Original Article

The Psychometric Hepatic Encephalopathy Syndrome score does not correlate with blood ammonia, endotoxins or markers of inflammation in patients with cirrhosis

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Background: The pathogenesis of hepatic encephalopathy (HE) remains unclear but impaired clearance of gut-derived neurotoxins and increased systemic inflammation are thought to play key roles. The diagnosis is based on detection of neurophysiological and neuropsychometric abnormalities. The Psychometric Hepatic Encephalopathy Score (PHES) have been found to correlate with markers of systematic inflammation including interleukin 6, C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α). This study explores the associations between the PHES score and systemic inflammation, endotoxins and disease severity using baseline data from a trial involving patients with cirrhosis and minimal or no HE (NCT01769040).

Methods: Arterial blood was obtained during hepatic vein catheterization, from 54 patients [median age 55 (range, 33–70) years; 83% men] with decompensated but stable cirrhosis. None had clinical evidence of HE but 34 (55.6%) had an abnormal PHES score indicating the presence of minimal HE. Relationships were sought between the PHES score and markers of systemic inflammation, high sensitivity-CRP, cytokines (SDF-1α, TGF-b1, IP-10, IL-6, 10 and 18, and TNF-α; lipopolysaccharide (LPS), the lipopolysaccharide binding protein (LBP) and soluble CD14 (sCD14); and the blood ammonia.

Results: No significant relationships were found between the PHES score and any of the variables tested with the single exception of the correlation with serum IL-6 (r=–0.29, 95% confidence interval, –0.53 to –0.02, P=0.031). No independent predictors of the PHES score were identified in regression analyses.

Conclusions: No predictive associations were identified between the PHES scores and circulating blood ammonia, endotoxins, or markers of systemic inflammation in this patient population.

Keywords: Cirrhosis; hepatic encephalopathy (HE); lipopolysaccharide binding protein (LBP); psychometry; portal hypertension; systemic inflammation

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Introduction

Hepatic encephalopathy (HE) is a common complication of cirrhosis; its presence significantly affects outcome. Patients with cirrhosis and HE have a one-year mortality of more than 60% (1). The severity of HE varies from only a few psychometric abnormalities to severe cognitive dysfunction and coma. Minimal hepatic encephalopathy (MHE) is a neuropsychiatric condition in patients with cirrhosis who

have no clinical features of HE but still have an impaired response to psychometric testing (2). People with cirrhosis and MHE have impaired sleep quality and a decreased quality of life (3,4).

The presence of MHE can be detected using a range of neuro-psychometric and neurophysiological tools. The latter has been thoroughly testes and validated in numerous countries (5-8). Several precipitating factors of HE have been identified, in particular infection and dehydration (9). The pathogenesis of HE remains unclear, but impaired clearance of gut-derived neurotoxins such as ammonia may both facilitate and prolong episodes (10). Activation of systemic inflammatory responses may also play a role in enhancing the effects of ammonia and may also induce neuroinflammation, facilitating the development of HE in cirrhosis (11,12). Several markers of inflammation have been demonstrated to be elevated in patients with MHE (13).

The degree of neuropsychiatric abnormality in HE varies considerably between different tests and between timepoints of assessment, even with comparable levels of impairment. Lipo-polysaccharides, interleukin-6 (IL-6), high-sensitive C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) have in some studies shown to be independent predictors of an abnormal Psychometric Hepatic Encephalopathy Score (PHES) (14), and to correlate with circulating ammonia levels, the PHES score or even health related quality of life (15-17). However, studies are characterized by small cohort sizes and are mostly unconfirmed.

The aim of this study was to explore the associations between presence of MHE defined by the absence of clinical features of HE and an abnormal PHES score and arterial blood ammonia concentrations, markers of systemic inflammation and endotoxemia and standard measures of disease severity.

Methods

This study used baseline data from a randomized clinical trial undertaken in patients with decompensated cirrhosis but without clinical evidence of HE (NCT01769040) enrolled between February 2013 and December 2015 at Amager-Hvidovre University Hospital (18). The randomized clinical trial was approved by the Danish Medicines Agency (EudraCT No. 2012-002890-71) and by the Scientific Ethics Committee of the Capital Region of Denmark (journal No. H-2012-078). All participants gave informed written consent to participation in the trial. The present cross-sectional study involved 54 participants [median age 55 (range, 33–70) years; 83% men; 79% alcohol-related cirrhosis, mean MELD score 11 (range, 6–25)]. Inclusion criteria were diagnosis of cirrhosis verified by clinical, biochemical, and ultrasound findings; clinical or ultrasound-verified ascites within the last three months; age 18 to 80 years; and portal hypertension with a hepatic venous pressure gradient ≥10 mmHg. Exclusion criteria were cardiac or respiratory failure, invasive cancer within the past five years, clinical or biochemical signs of infection, antibiotic treatment 14 days prior to inclusion, overt HE, kidney failure with serum creatinine above 200 µmol/L, transfusion-requiring bleeding within one week prior to inclusion, blood hemoglobin level below 5.5 mmol/L, continuous abuse of alcohol with symptoms of withdrawal; or expected survival of less than 3 months, as previously described (18,19).

Ten participants had a history of one or more episodes of overt HE. All were clinically stable at the time of inclusion; none was actively misusing alcohol nor had done so for a minimum of 3 months; none took illicit drugs nor were prescribed psychoactive medication; 11 were receiving treatment with lactulose 15–60 mL daily, of which 9 had had previous episodes of overt HE. Two were prescribed lactulose 15–30 mL daily due to constipation.

Mental status was examined at baseline, using West Haven criteria (5); psychometric performance was assessed using the PHES test (8) using a cut off-of <–4 to define abnormality. Treatment of HE was instituted if indicated. An investigational program including systemic haemodynamic assessment was performed on the same day. Twenty-five mL of blood was drawn from the femoral artery during hepatic venous catheterization, immediately placed on ice, and samples of whole blood and EDTA plasma were stored at –80 °C until analysed. All investigations were performed by trained physicians.

Analyses of inflammation markers

High sensitivity-CRP (hs-CRP), stromal cell-derived factor 1 alpha (SDF-1α), transforming growth factor beta 1 (TGF-β1), interferon gamma induced protein 10 (IP-10), interleukins 10 and 18 (IL-10 and IL-18) were analysed with a commercially available enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle (Quantikine,

R&D Systems Europe, Ltd. Abingdon OX14 3NB, UK). Sensitivity and the variation coefficient were reported previously (19).

The cytokines IL-6, TNF-α, IL-1β, IL-4, IL-10 and IL-18 were analysed in bulk with a high sensitive Luminex assay (Magnetic Luminex Performance, R&D Systems Europe, Ltd., Abingdon OX14 3NB, UK). Less than 0.5% cross-reactivity and interference between agents tested is seen. Sensitivity and variation coefficient have been reported previously (19,20).

Measurement of endotoxin markers

Lipopolysaccharide (LPS), lipopolysaccharide binding protein (LBP) and the functional receptor for LPS, soluble CD14 (sCD14), were measured in EDTA plasma. LPS levels were determined using the Limulus Amoebocyte Lysate kinetic chromogenic methodology, optimized for sensitivity (Vaiomer SAS, Toulouse, France) with a commercially available kit (Charles River) (21,22). The quantifiable limit for LPS was 0.024 EU/mL. LBP and sCD14 levels were determined using a commercially available solid-phase ELISA based on the sandwich principle. The quantifiable limits for LBP and sCD14 were 3.5 and 0.13 µg/mL, respectively.

Statistical analysis

Patient characteristics in the two groups divided by PHES score (below –4 and –4 or higher) were compared using the Mann Whitney U-test. Correlations between the numerical PHES scores and blood markers were performed using Spearman Rank test. Logistic regression analysis based on dichotomous division of the PHES score at the <–4 threshold were undertaken to determine predictors of the PHES score (as defined by German normative data, since no Danish normative data are available (8), and multivariate analysis with backwards elimination were performed to determine if any factor independently predicts an abnormal PHES score. Analyses were performed using Graph Pad Prism version 7.0 and SAS version 9.4. P-levels of 0.05 or less were considered significant. To avoid multicollinearity, albumin, coagulation factors and bilirubin levels were not included in the logistic regression.

Results

Data on effects and outcomes of the clinical trial is reported elsewhere (18,19). The median PHES score at inclusion was –6 (–15 to 3). Overall 34 patients (63%), had an a PHES score below –4. Patient characteristics in the two groups (PHES score ≥–4 or <–4) are presented in *Table 1*. The ten patients who had a previous history of one or more episodes of overt HE were more likely to have an abnormal PHES score than those who had not (*Table 1*). Otherwise there were no significant differences in clinical, demographic or standard biochemical variables, between the two groups.

No significant correlations were observed between blood ammonia, markers of systemic inflammation and of bacterial translocation and the PHES score, with the single exception of the correlation with serum IL-6 [r=–0.2937, 95% confidence interval (CI), –0.5264 to –0.0201, P=0.0311] (*Table 2*). Logistic regression analysis of single parameters did not reveal an association to abnormal PHES, *Table 3*.

Multivariate analysis with backward elimination of the inflammation markers IP-10, TGF-1β, IL-6, SDF-1α, IL-18, IL-10, hs-CRP, IL-1β and TNF-α, endotoxemia markers LBP and LPS, as well as markers for disease severity (Meld score, Child score, creatinine, glomerular filtration rate (estimated by chrome EDTA clearance), arterial ammonium, white blood cell counts, and sodium levels) left no parameters with significant values as prognostic indicators of an abnormal PHES score.

Discussion

In this cohort of patients with decompensated but stable cirrhosis approximately two-thirds had an abnormal PHES score. Patients with a history of previous episodes of HE were more likely to have an abnormal PHES score. We found a weak association between PHES score and IL-6, but no further evidence to suggest an association between other markers of inflammation, arterial ammonia or disease severity such as MELD and Child score to an abnormal PHES. Accordingly, this study did not find convincing evidence that PHES is associated with ammonia, inflammation or endotoxins. The small sample size and the relatively small number of patients could be important to the interpretation of the results and our findings should be assessed in larger studies.

The PHES score is a validated tool for diagnosing MHE and has been shown to predict development of overt HE in patients with cirrhosis (23). Associations between an abnormal PHES score and biological markers have also been examined, with the aim to find pathogenetic factors that facilitate HE and to find new targets for treatment of

Table 1 Characteristics in the included trial participants with cirrhosis, by PHES score

Characteristics	PHES ≥−4 (n=20)	PHES <−4 (n=34)	Significance (P)
Age (yr)	56 [34–74]	55.5 [33–68]	0.9
Proportion of men	16 (80%)	29 (85%)	NA
Previous hepatic encephalopathy	1 (5%)	9 (26%)	0.02
PHES score	−1.5 (−4 to 3)	−8 (−15 to −5)	NA
Child-Pugh score	7.5 [7–10]	8 [7–12]	0.85
MELD score	10.5 [6–17]	11 [6–25]	0.57
Plasma albumin (g/L)	30.5 [23–40]	29.5 [21–43]	0.5
Sodium (mmol/L)	136 [141–132]	135 [127–149]	0.07
Bilirubin (μmol/L)	18.5 [9–82]	21 [5–166]	0.24
Arterial ammonia (μmol/L)	46 [20–88]	53.5 [19–94]	0.31
WBC (10^9/L)	6.0 (3.5–10.8)	6.7 (2.6–16.9)	0.70
TNF-α (pg/mL)	8.6 (2.4–22.5)	8.9 (3.6–35.8)	0.36
IL1β (pg/mL)	0.18 (0.02–1.16)	0.11 (0.01–0.61)	0.51
Hs-CRP (ng/mL)	4,426 [837–25,829]	6,751 [138–38,779]	0.26
IL-10 (pg/mL)	0.38 (0.07–1.09)	0.17 (0.01–2.71)	0.16
IL-18 (pg/mL)	334.2 (132.4–3,080.4)	267.3 (92.5–2,939.0)	0.55
SDF-1α (pg/mL)	3,736 [2,231–6,137]	3,698 [2,753–5,273]	0.60
IL-6 (pg/mL)	2.68 (0.27–25.96)	6.16 (0.60–201.38)	0.08
TGF-1β (pg/mL)	10,249 (4,241–55,776)	7,627 (2,598–37,529)	0.08
IP-10 (pg/mL)	249.8 (140.8–407.3)	231.3 (81.4–1,166.3)	0.45
LPS (EU/mL)	0.09 (0.02–0.20)	0.09 (0.02–0.18)	0.49
LBP (μg/mL)	6.7 (3.4–16.1)	7.2 (3.4–24.8)	0.38

Data are expressed as median and range, unless otherwise stated. PHES, Portosystemic Hepatic Encephalopathy Score; MELD, Model for End Stage Liver Disease; WBC, white blood cells; LPS, lipo-polysaccharide; LBP, lipo-polysaccharide binding protein; EU, endotoxin unit; hs-CRP, high-sensitive C-reactive protein.

HE (13,14,24,25). In a cohort of eighty patients with MHE relations between heart rate variability, PHES score and inflammation markers, IL-6 significantly correlated with heart rate variability and neuropsychiatric performance (24). In a prospective trial with 22 months of follow-up, PHES score correlated with both IL-6, TNF-α and CRP; moreover, IL-6 was associated with an abnormal electro encephalogram (14). A small pilot study has even shown that inflammation markers may exacerbate the neurocognitive effects of ammonia in HE (26). However, in a large cohort, levels inflammation markers were higher in patients with MHE, but presence of MHE was independent of ammonia concentration and severity of cirrhosis. This raises the question of clinical relevance of inflammation markers and their validity as prognostic predictors. Older trials with small samples have indicated that TNF-α is involved in the pathogenesis of HE and MHE (16,27,28). Recently a randomized trial on lactulose plus albumin versus lactulose alone for 120 people with overt HE found a greater decrease of TNF-α, IL-6 and IL-18 in the lactulose plus albumin treatment group (29). However, in another recent randomized trial including patients with cirrhosis and MHE or no cognitive impairment, no such effect was demonstrated (19). Further research into the pathogenesis

Table 2 Relationship between the PHES score and markers of inflammation and disease severity in patients with cirrhosis

Variable	Correlation coefficient (r)	95% CI	Significance (P)	Pairs (n)
WBC (10^9/L)	–0.0243	–0.30 to 0.25	0.86	54
TNF-α (pg/mL)	–0.02	–0.29 to 0.26	0.91	54
IL-10 (pg/mL)	0.21	–0.12 to 0.51	0.2	38[A]
IL-6 (pg/mL)	–0.29	–0.53 to –0.02	0.03	54
Hs-CRP (ng/mL)	–0.17	–0.43 to 0.11	0.22	54
TGF-β1 (pg/mL)	0.19	–0.09 to 0.44	0.17	54
IP-10 (pg/mL)	0.03	–0.25 to 0.30	0.83	54
SDF-1α (pg/mL)	0.01	–0.26 to 0.29	0.92	54
IL-18 (pg/mL)	0.05	–0.23 to 0.32	0.73	54
IL-1β (pg/mL)	0.05	–0.23 to 0.32	0.74	53[B]
Ammonium (μmol/L)	–0.16	–0.43 to 0.13	0.26	51
MELD	–0.16	–0.49 to 0.12	0.24	54
Child	–0.28	–0.52 to –0.01	0.04	54
Albumin (g/L)	0.1523	–0.1283 to 0.4104	0.27	54

[A], IL-10 were below detection level in 16 patients. [B], IL-1β were below detection level in 3 patients. PHES, Portosystemic Hepatic Encephalopathy Score; MELD, Model for End Stage Liver Disease; WBC, white blood cells; hs-CRP, high-sensitive C-reactive protein.

Table 3 Variables associated with abnormal PHES score (<–4) by logistic regression

Variable	Hazard ratio	95% CI	Significance (P)	SE
Child score	0.74	0.47 to 1.17	0.19	0.173
MELD score	0.99	0.87 to 1.13	0.89	0.065
Albumin (g/L)	1.07	0.96 to 1.19	0.22	0.058
Ammonia (μmol/L)	0.99	0.97 to 1.023	0.75	0.092
WBC (10^9/L)	1.02	0.86 to 1.22	0.83	0.092
TNF-α (pg/mL)	1.05	0.97 to 1.15	0.21	0.044
IL-1β (pg/mL)	6.71	0.58 to 77.27	0.13	8.366
Hs-CRP (ng/mL)	1.00	0.99 to 1.00	0.98	<0.001
IL-10 (pg/mL)	1.40	0.57 to 3.42	0.46	0.639
IL-18 (pg/mL)	1.00	0.99 to 1.001	0.27	<0.001
SDF-1α (pg/mL)	1.00	0.99 to 1.001	0.23	<0.001
IL-6 (pg/mL)	1.00	0.99 to 1.02	0.93	<0.007
TGF-1β (pg/mL)	1.00	0.99 to 1.00	0.07	<0.001
IP-10 (pg/mL)	1.00	0.99 to 1.00	0.83	0.001
LBP (μg/mL)	1.00	0.89 to 1.13	0.98	0.061
LPS (EU/mL)	5,362.249	0.06 to 4.83×10^8	0.14	31,213.04

CI, confidence interval; SE, standard error; PHES, Portosystemic Hepatic Encephalopathy Score; MELD, Model for End Stage Liver Disease; WBC, white blood cells; LPS, lipo-polysaccharide; LBP, lipo-polysaccharide binding protein; EU, endotoxin unit; hs-CRP, high-sensitive C-reactive protein.

of both MHE and HE and their interaction is warranted. Also, novel biological markers, specifically useful for diagnosing MHE and scaling severity of HE, have not been identified. This is in agreement with the present study, which was unable to demonstrate an association between inflammatory cytokines to an abnormal PHES or overall disease severity.

In animal models, the anti-inflammatory drug ibuprofen has proven beneficial in MHE (30,31). In humans, several treatment options for HE and MHE have been explored, with focus on reducing ammonia such as rifaximin, non-absorbable disaccharides and branched chain amino acids (32-34), all drugs with a beneficial effect on preventing recurrent episodes HE and non-absorbable disaccharides being a corner-stone in the treatment of overt HE. Further trials with clinically relevant outcomes evaluating drugs for prevention and treatment of MHE are highly warranted. Other agents focusing on changing gut microbiota in order to prevent bacterial translocation and reduce ammonia scavengers have also been explored, especially various probiotics have been shown to reverse MHE and to prevent development of overt HE (35,36). Probiotics have few side effects, but evidence supporting their efficacy on mortality and quality of life is still scarce as well as dose and duration of treatment required needs further investigation (37). L-ornithine, L-aspartate is likewise beneficial in prevention of recurrent HE, but at present insufficiently assessed for MHE (38). Clinical studies investigating the effects of anti-inflammatory drugs in both MHE and HE in both the acute situation and as long-term prophylaxis are in demand, but NSAIDS remains contra indicated in cirrhotic patients with an increased risk of gastro intestinal bleeding. In the present study, we also looked for relations between abnormal PHES and clinical measures of disease severity. Apart from our finding that more patients with abnormal PHES had experienced a previous episode of HE, we found no evidence to support the assumption that an abnormal PHES score is related to a more advanced liver disease. MHE has not been shown to be related to an increased mortality, while overt HE predicts a poorer outcome for patients (39). However, MHE is associated with a decreased quality of life and a high burden of health care (3,40). New knowledge into the impact of MHE on health care resources, and risk of hospital admission during long-term follow-up should be the focus in future research.

Data for the present study was uniformly and consecutively collected according to study protocol in a real-time setting. However, the cohort was highly selected due to eligibility criteria for a randomized trial of portal hypertension and bacterial translocation, and presence or absence of MHE was not part of in- or exclusion criteria. MHE is a dynamic entity, and assessment in clinical practice is challenged by various testing modalities, diagnostic heterogeneity and inter test variability. Absence of options for treatment, as well as lack of clinical application of guidelines for diagnosis in practice also challenge the day to day management of this patient group (6,41-44). Future clinical practice should focus on accurate testing and concise diagnosis as well as motivation to test available treatment options in a structured manner is in high need. Moreover, efforts should be made to prevent episodes of overt HE, and to improve the quality of life in MHE patients. Advancing self-support should also be a future focus point in research and clinic.

When exploring the pathogenesis of HE and MHE, long term studies with an epidemiological approach including patients from the time of diagnosis are preferable as this would provide new knowledge into aetiology and precipitating factors of MHE and HE. A deeper insight into mechanisms facilitating and driving neurocognitive impairment in cirrhosis may allow for new advances in treatment and care.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The randomized clinical trial was approved by the Danish Medicines Agency (EudraCT No. 2012-002890-71) and by the Scientific Ethics Committee of the Capital Region of Denmark (journal No. H-2012-078). All participants gave informed written consent to participation in the trial.

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