

Reviews

Hepatic encephalopathy as a complication of liver disease

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INTRODUCTION

Hepatic encephalopathy (HE) is a frequent complication of chronic liver disease. It is defined as a characteristic functional and reversible alteration of the mental state, due to impaired liver function and/or increased portosystemic shunting.

In the brain of HE patients, neurons appear morphologically normal, but astrocytes show signs of Alzheimer type II degeneration, i.e. nuclear enlargement, peripheral margination of chromatin and prominent nucleoli. Ammonia is generally considered to play a central role in the pathophysiology of HE^[1]. In HE, selective alterations of blood-brain barrier permeability, changes in cerebral energy metabolism, an increased GABA-ergic tone, changes in neurotransmitter systems and alterations of gene expression. e.g. of monoamine oxidase, peripheral-type benzodiazepine receptor (PTBR) and neuronal NO synthase are found (reviewed in^[1-10]). The reversibility of HE symptoms and the reason for its precipitation by a variety of different factors has not been sufficiently explained yet (Table 1). Central insights into the etiology of HE have arisen from recent *in vitro* work with astrocytes. Astrocytes are important constituents of the blood-brain barrier, and uptake of substances from the blood into the brain is achieved by transastrocytic transport. Astrocytes communicate directly with neurons^[11], regulate neurotransmitter processing and ionic milieu and provide substrates for neurons^[12,13]. In brain, astrocytes are the only cells containing glutamine synthetase^[14] and represent the major site of cerebral ammonia detoxification. Upon exposure to ammonia, cultured astrocytes develop Alzheimer type II changes. These findings prompted the idea

that HE is a disorder of glial cells with a consecutive neuronal dysfunction^[7,15,16].

Although the symptoms of HE in *acute or chronic* liver failure are different, there are good reasons to assume that the pathophysiology of both conditions is similar, but may involve different kinetics. In acute liver failure, astrocytes swell and brain edema develops^[17]. HE in chronic liver disease is not accompanied by clinical signs of cerebral edema, but evidence for increased cell hydration has been given, as described later. A disturbance of astrocyte hydration is apparently a major pathophysiologic event in both forms.

MRS FINDINGS IN HE

MR-spectroscopy (H-MRS) studies in human brain initiated the idea that a disturbance of astrocyte cell volume homeostasis could be decisive for development of chronic HE^[18-20]. ¹H-MRS can be used to study metabolic abnormalities in the human brain *in vivo* and allows a myo-inositol signal to be picked up, which represents an osmosensitive myo-inositol pool^[18] of predominantly glial origin^[21]. Myo-inositol is an organic osmolyte in astrocytes^[22-24]. Such organic osmolytes play a decisive role in cell volume regulation: upon shrinkage, they accumulate inside the cells, in response to cell swelling they can be released from the cells via osmoregulated membrane channels^[25,26]. Consistently, *in vivo* ¹H-MRS studies on the brain from cirrhotic patients with HE show a depletion of myo-inositol which is accompanied by an increase in the glutamine/glutamate signal^[18,19,27-30], as shown in Figure 1. On the other hand, in cirrhotic patients, the implantation of transjugular intrahepatic-stent-shunt (TIPS) may lead to an aggravation of ¹H-MRS changes (Figure 2)^[18] and a normalization of MRS findings after transplantation has been described^[30]. *In vitro* studies from the rat have shown similar alterations after portocaval shunting^[28]. There is a good correlation between the extent of these ¹H-MRS changes and the clinical severity of HE^[18,19,29,30]. An increased glutamine/glutamate signal, together with a decrease of inositol signal, is observed in patients after TIPS implantation^[18], as depicted in Figure 2. A high sensitivity and specificity of the myo-inositol signal for the diagnosis of HE cirrhotics has been reported^[29,30], but these changes have also been reported in asymptomatic stages of hepatic encephalopathy^[18,19,29,30].

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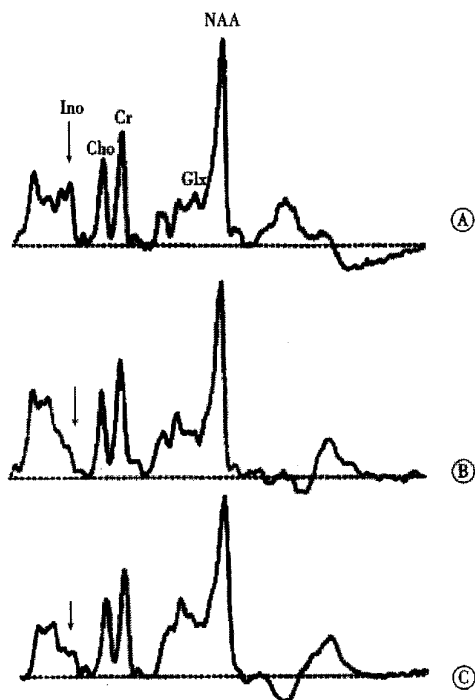


Figure 1 Parietal ^1H -MNR spectra from (A) a healthy person, patients with posthepatic cirrhosis and latent (subclinical) HE (B) and manifest grade I-II HE (C). An increase in the glutamine/glutamate signal (Glx) and a decrease of the inositol signal (Ino) is observed. Further abbreviations: Cho, choline; Cr, creatine; N-acetylaspartate (NAA)^[18].

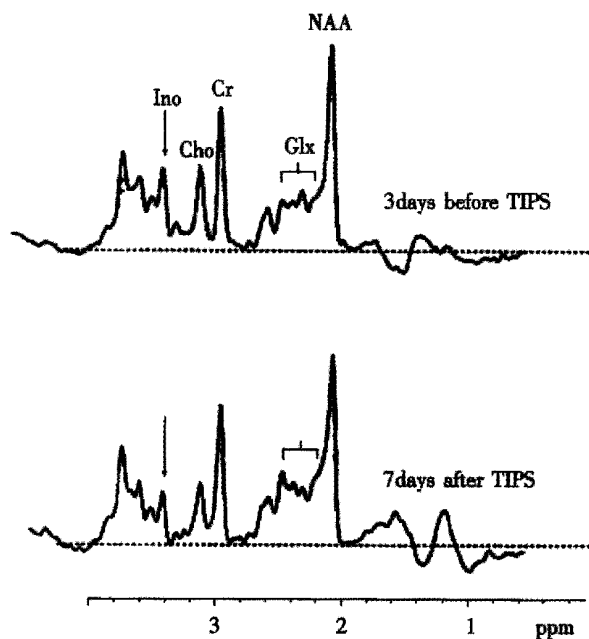


Figure 2 Parietal ^1H -MNR spectra from a 47-year-old patient with alcoholic cirrhosis 3 days before and 7 days after implantation of TIPS, showing an increased Glx signal and a decreased Ino signal. For abbreviations see Figure 1^[18].

IMPAIRED CELL VOLUME HOMEOSTASIS IN HE AND FUNCTIONAL CONSEQUENCES FOR ASTROCYTES

The MRS findings in HE make an impaired cell volume homeostasis in brain likely and suggest that cellular non-cytotoxic edema^[31] is present in hepatic encephalopathy. This edema is the result of an osmotically active intracellular accumulation of glutamine in response to hyperammonemia and a consecutive depletion of releasable myo-inositol and probably other osmolytes. Astrocytes swell in presence of ammonia^[7,32]. Ammonia induces brain edema and intracranial hypertension in the portocaval shunted rat *in vivo* in a largely methionine sulfoximine-sensitive way^[33]. PET studies with ^{15}N -ammonia on human brain from encephalopathic patients showed an increased cerebral metabolic rate for ammonia, suggestive of enhanced cerebral uptake of ammonia in HE and a stimulation of glutamine synthesis^[34]. Astrocyte swelling also occurs *in vitro* under the influence of hyponatremia^[35,36], some neurotransmitters^[35,37], TNF- α ^[38] and benzodiazepines^[7,37]. Apart from myo-inositol, recent data suggest that other organic osmolytes, such as taurine^[21,22] and α -glycerophosphorylcholine^[22,39], are depleted in order to counteract astrocyte swelling in HE. Small increases in astrocyte water content, as may occur in HE, could already have important functional consequences despite the absence of clinically overt increased intracranial pressure. Cell hydration is an independent signal which regulates cell function and gene expression, reviewed in^[40-43] and a variety of different osmosignalling pathways linking cell hydration and cell function have been identified^[44]. Extensive work from this laboratory has described the impact of cell hydration on cell function, cytoskeleton and gene expression^[45], mainly in liver. In brain, cell hydration is also considered a key trigger of cell function. Swelling of astrocytes in culture activates via phosphatidylinositol-3-kinase extracellular regulated protein kinases (Erks)^[36], i.e. members of the MAP kinase family with multiple functions, elevates intracellular calcium concentrations^[46] and upregulates the peripheral type benzodiazepine receptor (PBR, reviewed in^[47]) at the level of agonist binding^[48] and mRNA (D. Häussinger and R. Fischer, unpublished results). Further, astrocyte swelling increases the pH in endocytotic vesicles^[49] in an Erk-dependent osmosignalling pathway (R. Fischer and D. Häussinger). Several key findings in HE can thus partially be explained by an increase of astrocyte hydration. The endosomal alkalization following astrocyte swelling could affect receptor densities and neurotransmitter processing and swelling-induced changes of the activity of plasma membrane transporters may underlie the selective changes in "blood-brain barrier" permeability of HE. Cell swelling stimulates glycogen synthesis and inhibits

glycogenolysis^[45,50] and the increased deposition of glycogen in astrocytes in animal models of chronic HE^[7] may reside on cell swelling. Astrocyte swelling leads to an increased expression of PBR and augments the synthesis of neurosteroids, which are potent modulators of neuronal GABA_A activity^[7]. Thus the interaction between astrocyte swelling, PBR expression and increased neurosteroid synthesis may explain the increased GABA_A-ergic tone in HE^[9,51].

Table 1 Precipitating factors of HE

·Gastrointestinal or tissue bleeding
·Protein overload
·Sepsis
·Infection
·Catabolism
·Azotemia
·Acidosis
·Sedatives
·Diuretics
·Portocaval shunting (TIPS or surgical)
·Constipation

ASTROCYTE SWELLING AS AN INTEGRATIVE SIGNAL OF HE

An increase in astrocyte hydration, i.e. a low-grade cerebral edema, is a major pathogenetic event in the development of HE and induces a profound alteration of astrocyte function^[20]. Altered astrocyte function may eventually lead to a disturbance of glioneuronal communication and present as the clinical syndrome of HE. Bleeding, infection, sedatives or electrolyte imbalance may precipitate HE in the cirrhotic patient (Table 1). Apart from ammonia, an increase of astrocyte hydration is also induced by hyponatremia, benzodiazepines and cytokines. Multiple factors could thus obviously result in a common pathogenetic endpoint, i.e. glial swelling with its functional consequences. The osmolyte systems for counteraction of cell swelling are intact in non-cirrhotics and the precipitating conditions are well tolerated. In cirrhosis, however, organic osmolyte depletion is observed in order to compensate for glial glutamine accumulation and further challenges of cell volume can hardly be counteracted. The ¹H-MRS findings in nonencephalopathic cirrhotics could represent an early stage of a largely compensated disturbance of astrocyte volume homeostasis, where only few consequences yet for astrocyte hydration and function are observed. In response to HE-precipitating factors, a dysequilibrium of astrocyte volume results and hydration-dependent alterations of glial function will become clinically apparent. This unstable situation may explain the rapid kinetics of HE episodes and why severe brain edema with fatal

outcome can occasionally develop in endstage cirrhotics^[52].

DIAGNOSIS AND GRADING OF HE

Usually, HE is due to extensive porto-venous collateral shunting together with a decrease in hepatic function, resulting in increased cerebral ammonia load and diminished ammonia detoxification. Fulminant hepatic failure (FHF) means acute liver failure accompanied by hepatic encephalopathy. Sometimes, HE may be the result of metastatic liver disease^[53], portal vein thrombosis^[54], congestive heart failure^[55] or constrictive pericarditis^[56]. Even in the absence of overt liver disease, portosystemic shunting can induce HE^[57], reviewed in^[58]. Pre-TIPS encephalopathy is an important predictor of death during follow-up after placement of TIPS^[59].

The symptoms of encephalopathy in all of these circumstances are characteristic, but unspecific. They range from subtle neuropsychologic derangements to coma. The diagnosis is made by the recognition of an appropriate hepatic disorder and the presence of encephalopathy in the absence of any other likely non-hepatic causes.

Foetor hepaticus and an increased blood ammonia concentration may contribute to the diagnosis.

For study purposes, an exact quantification of HE is required and defined by the West Haven Criteria^[60,61]. The PSE index comprises the mental state, asterixis, number connection test results, electroencephalography and arterial blood ammonia concentrations. Subclinical hepatic encephalopathy (SHE) can only be diagnosed by subtle neuropsychological testing^[62]. Preliminary results show that hepatic retinopathy, as detected by neurophysiological testing, very sensitively reflects the degree of HE (G. Kircheis and D. H-ussinger, unpublished observation) and responds to HE therapy. At the bedside, HE grade I is characterized by desorientation, whereas grade II HE shows spontaneous or inducible asterixis. In HE grade III, the patient is somnolent, grossly desoriented and precomatose, whereas grade IV represents coma.

THERAPY OF HE

Treatment of HE focusses on the pathogenetic events present in the individual patient. The most important therapeutic approach is to identify the precipitating factors (Table 1) and to treat them vigorously. The required measures for precipitating factors are: therapy of GI bleeding together with bowel cleaning by lactulose, antibiotic treatment of concurrent infection, protein restriction, parenteral nutrition by an i.v. line and discontinuation of any diuretic therapy or sedatives. In patients with deterioration of HE after TIPS implantation, a

reduction stent may sometimes be necessary^[63,64]. Apart from treatment of precipitating factors, additional therapeutic measures interfere with ammonia generation/disposal. In placebo-controlled studies, conflicting data exist on the efficacy of most therapeutic substances. Administration of lactulose is considered as gold standard in the treatment of HE, even for subclinical encephalopathy^[65], but the beneficial effect of lactulose has not been precisely shown versus placebo, reviewed in^[66]. In a recent randomized crossover trial, plasma ammonia and nitrogen balance were significantly better on vegetable protein diet as compared to an isonitrogenous animal protein diet^[67]. Neomycin is equally effective as lactulose, but a placebo-controlled trial on neomycin showed little effectivity^[68]. Intravenous ornithine aspartate has proven its effectivity^[69,70] and the benefit of orally administered ornithine aspartate is currently evaluated. Most studies on oral branched-chain amino acids (BCAA) showed clinical improvement of latent or low-grade HE and of protein tolerance^[71], but studies on i.v. BCAA have not led yet to definite results. Benzodiazepine receptor antagonists have been reported to be of value in HE^[72,73] but, to date with only modest success in some patients. In experimental cirrhosis, zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity^[74] and a positive effect of zinc supplementation has also been shown in clinically overt HE^[75].

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