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UNDERSTANDING THE DISEASE

Understanding hepatic encephalopathy

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Hepatic encephalopathy (HE) is defined as a neurological or a neuropsychological complication caused by liver disease or portosystemic shunting. The clinical spectrum is highly variable ranging from mild neuropsychological disturbances to coma [1]. Depending upon the underlying liver disease, HE is classified into three types: type A, secondary to acute liver failure (ALF); type B, secondary to portosystemic shunting; and type C, secondary to cirrhosis in the presence or not of shunting [2]. The most recent human and animal data confirmed the previously supposed role of hyperammonemia, but also outlines the role of associated factors like inflammation in the development of HE (Fig. 1).

The main source of ammonia (NH_4^+) in the portal system has long be thought to be intestinal bacterial production explaining the use of non-absorbable disaccharides (e.g., lactulose) and non-absorbable antibiotics (e.g., rifaximin) [3]. Recent data shows, however, that the main source is glutamine catabolism by glutaminase in the gut [3]. Thus, polymorphisms in the gene coding for glutaminase predicts the development of HE in cirrhotic patients [4]. In the systemic circulation, NH_4^+ is increased because of reduced urea cycle enzyme activity that occurs in liver failure and/or portosystemic shunting. This increased amount of NH_4^+ is converted to glutamine in muscle cells and in astrocytes, through the action of glutamine synthetase [3, 5]. These aforementioned abnormalities both explain why sarcopenia represents a factor that makes patients susceptible to develop HE in cirrhosis and the development of brain edema in patients with ALF and cirrhosis. Only recently has directly targeting hyperammonemia by using ammonia-lowering agents been proposed (e.g., glycerol phenylbutyrate, L-ornithine-L-aspartate). According to its osmotic potential, the acute intracytoplasmic increase of glutamine in ALF is responsible for cytotoxic edema affecting the astrocytes and for vasogenic edema when the blood–brain barrier (BBB) is altered [3, 5]. In cirrhosis, the glutamine increase is gradual and astrocytes respond by progressively extruding intracytoplasmic myoinositol and taurine to try and maintain osmotic equilibrium. This largely explains why brain edema is rarely present in cirrhosis and/or in acute-on-chronic liver failure (ACLF) [6, 7]. In neurons, glutamine is deaminated into glutamate, the most important excitatory neurotransmitter in the brain, that stimulates neurons [8]. This could account for anxious behavior, agitation, or seizures in ALF. In contrast, in cirrhosis, compensatory mechanisms are responsible for a decreased expression of both glutamate carriers (GLT-1) and glutamate post-synaptic receptors that explains slowing, sleepiness, and altered consciousness.

Amino acid imbalance has been hypothesized to participate in HE physiopathology [5, 9]. Cerebral levels of aromatic amino acids (AAA) are increased as a result of altered liver function and increased amount of free tryptophan due to hypoalbuminemia but also to altered transport through the BBB. As a consequence, there is an imbalance in the synthesis of dopamine, norepinephrine, serotonin and the "false neurotransmitters" octopamine or tyramine [3, 5, 8]. Other pathophysiological mechanisms such as cerebral energy failure associated with hyperammonemia, altered immune responses, reduced blood flow, mitochondrial dysfunction, and inhibition of alpha-ketoglutarate dehydrogenase, a rate-limiting tricarboxylic acid cycle enzyme, have been described [9].

Whereas NH_4^+ is not directly correlated with neurological status, several studies demonstrated a good correlation with the presence of systemic inflammatory response syndrome (SIRS) and the blood amount of TNF-alpha or IL-6 [10]. Sepsis and systemic inflammation are a hallmark of the severity of cirrhosis, and infection is a

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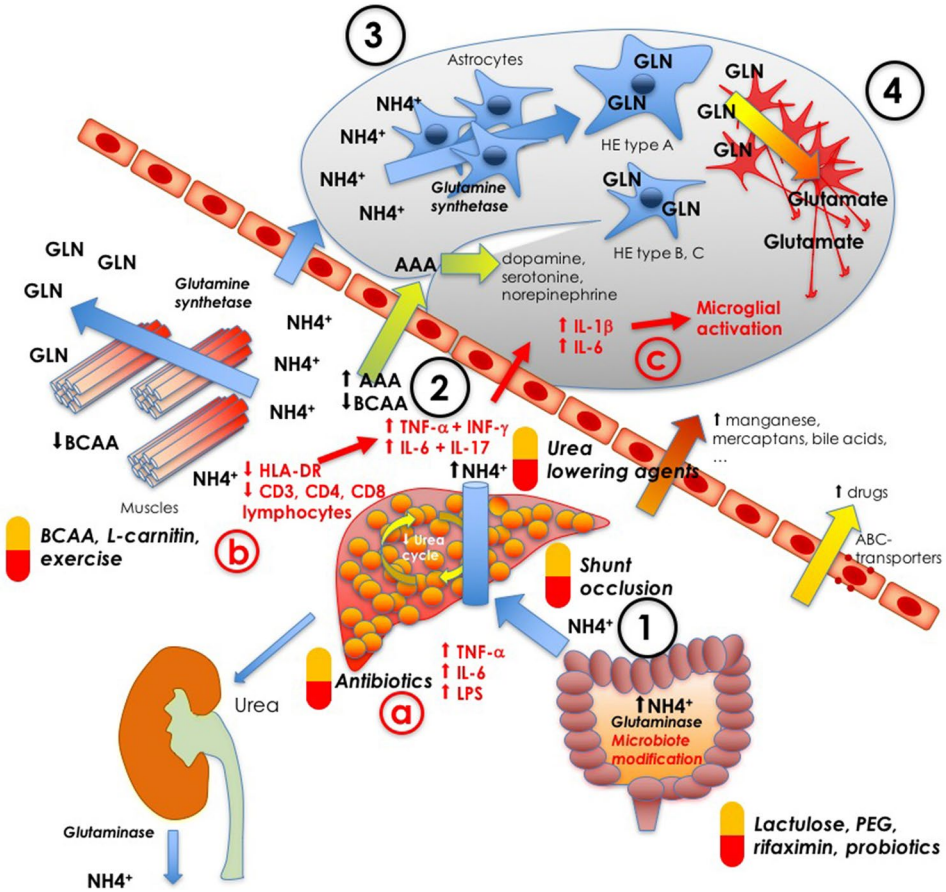

Fig. 1 Hepatic encephalopathy physiopathology hallmarks: ammonia (*1*, *2*, *3*, and *4*) and inflammation (*a*, *b*, and *c*) are the main actors. *1* As opposed to previous theories, the main source of NH_4^+ in the portal circulation is intestinal catabolism of glutamine. *2* Once increased in the portal circulation, NH_4^+ increases in the systemic circulation as a result of liver failure (reduced activity of urea cycle enzymes) and/or portosystemic shunting. *3* In the case of liver failure, NH_4^+ detoxification into glutamine through glutamine synthetase is only possible in the muscle cells and the astrocytes. In muscles cells, this reaction requires BCAA, which are decreased in cirrhosis. In astrocytes, the rapid increase in glutamine explains the occurrence of cytotoxic edema seen in the astrocytes through its osmotic potential. In more progressive disease, osmotic components, myoinositol and taurine, are extruded outside the cytoplasm to counterbalance the glutamine increase to try and prevent astrocytic edema. *4* The observed neuronal effects may vary; hyperstimulation and seizures may be due to accumulation of glutamate in the synaptic cleft; coma due to increased GABA in the brain; psychomotor disturbance due to other neurotransmitters. *a* As a result of modification of the gut microbiota, intestinal barrier function is altered and bacterial translocation abnormally increased. This leads to an increase of proinflammatory cytokines in the portal circulation. *b* Acquired cellular immune depression related to liver disease further favors proinflammatory cytokine production. *c* Systemic inflammation induces an alteration of blood–brain barrier permeability, and proinflammatory cytokines, especially IL-1β and IL-6, activate both astrocytes and microglial cells. Several of these steps can be worsened by hyperammonemia, as shown in vitro on cell cultures or in vivo in animal models. Other abnormalities have been described in HE physiopathology. Among them, accumulation of several substances such as increased AAA levels, increased GABA tone through benzodiazepine-like components or neurosteroids. Recent studies implicated drug accumulation in the cerebrospinal fluid as contributing to the physiopathology of HE. Different treatment strategies that have been validated or proposed in the treatment of HE are preceded by the *pill icon*. *AAA* aromatic amino acids, *ABC transporters* ATP-binding cassette transporters, *BCAA* branched-chain amino acids, *CD* cluster of differentiation, *GABA* gamma-aminobutyric acid, *GLN* glutamine, *HE* hepatic encephalopathy, *HLA-DR* human leukocyte antigen–antigen D related, *IFN* interferon, *IL* interleukine, *LPS* lipopolysaccharide, NH_4^+ ammonia, *TNF* tumor necrosis factor

classical triggering event of HE [11]. Outside the field of cirrhosis, encephalopathy related to sepsis has been described. Modification of the intestinal microbiota is emerging as a major factor associated with HE [5, 12]. It modulation has been proposed to explain the effect of lactulose and rifaximin with conflicting results. More recently, fecal transplantation has been proposed as a therapeutic strategy in HE. Liver failure is associated with altered intestinal barrier function, which is responsible for bacterial translocation and activation of the innate immune system. Nevertheless, this innate immune response is altered in liver failure as defined by altered

neutrophil phagocytic capacity, reduced reticuloendothelial system, and reduced hepatic synthesis of antimicrobial proteins [13]. ACLF is characterized by upregulation of proinflammatory cytokines (IL-1, IL-6, IL-17, TNF-alpha, IFN-gamma) compared to stable cirrhotic patients [14]. In the brain of HE patients, astrocytes and microglial cells respond to systemic inflammation by producing IL-1beta and IL-6 that stimulate adhesion of neutrophils and their transendothelial migration through the BBB, and the release of chemokines, proteases, and reactive oxygene species [5]. As a result, microglial cells present an activated phenotype. Current data suggest that the brain of patients with cirrhosis are sensitized to the effect of systemic inflammation and infection. Therefore, prompt treatment of any infection is an important therapeutic intervention. Note that anti-inflammatory treatments, i.e., indomethacin or ibuprofen, blocking microglial activation, are able to prevent both neurocognitive symptoms and brain edema in several animal models of HE [10].

Apart from hyperammonemia and inflammation, other factors are suspected to be involved in the physiopathology of HE. Thus, neurotransmission is largely impaired in HE, either as a consequence, as previously discussed for glutamate, dopamine, and serotonin, or as a cause, leading to increased intracerebral levels of benzodiazepine-like compounds or neurosteroids that end in an increased gamma-aminobutyric acid (GABA) tone [8]. The presence of benzodiazepine-like compounds explains why the use of flumazenil had been proposed in the treatment of HE. As a result of liver failure, several substances have been reported in excess in HE patients: phenols, mercaptans, short-chain fatty acids, manganese, and bile acids [9].

Using metabolomics, we recently showed that HE patients displayed several drugs, especially antimicrobial agents (e.g., metronidazole, fluconazole, or beta-lactamines), in their CSF [9]. This is in line with clinical studies that could link neurological symptoms with beta-lactams or proton pumps inhibitor intake in cirrhotic patients [15]. Remarkably, these drugs are all substrates of ATP-binding cassette (ABC) transporters expressed on the BBB and responsible for efflux of several drugs outside the brain. We recently showed in HE animal models that ABC transporter expression was altered compared to cirrhotic animals without HE (personal data). These data suggest that some neurological abnormalities could be related to drug-induced encephalopathy. Nevertheless, recent animal data showed that exposure to both bilirubin and bile acids could induce a downregulation of P-glycoprotein (P-gp), the main ABC transporter, on the BBB and that this decreased expression could favor cerebral GABA concentrations. Administration of these drugs should be carefully considered in cirrhotic patients and considered in the differential diagnosis of brain dysfunction.

Recent progress in cellular biology and immunology has modified our concept of HE physiopathology and will, in the future, provide new treatments.

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