

HEPATOLOGY

Malnutrition and hypermetabolism are not risk factors for the presence of hepatic encephalopathy: A cross-sectional study

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Key words

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Abstract

Background and Aim: Hepatic encephalopathy is a frequent complication of cirrhosis. The present retrospective investigation was conducted to characterize metabolic alterations in cirrhotic patients with and without hepatic encephalopathy. We tested the hypothesis that reduced nutritional status or the degree of tissue catabolism are associated with the presence of hepatic encephalopathy.

Methods: We investigated 223 patients with histologically confirmed nonalcoholic cirrhosis without hepatic encephalopathy and with hepatic encephalopathy (grades 1–3). To assess liver function, nutritional status, and energy metabolism, a variety of biochemical and clinical tests were performed including anthropometric measurements, bioelectrical impedance analysis, and indirect calorimetry.

Results: Nutritional status and tissue catabolism were not significantly different between patients with and without hepatic encephalopathy.

Conclusions: Our data do not support the hypothesis that malnutrition or tissue catabolism are independent risk factors for the presence of hepatic encephalopathy in patients with nonalcoholic cirrhosis.

Introduction

Hepatic encephalopathy (HE) is a frequent and severe complication of chronic liver disease, characterized by variable degrees of neuropsychiatric, neuropsychological, and neurological impairments. HE often starts with personality changes (e.g. euphoria or anxiety), cognitive impairment (e.g. attention deficit and memory dysfunction),¹ or bradykinesia.² In later stages, disturbances of intellectual function and consciousness are common.³

Reduced detoxification of neurotoxic substances, in particular ammonia, in the cirrhotic liver⁴ and subsequently alterations in several neurotransmitter systems⁵ and brain edema,⁶ are supposed to be major factors for the development of HE. Neurotransmitter systems affected by increased intracerebral concentrations of ammonia include the GABAergic,⁷ glutamatergic,⁸ and serotonergic systems.⁹ The liver, however, is not the only organ involved in ammonia metabolism.¹⁰ During hyperammonemia, other organs, including the kidneys^{11,12} and the skeletal muscles,¹³ detoxify ammonia via a temporary alternative pathway, the formation of glutamine from ammonia and

glutamate catalyzed by the enzyme glutamine synthase. In animal models of acute¹⁴ and chronic liver failure,¹⁵ hyperammonemia is associated with a rapid increase of glutamine synthetase activity in the skeletal muscle, resulting in an increase of the muscle's capacity to remove ammonia. In patients with cirrhosis, skeletal muscles may even metabolize more ammonia than the cirrhotic liver.¹³ These results suggest that muscle tissue, in part, compensates for the metabolic consequences of liver failure and thus plays an important role in the removal of blood-borne ammonia in hyperammonemia.

Chronic liver disease is commonly associated with malnutrition and hypermetabolism.^{16–20} Disorders of the protein metabolism induce skeletal muscle wasting, hypoalbuminemia, and an abnormal amino acid profile.²¹ Because of the important role of skeletal muscles in the detoxification of ammonia, we and others¹⁴ have hypothesized that malnutrition and hypermetabolism will be independently associated with the presence of HE. To test this hypothesis, we performed a retrospective, cross-sectional study on liver function, nutritional status, and resting energy expenditure in a large group of well-documented patients with nonalcoholic cirrhosis with and without HE.

Table 1 Parameters of liver function, nutritional status, and metabolism in hepatic encephalopathy (HE)

Parameter	Without HE	With HE grades 1–3	P-value
Age (years)	45 (17–63)	48 (16–67)	0.253
Albumin (g/L)	35 (21–57)	30 (16–46)	<0.001
AST (U/L)	43 (10–335)	40 (2–466)	0.969
ALT (U/L)	42 (4–261)	33 (6–1030)	0.138
Cholinesterase (kU/L)	1.9 (0.5–6.2)	1.2 (0.2–5.3)	<0.001
Transferrin ($\mu\text{mol/L}$)	57 (22–153)	43 (20–102)	<0.001
Prothrombin index (%) [†]	63 (15–100)	54 (10–100)	<0.001
Methionine ($\mu\text{mol/L}$)	60 (25–828)	72 (21–998)	0.002
Ammonia ($\mu\text{mol/L}$)	55 (17–202)	63 (20–245)	0.011
Bilirubin ($\mu\text{mol/L}$)	48 (5–434)	56 (7–984)	0.018
Body mass index (kg/m^2)	22.6 (17.5–28.4)	22.4 (14.5–36.3)	0.935
Fat free mass (% body mass)	75.6 (63.9–92.9)	74.9 (43.0–91.8)	0.834
Muscle mass (kg)	18.6 (9.3–34.2)	18.5 (9.8–31.9)	0.705
Respiratory quotient	0.78 (0.64–0.95)	0.78 (0.56–0.93)	0.867
Δ REE (%)	–6.2 (–21.3–56.8)	–0.7 (–27.8–32.5)	0.012

[†]The prothrombin index expresses the coagulation activity as a percentage of the activity of normal plasma. Δ REE denotes the difference between measured and predicted resting energy expenditure. The statistical threshold was set at $P < 0.004$ (after Bonferroni correction).

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Methods

Patients

We included 223 patients in this study (115 females, 108 males; median age, 47 years, range, 15–66 years). Patients were admitted to Hannover Medical School, Germany, as potential candidates for orthotopic liver transplantation. During a 2 to 3 week course, a broad spectrum of clinical and biochemical examinations were performed. At admission, extensive blood tests were performed, in part reported in Table 1. Also at admission, a comprehensive neurological examination was performed (see below).

Inclusion criteria for this study were (i) histologically proven cirrhosis; and (ii) either HE grade 0 (absence of overt HE) or HE grades 1–3. Exclusion criteria were (i) alcohol-toxic cirrhosis because toxic brain damage may interfere with the assessment of HE;²² and (ii) portosystemic shunt surgery. The etiology of cirrhosis included viral hepatitis (56%), biliary diseases (27%), and Budd–Chiari syndrome (3%). In 11% of the patients cryptogenic cirrhosis was diagnosed. On entrance all individuals were in a stable clinical state. According to the Child–Pugh classification,²³ 23% were in Child class A, 51% in B, and 26% in C. Seventy-two percent of all patients received diuretics (thiazide alone 2%, furosemide alone 3%, spironolactone alone 24%, spironolactone plus thiazide 12%, spironolactone plus furosemide 31%). Lactulose and/or neomycin were used by 129 patients (62%).

This study is part of a larger project on metabolic and nutritional parameters in cirrhotic patients scheduled for liver transplantation. Different aspects of this project have been published previously.^{19,20,24,25} All patients gave informed written consent to participate in this investigation, which was reviewed and approved by the Research Ethics Board of Hannover Medical School, Germany.

Neurological status

The diagnosis of HE was based on the results of a comprehensive neurological and neuropsychiatric examination at entrance,

performed by an experienced neurologist (KW). HE grade 1 was defined by psychomotor slowing, euphoria or depression, decreased attention, presence of cerebellar or extrapyramidal symptoms, and irritability and reversal of sleep rhythm; and HE grade 2 by disorientation, lethargy, and bizarre behavior.³ No evidence for overt HE was found in 85 patients. HE grade 1 was diagnosed in 123 patients, HE grade 2 in nine patients, and HE grade 3 in six patients.

Nutritional status

The body mass index (BMI) was calculated ($\text{BMI} = \text{body mass [kg]} / \text{height [m]}^2$). The thickness of the triceps skinfold was determined using a Lange caliper (Lennartz, Hamburg, Germany).²⁶ The arm muscle area was calculated from the midarm circumference and the triceps skinfold thickness and corrected for bone area using the equation of Heymsfield *et al.*²⁷ Bioelectrical impedance analysis was employed to assess fat mass and fat-free mass using a radio frequency current (800 μA , 50 kHz) between four electrodes attached to the dominant hand and the ipsilateral foot (BIA 101; RJL Systems, Detroit, MI, USA) as described previously.¹⁹ Muscle mass was calculated from arm muscle area.²⁷

Metabolic status

Concentrations of biochemical parameters and activities of liver enzymes were determined in a venous blood sample after an overnight fast by standard methods.²⁵ Indirect calorimetry was performed after an overnight fast to determine the respiratory quotient (RQ) and the resting energy expenditure (REE) using the ventilated hood technique (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki, Finland) as described previously.¹⁸ REE was expressed as the difference between the predicted and the measured REE (termed Δ REE). For each participant, REE was predicted based on weight, sex, and age using the formulas developed by Müller *et al.*¹⁷

Statistical analysis

All statistical analyses were performed using the statistical package R for Mac OS X (<http://www.r-project.org/>).²⁸ As most variables were not normally distributed, data were presented as median and range (minimum–maximum). The Mann–Whitney *U*-test was used for the comparison of both groups. Bonferroni correction was performed to account for 15 comparisons (Table 1). *P*-values < 0.004 were regarded as significant ($\alpha = 0.05/15 = 0.0033$). Multiple linear regression analysis was performed using the method of manual backward elimination. The least significant variable was eliminated from the linear model until only significant variables remained.

Results

Compared to patients without HE, patients with HE grades 1–3 had significantly lower concentrations of albumin and transferrin, decreased activities of cholinesterase, a lower prothrombin index, as well as increased concentrations of methionine (Table 1). No significant differences between groups were found for aspartate transaminase and alanine transaminase. No significant differences were seen between individuals with and without HE regarding nutritional status, RQ, or the difference between the predicted and measured REE (Table 1). Ammonia was not significantly correlated with the arm muscle area or the fat-free mass (data not shown).

Linear multiple regression analysis was performed with the presence of HE as a dependent variable and the parameters presented in Table 1 as independent variables. The variables cholinesterase ($F = 17.0$, $P < 0.001$), transferrin ($F = 11.0$, $P = 0.001$), and ammonia ($F = 4.2$, $P = 0.043$) best explained the presence of HE. Other parameters of liver injury and function (such as transaminase activities, albumin concentration, and bilirubin concentrations), nutritional status (such as the BMI and the muscle mass), or metabolic variables (such as the difference between predicted and measured REE) did not contribute to the regression model.

Discussion

This study on 223 patients with cirrhosis does not provide evidence that nutritional status, especially fat free and muscle mass, or energy expenditure are independent risk factors for the presence of HE.

Malnutrition and hypermetabolism

Malnutrition and tissue catabolism are common complications of chronic liver disease^{16,17,29} and predictors of an adverse outcome.²⁰ Although patients with cirrhosis are not homogenous regarding their nutritional status and metabolism, most of them are characterized by increased lipolysis, elevated protein turnover, and reduced body cell mass.²⁹ Hypermetabolism is often associated with an impaired nutritional status.¹⁷ As skeletal muscle plays a major role in metabolizing arterial ammonia,³⁰ muscle wasting may contribute to the accumulation of neurotoxins in patients with cirrhosis. Thus, malnutrition and, indirectly, hypermetabolism

might be independent risk factors for the presence of HE.³¹ An earlier investigation of our group on the effects of malnutrition in cirrhosis, however, did not find an increased incidence of overt HE in patients with reduced nutritional status.³² In agreement with these results, the data of the present study do not support an association between malnutrition or hypermetabolism and HE. Muscle mass assessed by anthropometric measurements,²⁷ fat mass and fat free mass assessed by BIA,³³ and REE³⁴ were not significantly different between patients with and without HE (Table 1). Corroborating these findings, a multiple regression analysis identified predictors for the presence of HE. After elimination of non-significant variables, the activity of cholinesterase and the concentrations of transferrin and ammonia best explained the presence of HE. The tested metabolic and nutritional variables, in contrast, were not significant.

Animal¹⁵ and human¹³ studies have demonstrated that the skeletal muscles of patients with liver disease increase their capacity to metabolize ammonia. In the present study, however, we did not find evidence that increased muscle mass was associated with lower concentrations of ammonia in patients with cirrhosis. Taken together, these findings do not support our initial hypothesis that malnutrition and hypermetabolism are independently associated with the presence of HE.

Liver function

The concentrations of serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) are sensitive indicators of liver cell injury, particularly active inflammation. In the present study, AST and ALT levels were not significantly different between patients with and without HE. Reduced hepatic protein synthesis is a key manifestation of cirrhosis, reflected by hypoalbuminemia,²¹ coagulation disorders,³⁵ and an abnormal amino acid profile.³⁶ In cirrhosis, the synthesis of several key proteins is reduced, including albumin, cholinesterase, transferrin, and blood coagulation factors. Albumin is the plasma protein with the highest concentration and is synthesized exclusively by the liver. Cholinesterase, catalyzing the hydrolysis of acetylcholine, and transferrin, the iron transport protein, are also synthesized in the liver. In addition, all coagulation proteins, except von Willebrand factor and factor VIIIc, are produced primarily in the liver. The prothrombin time (in the present study expressed as a percentage of the coagulation activity of normal plasma) is a widely used test to diagnose coagulation defects in patients with cirrhosis and reflects reduced synthesis of not only factor II (prothrombin), but also factors V, VII, and X. Methionine is an essential amino acid that serves as a methyl donor in transmethylation processes and as the main source of sulfur groups. Increased fasting concentrations of methionine, due to reduced hepatic synthesis of the main enzymes involved in methionine metabolism, are frequently found in patients with cirrhosis. Here we found significant differences between patients with and without HE regarding parameters of liver synthesis, in particular the activity of cholinesterase, the concentrations of albumin and transferrin, as well as the prothrombin index (Table 1).

Impaired liver function, however, is presumably an epiphenomenon of the biochemical changes that result in the development of HE. Several lines of evidence suggest that the decreased

detoxification of neurotoxic substances, in particular ammonia, and the accumulation of these neurotoxins in certain regions of the brain play a major role in the development of HE.^{4,37,38}

Limitations of the study

The present study is a cross-sectional study in which the diagnosis of HE is based on a comprehensive neurological examination, performed at the beginning of a 2 to 3 week clinical evaluation of potential candidates for liver transplantation. As the neurological and neuropsychological symptoms of patients with HE may change over time, this single neurological examination might not entirely represent the overall status in every single patient. However, all examinations were performed by a single, experienced neurologist (KW) who guaranteed a high consistency of diagnoses. In addition, only patients in a stable clinical condition were admitted to the pretransplantation evaluation. In these patients, quick changes of HE symptoms are less likely.

The assessment of muscle mass by anthropometric measurements^{39,40} and of body composition by BIA⁴¹ has been frequently used to study patients with cirrhosis. The precision of body composition analyses by BIA has been questioned in case of significant amounts of ascites.⁴¹ Studies by our group, however, demonstrated that even several liters of ascites have only minor effects on BIA results because the trunk contributes to no more than 11% of the whole-body resistance. Thus, we could show a high correlation between body cell mass assessed by BIA and by total body potassium counting even in patients with ascites.^{17,24,32}

In summary, the data presented in this investigation do not support the hypothesis that tissue catabolism or malnutrition, especially reduced muscle mass, are independent risk factors for the presence of HE in patients with nonalcoholic cirrhosis.

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