cordoba J. Prior hepatic encephalopathy and alcohol etiology determine cognitive function after liver transplantation. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 810.

Commentary

Kevin D. Mullen, MD
Professor of Medicine
Case Western Reserve University
Director, Gastroenterology Fellowship Program
Department of Gastroenterology
MetroHealth Medical Center
Cleveland, OH

There has been quite a bit of activity in the area of diagnosis and treatment of hepatic encephalopathy (HE) in the last few years. The 2010 European Association for the Study of Liver (EASL) meeting in Vienna illustrated this point well. Many very interesting abstracts were submitted on the topic of HE. Before specifically commenting on the abstracts included in this summary, it is worth considering a number of issues to put the field of HE into perspective.

The first is the major imperative to develop test systems to detect minimal HE. The Psychometric Hepatic Encephalopathy Score (PHES) has been declared the gold standard for the diagnosis of minimal HE by the World Congress consensus working party. The complete lack of normative data in the United States and some copyright concerns largely prevented the use of the PHES system, except in a few countries. Multiple alternative psychometric testing systems are being evaluated and will be available in the coming years for what we are going to call "covert" rather than "minimal" HE. The name change is primarily needed because "minimal" HE sounds like something unimportant. Despite its subtle presence, we have growing evidence that this covert form of HE significantly reduces the quality of life (QOL) for cirrhotic patients. It was formerly thought that QOL reduction in cirrhosis was related directly to the effect of cirrhosis. Studies now clearly implicate HE as the cause of this reduction of QOL.

Turning our attention to the abstracts, the first one cited by Sanyal and colleagues,[1] of which I am also coauthor, provoked some interest in light of the comments made above. This is a follow-up paper on the effect of rifaximin on HE, which was presented at the EASL meeting in Copenhagen in 2009.[2] This presentation reiterated the data showing the reduction (58%) in recurrent bouts of overt HE in a large group of cirrhotic patients (n=299) at risk for recurrent bouts of HE. However, the new analysis describes the significant improvement in the disease-specific Chronic Liver Disease Questionnaire (CLDQ), designed for liver patients by Younossi, when treated with rifaximin. As data accumulate that QOL can be improved by specific HE treatments, there will be major pressure to treat HE at its earliest stages, since minimal/covert HE clearly reduces QOL.

Another issue that has worried hepatologist for years is whether single or multiple episodes of overt HE lead to permanent loss of discrete domains of brain function. Bajaj and colleagues have 2 abstracts that address this point.[3,4] The first raised the concept that response inhibition testing can also be a measure of learning because the testing system has 2 identical halves. This is a tricky point because multiple factors effect "learning," not the least of which is motivation to perform the test well in the first place. Nonetheless, the "normal" learning effect seemed to be absent after patients had bouts of overt HE. Likewise in the other abstracts where multiple defects in many domains of brain function were noted to increase with the number and severity of bouts of overt HE in patients. Before dismissing this idea, it is important to note that detailed neurologic evaluations are rarely done on patients emerging from bouts of overt HE. Literally, we have not documented recovery from overt HE very well. One major study on this topic suggested that neurologic signs were present in many cirrhotic patients recovering or recovered from a bout of HE. What has been observed is recovery from severe HE to either absent, minimal, or low-grade overt HE; none of this has been sought specifically. Regardless, the 2 provocative abstracts of Bajaj and colleagues raise the possibility that bouts of overt HE lead, in some patients, to a potentially progressive neurologic degeneration. The more florid hepatocerebral degeneration syndromes have largely been thought to be irreversible even after liver transplantation, but a few reports of recovery of function and even reversal of severe brain atrophy makes one wonder if brain injury due to chronic liver disease/overt HE is uniformly irreversible.

The abstract of Diaz-Herrero and colleagues comes from the Seville unit, which has studied intestinal glutaminase in great detail.[5] This enzyme system releases the majority of the ammonia found in the portal vein. It provides an energy source for intestinal mucosa cells, and the enzyme is upregulated after creation of a portosystem shunt. Neomycin is known to inhibit this enzyme, but its toxicity has reduced its use as a treatment for HE. It is worth noting that most of the activity of neomycin against HE is mediated by inhibitor of glutaminase rather than its antibacterial properties. This abstract describes

a new inhibitor of intestinal glutaminase. THDP-17 inhibited glutaminase enzyme activity in an in vitro cell system. This report may be followed by others on this new therapeutic approach to the treatment of HE.

The abstract of Pasquale and colleagues addresses the issue discussed earlier about developing minimal/covert HE.[6] It examined the accuracy of reduced content psychometric test profiles to diagnose minimal/covert HE. Instead of the full set of tests in the PHES system, they found that a combination of just the digit symbol, line tracing, and serial dotting test was as sensitive in diagnosing minimal HE as the more elaborate full PHES system.

Following in the same vein, Randolph and colleagues, including myself, looked at another battery of neuropsychologic status tests called Repeatable Battery for the Assessment of Neurological Status (RBANS).[7] Minimal or mild HE (a term not generally used these days) was found in more than half the patients using this well-known diagnostic tool. As mentioned, these different attempts to develop and validate tests for the detection of minimal HE are ongoing in multiple centers.

The second abstract of Sanyal and colleagues, of which I am again coauthor, basically showed that accurately measured venous ammonia levels predicted the likelihood of HE recurrence.[8] It is important to note that the ammonia tests were done at set points during study follow-up. Therefore, they are not being done after a bout of overt HE has occurred. Instead, higher levels indicated that HE reoccurrence in the coming time period is likely.

Tsushima and colleagues looked at yet another battery of tests to detect minimal/covert HE.[9] ImPACT (Immediate Post-concussion Assessment and Cognitive Testing) was used in 90 patients at risk for minimal HE and compared to a paper and pencil battery of tests (number connector A and B, and digital symbol test). The test system generates scores for verbal memory, visual motor speed, and reactor time. As noted above, in time, we will potentially reduce the number of tests for minimal HE based on cost, convenience, and sensitivity.

Grande and colleagues reported the effect of 4 weeks of rifaximin treatment (1,200 mg/daily) or placebo.[10] Psychometric tests improved in the patients randomized to receive rifaximin in the second 4-week period. More data in manuscript form would help in analyzing the significance of this study.

Schranz and colleagues reminded us that saccadic latency can be measured with relative ease in patients with HE and could be an objective measure of HE to employ in the future.[11] These are not saccadic ocular pursuits, but more a measure of eye movement response times.

Finally, Garcia-Martinez and colleagues reminded us that brain atrophy is more prominent in patients with cirrhosis of an alcoholic etiology.[12] More specifically, this important study found a lack of full psychometric function return after liver transplant in these patients. The authors propose that more aggressive and early treatment of HE in patients with alcoholic cirrhosis may improve cognitive function in these patients after liver transplantation.

References

1. Sanyal A, Bass N, Mullen K, et al. Rifaximin treatment improved quality of life in patients with hepatic encephalopathy: results of a large, randomized, placebo-controlled trial. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 15.
2. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; 362: 1071-1081.
3. Bajaj J, Heuman DM, Schubert C, et al. Persistent deficity in learning of response inhibition following onset of overt hepatic encephalopathy in cirrhosis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 149.
4. Bajaj J, Schubert C, Sanyal AJ, Bell D, Pisney L, Heuman DM. Severity of chronic cognitive impairment in cirrhosis increases with number of episodes of overt hepatic encephalopathy. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 150.
5. Diaz-Herrero MM, del Campo JA, Carbonero P, et al. THDP-17 inhibits the glutaminase activity in Caco-2 cell cultures. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 161.
6. Pasquale C, Ridola L, Pentassuglio I, et al. Minimal hepatic encephalopathy (MHE): Simplified diagnosis and relationships with the development of overt hepatic encephalopathy (OHE). Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 185.
7. Randolph C, Bajaj J, Sheikh MY, et al. Mild hepatic encephalopathy (HE) assessed by the Repeatable Battery for the Assessment Neuropscyological Status (RBANS) is highly prevalent in ambulatory patients with cirrhosis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 189.
8. Sanyal A, Bass N, Poordad F, et al. Rifaximin decreases venous ammonia concentrations and time-weighted average ammonia concentrations correlate with overt hepatic encephalopathy (HE) as assessed by Conn Score in a 6-months study. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 195.
9. Tsushima M, Tsushima W, Tsushima V, et al. A case control study of IMPACT: a brief and effective web-based neuropsychological assessment battery to diagnose minimal hepatic encephalopathy (MHE). Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 202.
10. Grande L, Jover M, Fobelo M, et al. Double-blind crossover trial analyzing the usefulness of rifaximin in the treatment of minimal hepatic encephalopathy (MHE): an interim analysis. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 513.
11. Schranz M, Krismer F, Roos J, et al. Saccadic latency as an objective and quantitative marker of hepatic encephalopathy. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 536.
12. Garcia-Martinez R, Jacas C, Alonso J, Vargas V, Simon-Talero M, Cordoba J. Prior hepatic encephalopathy and alcohol etiology determine cognitive function after liver transplantation. Program and abstracts of the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria 2010; Abstract 810.

Notes


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