Research Article

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Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy

Ankur Gupta[2], Radha K Dhiman[1,*], Savita Kumari[2], Satyavati Rana[3], Ritesh Agarwal[4], Ajay Duseja[1], Yogesh Chawla[1]

[1]*Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India;* [2]*Department of Internal Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India;* [3]*Department of Gastroenterology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India;* [4]*Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India*

Background & Aims: Minimal hepatic encephalopathy (MHE) is the mildest form in the spectrum of hepatic encephalopathy. This cross-sectional study was carried out to elucidate the role of bacterial overgrowth of the small intestine and delayed intestinal transit among patients with MHE.

Methods: Two-hundred-thirty patients with cirrhosis were screened; 102 patients (44.4%) who met the eligibility criteria were included in the study. MHE was diagnosed when the psychometric hepatic encephalopathy score was $\leqslant -5$. All patients underwent a glucose breath test for small intestinal bacterial overgrowth (SIBO) and lactulose breath test for oro-cecal transit time (OCTT).

Results: Fifty-seven (55.9%) patients with cirrhosis had MHE. Among these patients with MHE, 22 (38.6%) had SIBO, while 4 (8.9%) without MHE had SIBO ($p = 0.001$). The prevalence of SIBO was higher in patients with CTP classes B and C (69.2%) compared to those in CTP class A (30.8%); $p = 0.054$. OCTT was significantly prolonged in patients who had SIBO than in those who did not have SIBO ($p < 0.0001$). Univariate analysis demonstrated that increased age, female gender, low educational status, low albumin, presence of SIBO, and prolonged OCTT were associated with the presence of MHE. Multivariate analysis demonstrated SIBO as the only factor associated with MHE.

Conclusions: Our study conclusively demonstrates high prevalence of SIBO in patients with cirrhosis with MHE. This study gives the rationale of treatment directed against SIBO and gut dysmotility, which may include non-absorbable antibiotics such as rifaximin, probiotics, and prokinetics.

Keywords: Minimal hepatic encephalopathy; Small intestinal bacterial overgrowth; Hepatic encephalopathy; Probiotics.

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* Corresponding author. Tel.: +91 172 2724450; fax: +91 172 2744401.

E-mail address: rkpsdhiman@hotmail.com (R.K Dhiman).

Abbreviations: CTP, Child-Turcotte-Pugh; FCT, figure connection test; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; NCT, number connection test; OCTT, oro-cecal transit time; P-HES, psychometric hepatic encephalopathy score; SIBO, small intestinal bacterial overgrowth.

Introduction

Minimal hepatic encephalopathy (MHE) is the mildest form of a portion of the spectrum of hepatic encephalopathy (HE) [1]. Patients with MHE have no recognizable clinical symptoms of HE but have mild cognitive and psychomotor deficits, which impairs health-related quality of life [2]. MHE also has prognostic significance and predicts the development of overt HE [3,4].

The pathogenesis of MHE is believed to be similar to that of overt HE and ammonia, derived primarily from enteric bacterial flora, which plays a key role [5,6]. Cirrhotic patients have substantial derangements in the gut microecology [7,8], which has been attributed, at least in part, to a decrease in small intestinal motility [7–12]. Gut flora also contribute to the pro-inflammatory state of cirrhosis even in the absence of overt infection [13]. Orthotopic liver transplantation has been shown to improve small bowel motility disorders in cirrhotic patients [14]. Modulation of gut flora may be an option for treating cirrhotic patients with MHE [2,15–17].

SIBO and intestinal dysmotility have not been studied in cirrhotic patients with MHE to date. We hypothesized that SIBO might be associated with the presence of MHE among patients with cirrhosis of liver; we tested this hypothesis by comparing the presence of SIBO in cirrhotic patients with and without MHE and correlated it with oro-cecal transit time (OCTT). We believe that this information would help modulate gut flora with interventions such as pre- or probiotic supplementation, and antibiotic or prokinetic therapy in prevention or treatment of the development of MHE in cirrhotic patients.

Patients and methods

The Ethics Committee of the Postgraduate Institute of Medical Education and Research (PGIMER), a tertiary level health care center in Chandigarh, India, approved the study. Each subject gave a written informed consent before inclusion in the study. The guidelines were laid down by the Indian Council of Medical Research (1994) and the Helsinki declarations (modified 1989) were adhered to in all patients in the study. A cross-sectional study was utilized.

Patient selection

Two-hundred and thirty patients with cirrhosis of the liver without evidence of overt HE who attended the outpatient Liver Clinic of the Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, were candidates for enrollment; 102 patients were included in the study and 128 patients were excluded as they fulfilled either one or more of exclusion criteria (Table 1). The diagnosis of cirrhosis of the liver was based on clinical, biochemical, and ultrasonographical, and/or liver histological data.

Etiology work-up of cirrhosis including alcohol, chronic hepatitis B and C, autoimmune, primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic steatohepatitis, and cryptogenic was performed as described in our previous study [2].

Exclusion criteria

Exclusion criteria included: Overt HE or a history of overt HE; history of recent (<3 months) alcohol intake; recent (<6 weeks) infection or antibiotic use; gastrointestinal bleeding; history of recent (<6 weeks) use of drugs such as benzodiazepines, antiepileptics, and psychotropics affecting psychometric performance; history of shunt surgery or transjugular intrahepatic porto-systemic shunt; electrolyte imbalance; renal impairment; presence of hepatocellular carcinoma; severe medical problems such as congestive heart failure, pulmonary disease, neurological and psychiatric disorders that could influence performance of neuropsychological tests.

Clinical and laboratory assessments

Clinical assessment included a thorough general physical and systemic examination, including a complete neurological and mental state examination using mini mental state examination to exclude the presence of any illness, which could cause or affect the neurological status. West Haven criteria for grading the mental state in patients with cirrhosis were used to differentiate between grade 0 and grade 1 HE [1]. In addition, special emphasis was given to the absence of disorientation, dysarthria, flapping tremors, increased tone, ataxia, and increased tendon reflexes [2].

Laboratory investigations included a complete hemogram, serum electrolytes, renal and liver function tests, and complete coagulogram. An upper gastrointestinal endoscopy was performed in all patients for the presence of esophageal varices, and the severity of liver disease was determined by CTP class and model for end-stage liver disease (MELD) scores.

Neuropsychological assessment

Psychometric hepatic encephalopathy score (PHES)

PHES has been validated in German [18], Spanish [19], and Indian [20] populations and can be performed in 15–20 min. PHES contains 6 tests: number connection test (NCT)-A, NCT-B, serial dotting test, digit symbol test, and the line tracing test for time (t) and for error (e). In the Indian version we replaced NCT-B with the figure connection test (FCT-A) because of concerns that some of our patients were not familiar with English alphabets and could not perform NCT-B. In principle, the FCT is similar to the NCT, except that numbers are replaced by figures (motifs) [21]. FCT is a universally applicable test to assess mental state, which transcends the barriers of linguistic differences and illiteracy. The clinical significance of these tests has been evaluated in a large number of healthy volunteers and patients with MHE [21].

Diagnosis of MHE

In Indian patients PHES $\leqslant -5$ was considered abnormal and was diagnostic of MHE [20].

Glucose hydrogen breath test (GHBT)

SIBO was diagnosed by measuring the early appearance of hydrogen following the administration of a challenge-dose of glucose [22]. The subject was asked to avoid carbohydrates that are slowly absorbed (bread, potato, and corn) and fiber for 3 days prior to the test evening to avoid delayed excretion of hydrogen in the breath [23]. None of the subjects had cigarette smoking or physical exercise for 2 h before and during the test, which might cause hyperventilation and consequent changes in breath hydrogen content [24]. Patients rinsed their mouths with 20 ml chlorhexidine 0.05%. Following a 12-h fast, a basal sample of end expiratory breath was collected before the test meal. The test consisted of the administration of a 75-g dose of glucose dissolved in water. Breath samples were measured for H_2 every 15 min for at least a 2-h period of time (SC Microlyzer, Quintron Instrument, Milwaukee, WI, USA). If bacteria existed in the small intestine, they would have competed with the natural digestive process and fermented the glucose before it could be absorbed. Results were expressed as parts per million; an increase of at least 12 ppm above the baseline value within the 2 h period was considered indicative of SIBO.

Table 1. Clinical and demographic characteristics of patients.

Parameter	Patients screened (n=230)	Patients enrolled (n=102)	MHE* (n=57)	NMHE* (n=45)
Male:female	186:44	84:18	43:14	41:4
Mean age in years, (95% CI)	49.56 (16-85)	47.91 (16-80)	50.28 (20-80)	44.91 (16-72)
CTP A	79, (34.3%)	48, (47.1%)	23, (40.4%)	25, (55.6%)
CTP B	106, (46.1%)	42, (41.2%)	27, (47.4%)	15, (33.3%)
CTP C	45, (19.6%)	12, (11.8%)	7, (12.3%)	5, (11.1%)
Varices Yes	173, (83.57%)	88, (86.27%)	50, (87.7%)	38, (84.4%)
No	34, (16.43%)	14, (13.73%)	7, (12.3%)	7, (15.6%)
Etiology Alcohol	110, (47.83%)	35, (34.31%)	21, (36.8%)	14, (31.1%)
HBV	27, (11.74%)	21,(20.59%)	11, (19.3%)	10, (22.2%)
HCV	42, (18.26)	19, (18.63%)	9, (15.8%)	10, (22.2%)
Others	51, (22.17%)	27, (26.47%)*	16, (28.1%)	11, (24.4%)
Education in years mean, (95% CI)	10.40, (0-18)	10.50, (0-18)	9.28, (0-18)	12.04, (0-18)

Abbreviations: CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; MHE, minimal hepatic encephalopathy; NMHE, no minimal hepatic encephalopathy; *non-alcoholic steatohepatitis 3 patients, autoimmune hepatitis 5, cryptogenic cirrhosis 18 and primary sclerosing cholangitis 1 patient.
*MHE and NMHE columns describe patients who have been enrolled; distinction between the 2 groups was based on the results of psychometric hepatic encephalopathy score.