TREATMENT OF HEPATIC ENCEPHALOPATHY

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Abstract: *Hepatic encephalopathy is a major complication due to severe liver injury which has to be diagnosed from its early stages to initiate promptly specific treatment measures, including identification and treatment of precipitating factors, decrease of serum ammonia, improving liver function and removal of toxic cerebral effects.*

Keywords: *hepatic encephalopathy, precipitating factors, serum ammonia*

Rezumat: *Encefalopatia hepatică reprezintă o complicaţie redutabilă ce apare în afectări profunde ale ficatului, care trebuie recunoscută încă din stadii incipiente în vederea instituirii unui tratament precoce. Acesta vizează identificarea şi tratarea factorilor precipitanţi, reducerea amoniacului seric, îmbunătăţirea funcţiei hepatice şi îndepărtarea efectelor nocive cerebrale.*

Cuvinte cheie: *encefalopatie hepatică, factori precipitanţi, amoniac seric*

INTRODUCTION

The hepatic encephalopathy (HE), also known under the name of portosystemic encephalopathy (PSE), is a complex potentially-reversible neuropsychiatric syndrome, that appears in severe liver diseases and it is characterized by behaviour, personality and cognitive function disturbances, asterixis, hepatic foetor and electroencephalogram modifications.There are two types of HE: the *acute HE*, potentially-reversible, with clear clinical manifestations, that appears in acute hepatic insufficiency, and the chronic HE, a progressive, subclinical form, that appears in chronic hepatic diseases.

Early diagnosis and prompt treatment initiation are essential for this pathology, and the treatment needs to achieve four main objectives:

1. recognition and elimination of precipitating factors,
2. lowering serum ammonia levels via cutting down it's production and decreasing protein intestinal absorption,
3. upgrading the hepatic functions,
4. removal of the cerebral toxic side-effects.

1. The early recognition of the **precipitating factors** is essential (1,2.3) because the HE initiated by these factors are reversible by eliminating them, leading to a symptoms and signs fading out. That is why we are going to specify the most frequent and important precipitating factors: hyperproteic diet, rebel constipation, infection (spontaneous bacterial peritonitis and urinary tract infection), gastrointestinal haemorrhage, hyperazotemia, hypokalemia, systemic alkalosis, acute viral or alcoholic hepatitis on a cirrhotic liver. Less common factors are: dehydration (high-volume paracentesis, diuretic excess, postlaxative osmotic diarrhoea, decreased fluid intake), hypotension (gastrointestinal bleeding, peripheral vasodilation), hypoxemia, anemia, hypoglycemia, sedatives, hypnotic-anesthetics, blood transfusion. Upper digestive hemorrhage through rupture of esophageal varices is a life threatening complication of liver cirrhosis (the main cause of HE (1,2,3)) and should be stopped immediately (drugs, endoscopy or surgery - ! attention to benzodiazepines and anaesthetics) to restore hemodynamic parameters (crystalloid or macromolecular solutions, red blood cell mass), ensuring good oxygenation (oxygen) and it is mandatory to insert a nasogastric tube.

2. **Decreasing serum ammonia levels** is carried out simultaneously on several planes:

a. ***reducing protein intake:*** protein intake in severe forms is initially zero, in a few days there are allowed 20 g / day and we can gradually increase with 10 g / day to a maximum of 50-60 g / day. In the moderate forms the protein intake can start at 20 g / day and in chronic fruste forms we can allow 50-60 g / day. The preferred proteins are of plant origin. Still some studies say that we can maintain a normal protein diet as long as there is an equal distribution of the protein intake during the day.(4,5) Enteral or parenteral nutrition with branched-chain aminoacids (BCAA 0.24 g / kg / day orally, 15 days) is another therapeutic means [6].

b. ***removing protein and ammonia from the gut:*** is achieved by using *lactulosis* and *lactitol*[7.8], two nonabsorbale disaccharides providing osmotic laxative bowel emptying. They absorb ammonia and remove it, and by lowering the colonic pH they reduce bacterial ammoniogenesis. The recommended dose ranges from 50-150 ml lactulosis / day, respectively 0,3-0,5 g lactitol / kg / day, but it is important to achieve the objective of 2-4 stools per day, avoiding the installation of diarrhoea. For the

same laxative effect it is recommended to give lactose to those with lactase deficiency.(2)

The important role of *antibiotics* usage, with a spectrum that covers ammoniagenic colon bacterias that also produce benzodiazepine-like ligands is well established in the treatment of HE (1,2,3,9): *rifaximine* (3 x 400 mg / day), *ampicillin* (4 x 1-2 g / day), *neomycin* (4 x 1 g / day), *metronidazole* (4 x 200 mg / day), *vancomycin* (2 g / day - recommended in HE resistant to lactulosis). The duration of the therapy depends on the severity of HE. However, studies have not yet been able to determine whether it is more effective the monotherapy either with the disaccharides laxatives or with antibiotics or the mixed treatment, but they all stressed the significant lower cost of lactulosis.

As adjuvants there can be administered *probiotic yogurt*s (Lactobacillus spp) or *Enterococcus faecium* (SF68) (10.11). We remind the *nasogastric tube* indispensable in gastrointestinal bleedings.

c. ***neutralization and elimination of serum ammonia***: can be achieved by using *phenylacetate sodium* (2-10 g / day), *phenylbutirate sodium* or *benzoate sodium* (2x5 mg / day) that are as effective as lactulosis [3]. With the same purpose we can use *L-ornithine phenylacetate* or *LOLA* (L-ornithine-L-carnitine) with the recommended dose of 9-12 g / day in a 4-8 hours endovenous infusion or orally for 7 days, but they work only in less severe forms.(3,12)

Zinc supplementation (zinc sulfate 600 mg / day per os, 3 months) hastens the formation of urea from aminoacids and ammonia(3).

3. ***Improving liver function*** (1,2,3) can be made with adjuvant treatments with *vitamins*, *arginine sorbitol*, *aspatofort* (2-4 g / day) infusion of glucose 5% / 10% that bring energy and metabolic support. Also, in case of exacerbation of chronic hepatitis and autoimmune hepatitis, *corticosteroid* administration iv or orally is necessary and can have spectacular effects. The *ortotopic liver transplantation*, the only radical and effective therapeutic solution is the last option on the list, at least in Romania, where the concept of organ donation is not well implemented.

4. ***Removal of the cerebral toxic side-effects*** .

The benzodiazepine-like ligands hypothesis, that bind to the GABA receptors in the CNS, supports the administration of *flumazenil* (benzodiazepines antagonist-1-2 mg iv) in HE (1,2,3) Its administration is justified in fighting the effects of exogenous benzodiazepines used to sedate patients before the endoscopy. *Naloxone* (opiate antagonist) can be used to combat the effects of anesthetic agents.

Studies related to the administration of *L-dopa* and *bromocriptine* that improve the dopaminergic neurotransmision (its reduction would have a role in the pathogenesis of HE), have shown beneficial effects.(1,2,3)

Removal or prevention of manganese deposits in the basal ganglia (globus palidus) can be done with *edetate disodium monocalcium* or *para-aminosalicilic acid* with chelating effect of manganese.(3)

In the severe forms of HE we need to switch to advanced vital support with mechanical ventilation of the patient, sedation with Fentanyl, treatment of cerebral edema with Mannitol 0.5 g / kg administered in 10 minutes and endovenous infusions with acetilcisteyn which improves cerebral blood flow and the oxygenation rate. We can see similar effects after the administration of epoprostenol (prostaglandin I_2). Glycemia monitorisation is recommended every 4 hours to avoid hypoglycemia - a fatal complication.(3)

Finally it is important to periodically estimate the effectiveness of treatment by assessing the cognitive function and mental status, the flapping tremor, the serum levels of ammonia, the electroencephalogram, the tests of memory and the Reitan test and subsequently maintain or adjust it.

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