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Review Article

Sex differences in hepatic encephalopathy: addressing the knowledge gap

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ABSTRACT

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portal-systemic shunting with a significant impact on patients' quality of life and healthcare systems. This narrative review was elaborated by the Special Interest Group (SIG) "Gender in Hepatology" of the Italian Association for the Study of the Liver (AISF) and addresses the underexplored area of sex differences in HE, examining epidemiological trends, clinical manifestations and potential underlying mechanisms. Current evidence suggests that men and women may experience different prevalence rates, risk factors and disease progression due to biological and psychosocial factors. However, these differences remain poorly understood, with limited research on sex-specific outcomes, treatment adherence and psychological effects. Emerging data on body composition, gut microbiota and experimental models highlight potential mechanisms contributing to these differences. Given the evolving epidemiology of liver disease, this review highlights the need for targeted studies and sex-specific approaches in the management of HE to advance personalised medicine and improve outcomes.

1. Introduction

Hepatic encephalopathy (HE) refers to brain dysfunction caused by liver insufficiency and/or portal-systemic shunting, presenting a range of neurological or psychiatric abnormalities from asymptomatic states to coma [1]. From an epidemiological perspective, HE is the most prevalent complication of cirrhosis, leading to hospitalisations and recurrent readmissions. Consequently, the healthcare burden associated with managing HE is significant. Moreover, studies have also shown that this condition has a significant psychological impact including persistent deep emotions such as fear, anger, misery, anxiety, and sorrow. It affects patients' daily routines, independence, quality of life, socio-economic status, sleep-wake patterns, and the dynamics between patients and their families [2–4]. In this context, as seen in other diseases with a psychological impact, gender may influence the perception of the disease and the severity of associated symptoms [5]. Current literature suggests that covert HE occurs equally in both sexes [6], as does overt HE, [7], even if a single study has suggested that HE may be the only complication of cirrhosis that is more common in women [8]. For post-TIPS HE, which is clinically relevant given the widespread use of TIPS in recent years, available studies have not shown epidemiological differences between the two sexes [9,10]. However, some distinct gender-specific risk factors have been identified in these patients, particularly factors related to body composition [11]. Other aspects, such as gender differences on mortality, hospitalisation, perception of HE and its psychological impact, remain underexplored in the literature. It is important to emphasise that this gap may be partly due to the lack of clear evidence that sex differences in HE have practical implications for clinical or therapeutic approaches. On the other hand, gender-specific risk factors may influence the prevalence and severity of HE. Men

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and women may exhibit different symptoms and disease progression, which may affect diagnosis and treatment. Differences in behaviour and adherence to medical treatment could also be relevant to note. In light of these considerations, it is worth exploring whether and in what ways gender might have an impact on this condition.

2. Epidemiology of HE

2a. Prevalence of minimal and covert HE in men and women

Covert HE is a condition that includes patients who have minimal or no visible signs or symptoms but who have abnormalities that can be detected by neuropsychological and/or neurophysiological testing (minimal HE) [12,13]. It also includes patients classified as having grade I hepatic encephalopathy according to the West Haven criteria [12].

The prevalence of covert encephalopathy (CHE), evaluated with psychometric hepatic encephalopathy score testing (PHES), ranges between 20 and 37 % in subjects with cirrhosis [6,14,15]. However, the prevalence of minimal encephalopathy, diagnosed with the Stroop Encephal App (EncephalApp) using adjusted population norms, has been reported to be even higher reaching 54 % in a multicentre American study [15].

The prevalence of covert or minimal HE has been analysed in a systematic review and meta-analysis in patients with cirrhosis including a total of 101 studies extracted by PubMed, Embase and Cochrane Library databases [16]. No statistically significant differences were observed between patients with covert/minimal HE in relation to gender. Notably, it should be considered that the prevalence of male cirrhotic patients is higher than females in the majority of cohorts, and that the origin of liver disease may also be different according to patient's sex. These aspects may represent a possible confounding factor.

2b. Prevalence of Overt HE in men and women

The incidence of overt HE evaluated in prospective studies is 10 % at 1 year in patients with Child A cirrhosis and increases to 25 % in those with Child B [7].

Changes in the demographic and clinical characteristics of patients with cirrhosis are critical to consider for HE. In a study by Orman et al. [17], shifts in the epidemiology of newly diagnosed cases of cirrhosis, with a prevalence of metabolic related causes of the disease, caused modifications in patients age distribution. This trend may also impact the sex distribution of cirrhosis in the future, further highlighting the importance of monitoring demographic changes to inform tailored interventions and treatment approaches. However, the article by Orman et al. [17] does not address the potential impact of gender on the presentation of HE, nor does it explore gender disparities in the clinical manifestations of HE.

Nowadays the most important aetiologies accounting for cirrhosis are metabolic-associated steatotic liver disease (MASLD) and alcoholic liver disease. MASLD is a novel nomenclature proposed in 2020 by a group of experts to overcome the issues related to the old terminology (Nonalcoholic fatty liver disease-NAFLD) [18] . Emerging evidence suggests that cirrhotic patients with metabolic syndrome may experience cognitive dysfunction [19]. Factors responsible for this cognitive dysfunction include neurodegenerative changes, activated microglia, microvascular dysfunction, systemic inflammation, obstructive sleep apnoea, altered gut microbiota and fatty liver [20]. The major challenge for clinicians is to distinguish this multifunctional metabolic encephalopathy from HE in patients with MASLD cirrhosis. Alcohol-related etiology can also lead to greater cognitive impairment and axonal damage, making patients more susceptible to the development of HE [21]. In fact, alcohol can have an impact on the brain of cirrhotic patients, regardless of the presence of HE, trough direct brain tissue toxicity, neuroinflammation, induced nutritional deficiencies [22].

Both MASLD and alcohol liver disease are more frequently reported in males [23] which could possibly explain a higher incidence of HE in the male than in the female sex.

In contrast with this consideration, a recent study analysing gender differences among 555,017 patients hospitalised with cirrhosis in USA [8], showed that women had lower rates of decompensation than men, but HE was the only complication of cirrhosis that was more common in women than in men (17.8 % vs 16.8 %, $p < 0.001$).

2c. Overt HE after TIPS placement in men and women

An unresolved issue that significantly complicates the management of cirrhotic patients with portal hypertension is the occurrence of HE following the placement of a transjugular intrahepatic portosystemic shunt (TIPS) [24,25]. TIPS is a widely adopted procedure used to address complications related to portal hypertension, such as recurrent variceal bleeding or intractable ascites [26]. TIPS procedure is often lifesaving, but it is associated with the development of HE, particularly in the immediate post-procedural period due to the diversion of blood directly into the systemic circulation [25]. The overall incidence of post-TIPS HE falls within the range of 25 % to 45 % in various studies [27–30].

Age, previous history of HE, stent diameter, presence of sarcopenia are known to be associated with an increased risk of post-tips HE [31–33].

In this context, the role of gender has never been explored. Studies conducted for other reasons have not found a significant difference according to gender in post-TIPS HE [9,10,34,35].

Finally, in the recent study by Nardelli et al. only age, low albumin and pre-TIPS OHE were reported as associated with post-TIPS HE. Gender did not influence this manifestation [36].

3. Consequence of HE: impact of sex

3a. Hospitalization and mortality

In the majority of studies evaluating risk factors for hospitalization due to HE, sex was not considered [37–39]. In a recent prospective multicenter Italian study, Riggio O. et al. [40] showed that males were more frequently admitted in hospital for HE than for other liver decompensation events ($p = 0.01$). However, sex was not included among the variables considered as risk factors for hospital readmission, death or liver transplantation at uni/multivariate analysis [40].

In a large cohort of American patients with HE, gender differences were not associated with longer length of hospitalization or with higher rates of 30-days readmission [41]. Conversely, another study conducted by Chen et al., in the years from 2010 to 2014, female sex was associated with an increase risk of 30-day readmission of patients hospitalized for HE in US [42].

3b. HE perception

Hepatic encephalopathy, whether overt or covert, negatively impacts patients' health-related quality of life, further contributing to overall health-care costs [43]. Health-related quality of life (HRQOL) is a crucial patient-reported outcome in clinical trials and studies. Most studies on HRQOL in HE has included both patients with covert HE and patients with a previous episode of overt HE, using various kind of methods of assessment. The most commonly used tools are the generic Short-Form 36 test (SF-36), the generic Sickness Impact Profile (SIP) and the liver-specific Chronic Liver Disease Questionnaire (CLDQ) [2]. Studies that did not find a significant impact of HE on HRQOL often used less specific instruments like the SF-36 [44]. Conversely, studies performing more extensive evaluation such as the SIP, or liver-specific instruments like the CLDQ, typically found a negative impact of HE on HRQOL [45].

Moreover, the burden of caring for patients with HE significantly impacts the entire family, unlike most other complications of cirrhosis. Caregivers are typically relatives, unprepared for the challenges they face [46].

Patients with HE frequently experience hospital readmissions, progressive worsening of cognitive performance and loss of independence. This burden extends across medical, psychosocial, and financial domains, intensifying as HE progresses from covert to overt stages, particularly in older patients. Consequently, the impact of HE on daily function and quality of life affects not only the patient but also the patient's family, necessitating a holistic approach to care and resource allocation [47]. In other conditions sex has been shown to play a role in the perception of the disease [48].

Biological sex, including hormonal influences and other physiological differences, may make individuals more susceptible to certain diseases manifestations [49]. An equally important dimension is the social construct of gender, which evolves over time and varies in different cultural contexts. This social aspect of gender is particularly important when considering the psychological impact of a disease [49]. Gender roles, expectations and the social positioning of individuals based on their sex can significantly shape their experience of illness, coping mechanisms and access to support systems [50].

4. Why differences in men and women? Possible explanations

4a. Body composition

Wang et al. analyzed the predictive value of body compositions, measured by CT, for HE in 191 cirrhotic patients following transjugular intrahepatic portosystemic shunt (TIPS) [11]. They showed that female patients with low subcutaneous fat area index are more likely to develop HE following TIPS, whereas low visceral fat area index are associated with a higher incidence of post-TIPS HE in male patients. Loss of subcutaneous adipose tissue may reflect severe energy depletion triggered by cirrhosis, leading to worse clinical outcomes, including HE. In addition, the authors reported that serum pre-albumin, a sensitive indicator of nutritional protein, was an independent predictive factor of post-TIPS HE in females. These data however were not confirmed in another similar study [51].

Analyzing body compositions could therefore be utilized to predict the risk of HE in cirrhotic patients following TIPS using different parameters in the two sexes. In addition, these data about adipose tissue deposits may even better framing the risk of HE related to sarcopenia.

Ammonia is a gut-derived neurotoxin of major importance in the pathogenesis of HE but its predictive value is unknown. The validated AMMON–OHE model, which uses readily available clinical and biochemical parameters including sex, performed significantly better than the traditionally used neuro- psychological or psychophysical tests and disease severity scores for the prediction of a first episode of OHE and its recurrence [52].

Sarcopenia has a central role in cirrhosis, especially regarding ammonia clearance. A tendency to higher ammonia levels was seen in females compared with males and female sex was independently associated with OHE occurrence. Whether this difference was associated with a lower muscle mass in females could not be confirmed in this study, because the authors did not assess markers of sarcopenia [52].

4b. Gut Microbiota

Modifications in microbial composition between sexes may also be important in potentially individualizing the therapy for HE patients. In a cross-sectional study of 761 subjects, 619 cirrhosis (466 men,153 women) and 142 controls, there was a sex difference with HE therapies focused on Lactobacillaceae and Veillonellaceae and androstenedione degradation [53]. Saboo et al. found that as liver cirrhosis progressed in men, their microbial composition began to approach that observed in women, with changes in specific microbes that are associated with male hormone metabolism. Further studies linking these to sex-specific outcomes are needed [53].

4c. Adherence to therapy

It should be stressed that the analysis of 17 interventional clinical trials downloaded from the Clinical trials.gov web-site showed that sex was not considered as a factor associated with the therapeutic effect of drugs active in HE [54].

Lactulose is an effective first-line medication for both treatments and for secondary prophylaxis for HE. Despite its effectiveness, adherence to lactulose is a challenge for many patients. This is in part due to difficulty in titrating the dose, the medication's sweet taste, and its diverse side-effect profile (diarrhea, bloating, and dehydration). Non-adherence to lactulose is one of the most frequently reported factors to precipitate hospital admission for HE. Chow KW at all. analysed the treatment adherence by Morisky Adherence Scale 8 (MAS-8) and a customized 16-question survey in a cohort of 129 cirrhotic patients. Patients were similar in sex distribution in the two groups (adherent vs no adherent) [55].

5. Experimental research work

Tong et al. confirmed that gender and age play a role in the severity of HE development and that the presence of one or more liver toxins may exacerbate the severity of the disease progression. They found that aged males and young/aged females rats are more prone to develop brain edema in the presence of one or more liver toxins. Most experimental studies have focused utilized mainly male animals, hindering our understanding of female-specific mechanisms. The lack of data on females and age differences hampers the applicability of the results obtained from adult rats in young, adult, or aged females [56].

Starting from the need for data in the female population, Macedo de Oliveira and colleagues used the well-characterized bile-duct ligated (BDL) rat model of CLD and HE in female rats to evaluate the impact of sex on the pathogenesis of CLD, HE, muscle mass loss as well as the susceptibility to severe HE. Six weeks following BDL, the female rats developed similar hepatic damage/injury compared to the male BDLrat. Both female and male BDL rats develop HE, but females had distinct features such as lack of anxiety and brain oedema and intact short- term memory. Interestingly, despite similar ammonium levels between the two sexes, differences were found in muscle mass; indeed females were safeguarded against muscle mass loss while males developed a progressive loss of muscle mass together with an up-regulation in glutamine synthetase activity. A higher systemic antioxidant capacity found in females naturally protected female BDL rats from enduring an ammonia- induced episode of OHE. Our results suggest that the occurrence and development of CLD-induced complications differs between male and females and that sex-specific management of patients merits further attention [57].

6. Conclusions and further directions

In this review, we aimed to highlight a significant knowledge gap in the scientific literature regarding sex differences in HE. By analysing existing studies, including those from related fields, or HE research conducted with other aims, we sought to emphasise the importance of addressing this understudied area. In addition, we considered emerging epidemiological shifts in liver disease, and consequently HE, as critical factors that should inform future research. These evolving trends provide a strong rationale for the de-

velopment of targeted clinical trials to better understand sex differences in HE. Ultimately, this line of research is essential to advance personalised medicine and improve patient outcomes in the management of hepatic encephalopathy.

Conflict of interest

The authors declare that they have no conflicts of interest related to this manuscript. No financial, personal, or professional relationships that could influence the content of this work exist between the authors and any organizations or entities.

All authors have participated in the preparation of this manuscript and have approved the final version for submission to *Digestive and Liver Disease*.

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