Research Article

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Increased risk of cognitive impairment in cirrhotic patients with bacterial infections

Manuela Merli[1,*], Cristina Lucidi[1], Ilaria Pentassuglio[1], Valerio Giannelli[1], Michela Giusto[1], Vincenza Di Gregorio[1], Chiara Pasquale[1], Silvia Nardelli[1], Barbara Lattanzi[1], Mario Venditti[2], Oliviero Riggio[1]

[1]*Gastroenterology, Department of Clinical Medicine, "Sapienza" University of Rome, Italy;* [2]*Department of Infectious Disease, "Sapienza" University of Rome, Italy*

Background & Aims: A causal relationship between infection, systemic inflammation, and hepatic encephalopathy (HE) has been suggested in cirrhosis. No study, however, has specifically examined, in cirrhotic patients with infection, the complete pattern of clinical and subclinical cognitive alterations and its reversibility after resolution. Our investigation was aimed at describing the characteristics of cognitive impairment in hospitalized cirrhotic patients, in comparison with patients without liver disease, with and without infection.

Methods: One hundred and fifty cirrhotic patients were prospectively enrolled. Eighty-one patients without liver disease constituted the control group. Bacterial infections and sepsis were actively searched in all patients independently of their clinical evidence at entry. Neurological and psychometric assessment was performed at admission and in case of nosocomial infection. The patients were re-evaluated after the resolution of the infection and 3 months later.

Results: Cognitive impairment (overt or subclinical) was recorded in 42% of cirrhotics without infection, in 79% with infection without SIRS and in 90% with sepsis. The impairment was only subclinical in controls and occurred only in patients with sepsis (42%). Multivariate analysis selected infection as the only independent predictor of cognitive impairment (OR 9.5; 95% CI 3.5–26.2; $p = 0.00001$) in cirrhosis. The subclinical alterations detected by psychometric tests were also strongly related to the infectious episode and reversible after its resolution.

Conclusions: Infections are associated with a worse cognitive impairment in cirrhotics compared to patients without liver disease. The search and treatment of infections are crucial to ameliorate both clinical and subclinical cognitive impairment of cirrhotic patients.

Introduction

Cirrhotic patients, especially in the decompensated stage of the disease, are particularly susceptible to bacterial infections [1–3]. In these patients, infections represent a serious burden and a negative prognostic factor for survival [3,4]. Moreover, an infectious episode may predispose to complications such as variceal bleeding [5] or renal failure [6], adding further complexity to the patients' management. Hepatic encephalopathy (HE) is among the complications triggered by a bacterial infection. In fact, a concomitant infection is frequent in cirrhotic patients with overt HE [7] being a common precipitating factor for this neurocognitive alteration [8]. A causal relationship between infection, systemic inflammation, and HE has been suggested by several authors [9,10]. Although the mechanism is not completely elucidated, inflammatory cytokines may induce astrocyte swelling and a low-grade cerebral oedema, which have been implicated in the pathophysiology of HE [11].

In cirrhotic patients with sepsis, the prevalence of overt HE has been reported to be higher than in those without infection in some studies [12], but not in others [13]. However, no study has specifically examined, in cirrhotic patients with infections, the complete pattern of cognitive alterations including the subclinical impairment known as "covert" or minimal hepatic encephalopathy (MHE). Although subclinical, MHE is considered clinically relevant, being associated with a reduced driving capacity [14], the occurrence of falls [15] and development of overt HE [16]. It is still unclear whether MHE has a distinct pathogenesis, or should be considered a milder form of overt HE, and whether or not it is a stable disorder or a fluctuating condition triggered, as overt HE, by a precipitating event. In particular, few pieces

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* Corresponding author. Address: II Gastroenterologia, Dipartimento di Medicina Clinica, "Sapienza" Università di Roma, Viale dell'Università 37, 00185 Roma, Italy. Tel.: +39 0649972001; fax: +39 064453319/064440806.

E-mail address: manuela.merli@uniroma1.it (M. Merli).

Abbreviations: HE, hepatic encephalopathy; SIRS, systemic inflammatory response syndrome; MHE, minimal hepatic encephalopathy; TMT-A, trail-making test A; TMT-B, trail-making test B; DST, digit-symbol test; CRP, C-reactive protein.

of information are available about the relationship between MHE and infections. Shawcross and colleagues reported that MHE was independent of severity of liver disease and that markers of inflammation were significantly higher in cirrhotic patients with MHE [17]. Montoliu and colleagues suggested that serum levels of some cytokines (IL-6 and IL-18) may discriminate cirrhotic patients with and without MHE [18]. Furthermore, Gupta and colleagues showed a high prevalence of small intestinal bacterial overgrowth in patients with MHE [19].

A possible confounder for the role of infection in HE is represented by the fact that, during infection, also patients without liver disease may develop changes in the mental state, the so called "sepsis-associated encephalopathy". A large number of patients with bacteraemia may in fact exhibit electroencephalographic alterations and neurological symptoms, ranging from lethargy to coma [20], and multiorgan failure induced by severe sepsis may include signs and symptoms of brain dysfunction [21]. The pathogenesis of neurological alterations in this setting is complex, resulting both from inflammatory and non-inflammatory processes that induce blood brain barrier loss, dysfunction of intracellular metabolism, and brain cell damage and death [22].

The current prospective study was aimed at describing the characteristics of cognitive impairment (both overt and covert) in cirrhotic patients with bacterial infection and at evaluating the specificity of these changes. For this aim, a large cohort of hospitalized cirrhotic patients, prospectively enrolled also in an observational study on bacterial infection in liver cirrhosis [3], was submitted to a detailed neurological and psychometric assessment. The results obtained in the cirrhotic patients were compared to those obtained in hospitalized patients without liver disease. In both groups, a comparison between patients with and without infection and a longitudinal assessment following the episode of infection were made.

Patients and methods

We prospectively enrolled in the study all consecutive cirrhotic patients hospitalized at our University Department (a tertiary referral centre for patients with liver failure and portal hypertension) from October 2008 to June 2009. Data regarding the prevalence and prognostic significance of infection in this cohort of cirrhotic patients has been previously reported [3]. Diagnosis of cirrhosis was based on liver biopsy, when available, and/or on clinical, biochemical, ultrasonography and endoscopic features. Exclusion criteria were a concomitant HIV infection, high dose corticosteroid treatment, and immunosuppressive therapy.

The control group consisted of consecutive patients without liver disease hospitalized in the Department of Internal Medicine and the Department of Infectious Disease of the same University Hospital (Policlinico Umberto I, Rome), from January 2010 to December 2010. Exclusion criteria were the same applied to the cirrhotic patients. In the control group, the presence of liver diseases was carefully evaluated based on history, clinical examination, laboratory and ultrasonography findings. Any sign of liver impairment was considered a criterion of exclusion.

All patients or caregivers consented to participate in the study after an exhaustive explanation of the aims and methods. The study was approved by the ethical committee of the Policlinico Umberto I, "Sapienza" University Hospital of Rome.

Assessment of infection

According to our protocol, in all cirrhotic and control patients, bacterial infections and systemic inflammatory response syndrome (SIRS) were actively searched at hospital admission through: (a) medical history and physical examination focused on signs and symptoms suggestive of a specific infectious site; (b) blood pressure, heart rate, respiratory rate, and body temperature; (c) laboratory tests including polymorphonucleated cell (PMNC) count, inflammatory indices, hepatic and renal function and urinalysis including fresh urine sediment; (d) analysis of biological fluids such as ascites and pleural effusion, when present; (e) chest x-ray film; and (f) abdominal ultrasound. Further specific investigations including cultures of blood, urine, sputum, ascitic and/or pleural fluid or purulent secretions were carried on according to the results of the above mentioned tests and to the patient symptoms. The diagnosis of bacterial infection was based on standard criteria which have been previously reported [3]. Patients were considered to have SIRS when they fulfilled the criteria established by international guidelines. Sepsis was diagnosed in presence of SIRS and a known or highly suspected infection [23].

The assessment of infection was performed at hospital admission and at any time during hospitalization if a diagnosis of infection was suspected according to clinical findings or biochemical alterations (i.e., peripheral leukocytosis, increase in inflammatory indices, development of renal failure, etc.) or changes in mental state. Cirrhotic and control patients were divided into 3 groups: (a) patients without sepsis or infections, (b) patients with infections without SIRS, and (c) patients with sepsis (infection + SIRS).

Evaluation of cognitive impairment

In all patients, a pool of standardized closed questions aimed at determining time and space orientation, were used to detect clinically evident alterations in patients' mental state.

In cirrhotic patients with altered mental state, the diagnosis of overt HE was made, and the West Haven criteria were then applied to grade its severity.

In cirrhotic and control patients with no alterations in mental state, dementia was also excluded by means of a Mini-Mental State (MMS) >26.

The cirrhotic and control patients with normal mental state and no dementia were then submitted to a paper and pencil test battery, including the Trail-Making Test A (TMT-A) and the Trail-Making Test B (TMT-B), which allows to evaluate the attention and concentration, psychomotor speed, mental flexibility, efficiency in the visual scanning, and ability to sequencing; and the Digit-Symbol Test (DST), which assesses the associative learning, motor speed graph, speed of cognitive processing, visual perception, and working memory. A diagnosis of cognitive impairment was made in all patients with a Z-score greater than 2 standard deviations compared to that observed in a healthy Italian population adjusted for age and education in at least one of the above tests [24].

The clinical and psychometric evaluation was performed at entry in all cirrhotics and controls. Venous blood ammonia levels were also determined in cirrhotic patients. In cirrhotic patients, the clinical and psychometric evaluation was repeated after the resolution of infection. In case of a nosocomial infection, the psychometric evaluation was repeated at the time of the diagnosis as well as at resolution.

After discharge, all cirrhotic patients who survived were re-evaluated as outpatients after three months. Among the control patients, those showing any cognitive impairment during infection were also re-evaluated.

Statistical analysis

All the values are reported as means ± SD and p values <0.05 were considered statistically significant. Groups were compared using the Student's t test for unpaired data, Chi square test, ANOVA and Newman-Keuls multiple-comparison test, as appropriate. The paired sample t-test was used to longitudinally compare psychometric performances. The correlation between psychometric tests and inflammatory indices was analyzed by Pearson's correlation. The logistic regression analysis was employed to identify possible predictors of the cognitive impairment. The software used for the analysis was NCSS (Number Cruncher Statistical System) 2007.

Results

In the cirrhotic group, four patients were excluded, one for high-dose steroid therapy, and three because they were following an immunosuppressive therapy due to a recurrence of cirrhosis after liver transplantation. The characteristics of the 150 cirrhotic patients enrolled are reported in Table 1. Cirrhosis was due to hepatitis C in 51% of cases and alcohol abuse in 19%. Child class was A in 30%, B in 39%, and C in 31% of patients and the median MELD score at admission was 13.5 (range: 6–25). The main