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The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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MINIREVIEWS

Quality of life in patients with minimal hepatic encephalopathy

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Abstract

Minimal hepatic encephalopathy (MHE) represents the mildest type of hepatic encephalopathy (HE). This condition alters the performance of psychometric tests by impairing attention, working memory, psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures. MHE is a frequent complication of liver disease, affecting up to 80% of tested patients, depending of the diagnostic tools used for the diagnosis. MHE is related to falls, to an impairment in fitness to drive and the development of overt HE, MHE severely affects the lives of patients and caregivers by altering their quality of life (QoL) and their socioeconomic status. MHE is detected in clinically asymptomatic patients through appropriate psychometric tests and neurophysiological methods which highlight neuropsychological alterations such as video-spatial orientation deficits, attention disorders, memory, reaction times, electroencephalogram slowing, prolongation of latency evoked cognitive potentials and reduction in the critical flicker frequency. Several treatments have been proposed for MHE treatment such as non-absorbable disaccharides, poorly absorbable antibiotics such rifaximin, probiotics and branched chain amino acids. However, because of the multiple diagnosis methods, the various endpoints of treatment trials and the variety of agents used in trials, to date the treatment of MHE is not routinely recommended apart from on a case-by-case basis. Aim of this review is analyze the burden of MHE on QoL of patients and provide a brief summary of therapeutic approaches.

Key words: Cirrhosis; Minimal hepatic encephalopathy; Covert hepatic encephalopathy; Health related quality of life

Core tip: Minimal hepatic encephalopathy (MHE) being related to falls, an impairment in fitness to drive and the development of overt hepatic encephalopathy (HE), severely affects the lives of patients and caregivers by altering their quality of life (QoL) and their socioeconomic status. The aim of this review is to analyze the burden of MHE on QoL of patients and provide a brief summary of therapeutic approaches.

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INTRODUCTION

Hepatic encephalopathy (HE) is a complex neurological syndrome, typical of liver advanced liver disease, which determines a wide and complex spectrum of nonspecific neurological and psychiatric manifestations[1]. In its mild expression, minimal HE (MHE)[2,3], this condition impairs the performance of psychometric tests, such as working memory, psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures, without, however, any evidence of apparent and classical clinical manifestations[4,5]. MHE is a frequent complication of liver disease and is considered as one of the worsts manifestations, severely affecting the life of patients and caregivers. Moreover, the cognitive impairment results in the use of more healthcare resources than other liver diseases[6-11]. Depending on the population studied and the diagnostic tool used, MHE incidence may vary, ranging between 20% and 80% of patients with cirrhosis[12-17]. A full overview of the different diagnostic modalities of MHE has been recently published[18]. MHE, involves the areas of attention, alertness, response inhibition, and executive functions[19-22] reducing the safety and quality of life (QoL), both of patients and caregivers. Moreover, those patients show also sleep disorders[23-26] and deficits in specific activities such as driving, which are dangerous for themselves and for others. As low-grade HE (grade Ⅰ) is difficult to diagnose, the term "covert" has been recently introduced combining MHE and Grade Ⅰ HE[27]. The term "covert" has been debated since the condition is simply not overt, obvious and severe or clinically unquestionable, but is not really unapparent (latent, subclinical, minimal). Finally, MHE and covert hepatic encephalopathy (CHE) are well known risk factors for the development of overt hepatic encephalopathy (OHE). In fact, the risk for a first episode of OHE range from 5% and 25% within 5 years after cirrhosis diagnosis, depending on risk factors, such as other complications related to cirrhosis (MHE or CHE, infections, variceal bleeding, or ascites) and possibly diabetes and hepatitis C[28-33]. Under this light, it appears clear that the presence of MHE has a detrimental role on the QoL of patient and, at this regard, a survey of the American Association for the Study of Liver Diseases of 2007[34], showed that most clinicians believe MHE to be a significant problem, remaining unfortunately under investigated. In fact, only 50% of clinicians had screened their patients for MHE, and 38% had never studied their patients with liver cirrhosis using psychometric assessment. MHE impairs patients' QoL, increases the occurrence of disability, and has a negative effect on their daily activities. The impact of the perception of the disease, in the form of a "Sickness Impact Profile (SIP)", has been investigated in patients with cirrhosis to assess QoL indicators, *i.e.,* sleep, rest, eating, work, home management, recreation, walking, daily care, movement and emotional behavior. These conditions resulted significantly altered in patients with MHE compared to individuals without MHE[35]. In addition, in the presence of MHE, QoL indicators, such as the capacity to drive a car, and the incidence of sleep disorders were impaired[36]. Aim of this review is analyze the burden of MHE on quality of life of patients and provide a summary of the proposed therapeutic approaches.

IMPACT OF MHE ON QOL

Although liver cirrhosis presents a poor prognosis, recent findings in diagnosis, therapeutic strategies and general management of this disease have significantly improved survival rates. Several studies have shown that liver diseases severely worsen the health-related QoL (HRQoL)[37-39], especially in relation to hospitalizations, severity of the disease, and its complications such as recurrent HE or OHE, as well as the coexistence of sleep disorders[40]. Recent evidence suggests that OHE leads to persistent cognitive impairment even after its resolution.

In accordance with the growing interest in the central role of perception in a patient's state of health, the evaluation of HRQoL is acquiring importance in clinical practice as well as in planning therapeutic strategies. It has in fact already been shown that "quality" and "disability" of daily life have a stronger impact than "longevity" on patients' expectation of life[41]. A series of evidences show that HRQoL may appear to be influenced by the coexistence of MHE[10,35,36,42-45]. These findings have enhanced the interest to verify whether the specific treatment of these condition could lead to a consequent improvement in HRQoL. In decompensated cirrhosis, MHE worsens the domains of activity, emotional function and global scoring on the chronic liver disease questionnaire (CLDQ). MHE also alters appetite in cirrhosis and, consequently the liver function impairment, a condition of malnutrition occurs adversely impacting quality of life[46]. Prasad *et al*[10] showed more than 10 years ago that lactulose treatment of MHE patients significantly improved not only psychometric performance, but also their HRQoL. In 75% of patients with MHE resolution, a significant improvement in the "SIP" and a correlation between improvement in psychometric performance and QoL were observed[43].

Furthermore, Sanyal *et al*[47] demonstrated that the chronic administration of rifaximin in patients without OHE at enrollment, but with a history of recurring HE, significantly improved HRQoL.

Strongly related with QoL is, in our opinion, the relationship between MHE and falls. In fact, patients with liver cirrhosis are at risk of fractures due to osteoporosis secondary to malnutrition, hypogonadism and liver failure[48-50]. The injuries, especially fractures and subsequent surgical sequelae, and related hospitalizations, determine morbidity and mortality in patients with cirrhosis[51] and therefore can be considered well related with QoL. The falls and subsequent fractures also have a serious impact on the patient's family and community and have a high economic impact[52,53]. Román *et al*[54] have shown that, because of falls, the need for healthcare (8.8% *vs* 0%, P = 0.004), whereas hospitalization (6.6% *vs* 2.3%, P = NS) was greater in patients with MHE than in cirrhotic patients without MHE. Multivariate analysis identified MHE [odds ratio (OR) = 2.91, 95% confidence interval (CI): 1.13-7.48, P = 0.02], in addition to a previous history of OHE (OR = 2.87, 95%CI: 1.10-7.50, P = 0.03) and taking psychoactive drugs (OR = 3.91, 95%CI: 0.96-15.9, P = 0.05), as factors independently associated with falls. These findings were subsequently confirmed by Soriano *et al*[55] in a larger patient cohort. The authors were able to conclude, using multivariate analysis, that the presence of cognitive impairment, or the presence of MHE diagnosed by an abnormal Psychometric Hepatic Encephalopathy Score (PHES) were the only independent factors predictive of a fall (OR = 10.2 95%CI: 3.4-30.4, P < 0.001). Moreover, the probability of a fall in one year was found to be significantly higher in patients with MHE (52% *vs* 6.5%, P < 0.0001) compared to those without MHE. Urios *et al*[56] demonstrated that patients with MHE show an altered balance, mainly if evaluated on an unstable surface with eyes open, with longer reaction and confinement times and lower success in stability test limits, than patients free from MHE. Finally, patients with MHE may experience also sleep disorders, severely affecting quality of life. Singh *et al*[57] evaluated sleep disorders in MHE and assess the effect of lactulose on sleep disturbances and HRQoL, concluding that excessive sleepiness on day time and an impairment in sleep quality are common in patients with MHE. The administration of lactulose also leads to improvement in MHE as well as sleep disturbances and HRQoL.

MHE AND HRQOL ASSESSMENT

There is no single optimal measure to assess the presence of MHE. In fact, none of the methods proposed cover all aspects of HE, appropriate norms are needed for a good sensitivity and specificity in identifying patients at risk of overt HE, the rate of pathological results in patient groups without overt HE differs markedly and finally the results of the various methods are not consistent. However, with a significant negative impact on the daily lives of patients and caregivers, MHE is still likely to be ignored by most clinicians if standards of neuropsychological testing are not followed while testing a patient for MHE. Magnetic resonance imaging has recently proposed with promising results to assess the presence of MHE[58,59]. A comprehensive review on the diagnostic modalities was previously published by our group[18].

SIP

The SIP questionnaire (Medical Outcome Trust, Boston, MA) was used to assess the influence of disease and treatment on daily functioning. The questionnaire is based on 136 items grouped into 12 scales (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness, emotional behavior, and communication)[60]. The SIP provides the opportunity to calculate a total score, ranging from 0 (best) to 100 (worst), and patients mark only items that relate to their health at that time. Change in the total SIP score after a predetermined period of time of treatment or follow-up could be a measure of change in overall HRQoL.

CLDQ

The CLDQ is a validated tool for evaluating quality of life in subjects with chronic liver disease[61]. The CLDQ contains 29 items grouped in six domains: abdominal symptoms (three items), fatigue (five items), systemic symptoms (five items), activity (three items), emotional function (eight items) and worry (five items). For each question patients were ranked on a 7-point scale, with higher scores indicating better HRQoL. Data are presented by domain, overall and by items.

Short Form-36

Short Form-36 (SF-36) is a paper-pencil test corrected for age, education and occupation of a healthy Italian population sample[62], which investigates the full range of the patient's health status by 36 multiple-choice questions. The test measures eight domains, four in the area of "physical health" (physical functioning, role limitation-physical, bodily pain, general health) and four in the area of "mental health" (role limitation-emotional, vitality, mental health and social functioning). Each domain is scored between 0 and 100 points, when higher scores indicate a better HRQoL. It includes a final question on the patient's perception of changes in his/her health condition in the previous 12 mo. The physical component summary (PCS) and the mental component summary (MCS) may also be computed. The SF-36 has a strength limitation, it is validated only in italian population.

THE ROLE OF MHE TREATMENT ON QOL

MHE and CHE can alter severely patient's daily life, and in certain cases (*e.g.*, impairment of driving skills or work performance, poor QoL, or cognitive complaints) the

Table 1 Published studies aimed to assess the role of treatment on quality of life of patients with minimal hepatic hencephalopathy

Author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Prasad *et al*[10]	2007	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose	45 (25)	12	Psychometry, QoL	Significant improvement in psychometry: $P < 0001$; and QoL: $P < 0.002$. Improvement in HRQoL was related to the improvement in psychometry.
Sidhu *et al*[43]	2011	Original, randomized	NCT A, FCT A, Digit Symbol test, BDT, PC	Rifaximin	94 (49)	8	MHE reversal, QoL	MHE reversal in 37/49 *vs* 9/45. Improvement in QoL. Improvement in HRQoL correlated with improvement in psychometry
Sidhu *et al*[65]	2016	Original, randomized	NCT A, FCT A, Digit Symbol test, BDT, PC	Lactulose *vs* Rifaximin	112 (55/57)	12	MHE reversal, QoL	MHE reversal in 38/55 and in 42/57; HRQoL was significantly improved in both groups
Mittal *et al*[68]	2011	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose or Probiotics or LOLA	160 (40/40/40)	12	Psychometry, ammonia, QoL	MHE reversal in 19/40 *vs* 14/40 *vs* 14/40 *vs* 4/40. Improvement in QoL.
Bajaj *et al*[72]	2008	Original, randomized	NCT A, Digit Symbol Test, BDT	Probiotic yogurt	25 (17)	8	MHE reversal, OHE development, QoL, ammonia, cytokines	MHE reversal in 71% *vs* 0%; OHE development in 0% *vs* 25%; no differences in QoL and cytokine Levels. Excellent adherence in cirrhotics after probiotic yogurt supplementation with potential for long-term adherence
Bajaj *et al*[81]	2011	Original, randomized	NCT A, NCT B, Digit Symbol test, BDT, ICT	Rifaximin	42 (21)	8	Psychometry, QoL, driving ability, anti-inflammatory interleukins	Improvement in psychometry, driving performance and QoL
Malaguarnera *et al*[76]	2018	Original, Observational	NCT-A, NCT-B, LTT, SDT, DST	Resveratrol	35 (35)	Variable	QoL, ammonia levels	Resveratrol showed efficacy in the treatment of depression, anxiety, and ammonia serum levels, and improved the quality of life Of MHE patients.
Malaguarnera *et al*[77]	2011	Randomized, double-blind, placebo-controlled study.	TMT-A, TMT-B	Acetyl-L-carnitine twice a day	33 (34)	13	Clinical and laboratory assessments, psychometric tests and automated electroencephalogram (EEG) analysis and QoL evaluations	treatment is associated with significant improvement in patient energy levels, general functioning and well-being. The improvement of quality of life is associated with reduction of anxiety and depression.
Zhang *et al*[82]	2015	Original	NCT A, NCT B, Digit Symbol test	Rifaximin	26 (26)	1	Psychometry, ammonia, SIBO	MHE reversal in 15/26; reduction in SIBO and ammonia levels
Bajaj *et al*[83]	2014	Original, randomized	NCT A NCT B, Digit Symbol test, BDT	Probiotics	30 (14)	8	Psychometry, ammonia, inflammatory markers, QoL	Reduction in endotoxin and TNF-α but not in cytokines. No effects on psychometric performance
Luo *et al*[84]	2011	Meta-analysis	Different diagnostic tools	Lactulose	434	Variable	Psychometry, ammonia levels, QoL, progression to OHE	Lactulose superior to placebo on all outcomes (psychometry: RR = 0.52, 95%CI: 0.44-0.62, $P < 0.00001$)

MHE: Minimal hepatic encephalopathy; OHE: Overt hepatic encephalopathy: HRQoL: Health related quality of life; NCT-A: Number connection test-A; NCT-B: Number connection test-B; BDT: Block design test; SDT: Serial dotting test; DST: Digit symbol test; LTT: Line tracing test; PHES: Psychometric hepatic encephalopathy score; ICT: Inhibitory control test; CFF: Critical flicker frequency; EEG: Electroencephalogram; ICT: Inhibitory control test; BCAA; Branched chain amino acids; SIBO: Small intestine bacterial overgrowt; CEP: Cognitive evoked potentials; TNF: Tumor necrosis factor.

indication to adopt any given pharmacological treatment may prevail. However, because of various methods used to assess the presence of MHE and CHE, the varying and multiple endpoints, the short-term treatment trials, and differing agents used in trials to date, recently published guidelines state that treatment of MHE and CHE is not routinely recommended apart from on a case-by-case basis[63]. Table 1 provides a complete overview of the studies of MHE treatment in the specific setting of QoL.

Concerning specific treatments, rifaximin is an oral non-systemic broad-spectrum antibiotic, similar to rifampin. Rifaximin, after concentrating in the gut, is able to modulate the intestinal to reduce intestinal ammonia and toxin formation. Bajaj *et al*[64] demonstrated that patients with MHE treated with rifaximin for an 8-wk period showed significantly greater improvements in the psychosocial dimension of the SIP and in driving and cognitive performance than patients treated with placebo. These results were confirmed in another randomized controlled trial (RCT), in which the authors demonstrated that rifaximin is significantly able to improve both cognitive functions and HRQoL in patients with MHE[43]. Recently, an RCT comparing rifaximin with lactulose for MHE reversal and HRQoL amelioration failed to demonstrate significant differences between groups[65].

Lactulose or lactitol are non-absorbable disaccharides used widely in the management of OHE. Lactulose is fermented in the colon, being metabolized to acetic and lactic acid, acidifying intestinal contents and conversion of ammonia (NH_3) to ammonium (NH_4^+) that is not systemically absorbed and is excreted in stool. Moreover, lactulose also has a cathartic effect, increasing nitrogen excretion fourfold. Although Prasad *et al*[10] concluded that lactulose treatment improves both cognitive function and HRQoL in MHE patients, most subsequent studies have not provided strong evidence confirming the efficacy of non-absorbable disaccharides in MHE treatment[43,66-69]. A meta-analysis evaluating the role of pharmacological treatment with non-absorbable disaccharides in patients with MHE failed to show clear evidence that any treatment played a convincing role in improving cognitive function and HRQoL[70].

Probiotics are live microorganisms and synbiotics are probiotics with the addition of fermentable fiber able to change the balance of intestinal microflora. The supposed mechanism of action is that, reducing intestinal bacterial urease activity, these drugs decrease the absorption of ammonia and other gut-derived toxins potentially involved in the pathogenesis of (M)HE. Seven recently published RCTs were aimed to evaluate the role of probiotic treatment/supplementation in treating MHE. Unfortunately, the results do not support the evidence on the efficacy in MHE reversal of a treatment with probiotics alone or in addition to other drugs[67-69,71-74]. In fact, no significant difference in the improvement of QoL, MHE, hospitalization rates, or progression to OHE has been reported when probiotics were compared with lactulose[75]. Carnitine a resveratrol have also been proposed with encouraging results in MHE treatments[76,77], as well as polyethylene glycol[78]; or nitazoxanide[79], actually proposed for OHE treatment, could be considered for future studies for MHE treatment. Finally, recently published European Association of Liver disease Clinical Practice Guidelines on Nutrition in chronic liver disease highlight to avoid protein restriction in patients with HE[80].

CONCLUSION

MHE and CHE represent a broad spectrum of neuropsychological manifestations of liver disease in which the detection of risk thresholds for the occurrence of OHE, impairment in daily life activities and in QoL has unfortunately not yet been well defined. Studies specifically aimed at establishing whether a treatment of MHE is able to affect clinically relevant endpoints are still needed[27]. The presence of minimal or CHE should be assessed following objective and universal modalities. Following this direction, only changes of psychometric tests should not be chosen as the main endpoint of the study; being only used as a criterion to include comparable patients. The sample size should be assessed according to clinically relevant endpoints, such as the quality of life or the occurrence of OHE during the follow up. For the assessment of the efficacy of a treatment in patients with MHE, the organization of large multicenter studies is considered mandatory, as well as a parallel design with a placebo or a no-treatment arm should be considered necessary. In this specific setting, the majority of studies enrolled patients with MHE diagnosed with different modality and studies have been designed with a different aim. Therefore, these evidences cannot be comparable, and we cannot draw unequivocal conclusions. Moreover, because MHE is a chronic condition, the tested drug should be administered for a very long period of time without significant side-effects. Among the emerging drugs, modulators of the intestinal bacterial flora should be the first candidates to be tested in this field. Future studies should fill the gaps in our knowledge.

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