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Is it time to target gut dysbiosis and immune dysfunction in the therapy of hepatic encephalopathy?

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The development of overt hepatic encephalopathy (HE) in a patient with cirrhosis confers a damning prognosis with a 1-year mortality approaching 64%. This complex neuropsychiatric syndrome arises as a consequence of a dysfunctional gut–liver–brain axis. HE has been largely neglected over the past 30 years, with the reliance on therapies aimed at lowering ammonia production or increasing metabolism following the seminal observation that the hepatic urea cycle is the major mammalian ammonia detoxification pathway and is key in the pathogenesis of HE. The relationship with ammonia is more clear-cut in acute liver failure; but in cirrhosis, it has become apparent that inflammation is a key driver and that a disrupted microbiome resulting in gut dysbiosis, bacterial overgrowth and translocation, systemic endotoxemia and immune dysfunction may be more important drivers. Therefore, it is important to re-focus our efforts into developing therapies that modulate the disrupted microbiome or alleviating its downstream consequences.

Hepatic encephalopathy (HE) remains one of the major challenges facing patients with cirrhosis. Compared with variceal bleeding and ascites, the development of HE alone is associated with a worst outcome, with the 1-year mortality reported being as high as 64% conferring a damning prognosis [1]. Even in its subclinical or covert state, it exerts a profound negative influence on the functional capability and both patient's and carer's quality of life [2]. It has largely been a neglected complication of cirrhosis, and it is sorrowful that few large randomised controlled trials have been performed. After lactulose and non-absorbable antibiotics became standard of care in the late 1970s/early 1980s, three decades passed before the US FDA approved a novel therapy for HE in 2010. Hepatologists should be ashamed.

HE encompasses a diverse spectrum of complex neuropsychiatric disturbance arising as a consequence of a dysfunctional gut–liver–brain axis. It is characterised by deficits in psychiatric, cognitive and motor function, ranging in severity from minimal (or covert) hepatic encephalopathy (MHE) to overt hepatic encephalopathy, delirium and coma. Sleep–wake reversal, short-term memory loss and poor concentration are the frequently reported symptoms. Patients with MHE have neurocognitive deficit, which may only become apparent on formal neuropsychological function testing whereby impairment of executive higher function is frequently prominent [3].

Ammonia has been regarded as the main metabolic factor underpinning the development of HE for over 125 years and its place in the medical text books is firmly set in stone [4]. HE develops rapidly in acute liver failure as hepatic necrosis leads to decreased ammonia utilisation, the hepatic urea cycle being the major mammalian ammonia detoxification pathway. The rising blood ammonia readily crosses the blood brain barrier. Cerebral ammonia detoxification occurs via glutamine synthetase,

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exclusively expressed in astrocytes, with the formation of glutamine which culminates in astrocyte swelling. In around a quarter of acute liver failure cases, this may be catastrophic leading to the development of intracranial hypertension and brain herniation [5].

When HE develops in the setting of cirrhosis, however, such a tight relationship with ammonia may not be so robust [6]. There is no doubt that patients with cirrhosis have higher circulating ammonia levels and spontaneous (or surgically engineered) portosystemic shunts drive increased ammonia delivery to the brain. However, the correlation between the arterial ammonia concentration and the clinical manifestation of HE is often poor [7] and single time point ammonia measurements are frequently noncontributory to the diagnosis of HE [8]. We are now beginning to understand that infection is an important precipitant of HE [7,9] and that a systemic inflammatory milieu propagates the cerebral consequences of ammonia toxicity in a synergistic fashion in acute liver failure [10] as well as cirrhosis [11].

The liver is of paramount importance in generating an effective innate immune response and is the first organ to encounter bacteria or toxins absorbed from the gut. Small bowel bacterial overgrowth and increased bacterial translocation arising from changes in the integrity and function of the mucosal barrier can lead to an increased delivery of bacteria to the liver via the portal vein. Also, portosystemic shunting results in bypassing of the reticuloendothelial system and delivery of bacterial degradation products to the systemic circulation [12]. Bacteria and their by-products termed endotoxins can activate hepatic macrophages through activation of Toll-like receptors (TLRs) such as TLR4 which recognise structurally conserved microbe-derived molecules such as lipopolysaccharides, generating a pro-inflammatory response with the production of tumour necrosis factor-α and interleukin-8, which is a potent neutrophil chemoattractant driving hepatic neutrophil and monocyte infiltration and inducing hepatic inflammation and injury [13]. The gut flora, intestinal barrier function and the generation of systemic inflammation are, therefore, intimately related. Those with established cirrhosis have been shown to have escape of bacterial degradation products across the gut wall which becomes more permeable, culminating in systemic endotoxemia and immune dysfunction. In addition to bacterial overgrowth in small bowel and increased bacterial translocation, 'dysbiosis' of gut microbiota is well documented in patients with cirrhosis; this phenomenon is independently associated with the severity of liver disease and the development of complications, which suggests a direct pathogenic role [14]. Quantitative metagenomics has revealed over 75,000 genes that differ in abundance between patients with cirrhosis and healthy controls, with 75% of them being of buccal origin suggesting an invasion of the gut from the mouth [15]. Studies have shown that modulating the gut microbiota with a non-absorbable antibiotic such as rifaximin-α is associated with improved cognitive performance and a reduction in endotoxemia in patients with cirrhosis [16].

Functional immune paresis is well documented in cirrhosis and maintaining the critical balance between having an overly exuberant systemic inflammatory response and compensatory anti-inflammatory response may ultimately lead to multiorgan failure and death. 'Paralysed' monocytes with reduced monocyte HLA-DR expression have been shown to be an independent predictor of poor outcome in patients with decompensated cirrhosis [17] and neutrophil bacteriocidal capability is impaired with the most significant dysfunction being observed in those with advanced disease and in those treated with propranolol. This circulating neutrophil dysfunction has been shown to predict the development of infection, organ dysfunction and survival at 90 days and 1 year [18]. Interestingly, it has been shown that ammonia itself can induce neutrophil malfunction with excessive and inappropriate release of reactive oxygen species and failure to move towards and phagocytose bacteria such as *Escherichia coli*, which may offer some insight as to why ammonia and inflammation may be synergistic partners in the pathogenesis of HE [19].

Is it, therefore, time to re-write the textbooks as historically all therapeutic strategies in HE have focussed on the manipulation of ammonia metabolism, both attempting to reduce its generation as well as absorption from the gut [20]? Lactulose has been the mainstay therapy for HE based upon the hypothesis that the colon is the primary organ responsible for generating ammonia as colonic bacteria produce ammonia by splitting urea and amino acids. Lactulose lowers the colonic pH through the production of organic acids by bacterial fermentation, thus creating an environment which is hostile to the growth of urease-producing gut flora and conducive to the growth of non-urease–producing species such as lactobacilli. The overall effect is to reduce ammonia production in the colon. The acidification of colonic secretions also reduces absorption. Lactulose improves quality of life and cognitive function in patients with MHE [21]; however, a systematic review has not demonstrated a mortality benefit in patients with cirrhosis presenting with acute hepatic encephalopathy [22]. Antibiotics such as neomycin, metronidazole and vancomycin have been used with the aim of reducing the production of ammonia by gut microbiota, but their long-term use has been associated with adverse side effects of nephrotoxicity, ototoxicity and peripheral neuropathy. Selective gut decontamination may therefore have utility, but this does not, however, explain why germ-free animals whose guts have been totally irradiated still develop HE and why therapies such as glyceryl phenylbutyrate [23], L-ornithine L-aspartate [24] and L-ornithine phenylacetate [25], which increase ammonia removal, are efficacious. This indicates that other pathophysiological factors may also have importance, including the presence of phosphate-activating glutaminase in enterocytes resulting in net ammonia production and the impact that systemic inflammation alone has on neurocognitive function in those without evidence of liver disease, such as those with septic encephalopathy or delirium [20]. There is increasing evidence to show that reducing the inflammatory burden in HE is efficacious, and therefore, novel pharmacotherapeutic strategies that target the evolution of bacterial translocation, endotoxemia and immune dysfunction are likely to be the logical steps that

we should be focussing on. So what might these novel targets be and what interventions might we test?

If we focus purely on the gut microbiome, then strategies may include the use of pre-, pro- or synbiotics, selective gut decontamination with non-absorbable, non-toxic antibiotics, or faecal microbiota transplantation. Probiotics may have a role in reducing bacterial translocation and one study showed a reduction in blood ammonia, endotoxemia and an improvement in MHE symptoms in those who were administered a synbiotic [26]. *Lactobacillus* GG is safe and well tolerated in cirrhosis, and is associated with a reduction in endotoxemia and dysbiosis [27]. A randomised controlled trial of 6 months treatment with VSL#3 significantly reduced the risk of hospitalisation for HE [28]. Responses may, however, differ depending on the type and quantity of the probiotic administered. In patients with alcohol-related cirrhosis, probiotics have also been shown to restore neutrophil phagocytic activity by lowering endogenous levels of IL-10 and TLR4 expression [29]. Selective gut decontamination with rifaximin-α, whilst improving neurocognitive function in MHE, has not been shown to reduce blood ammonia levels, but does reduce endotoxemia and lead to a specific increase in serum fatty acids, thus impacting on bacterial function rather than composition *per se* [16]. Targeting specifically the innate immune dysfunction raises the possibility of examining the impact of immunomodulatory diets, antioxidants such as *N*-acetylcysteine and human albumin, TLR antagonists, plasmapheresis, leucopheresis, artificial and biological liver support devices that can remove endotoxin, minocycline, caspase and programmed death receptor-1 inhibitors and hypothermia.

It is time now to stop thinking that HE may be a primarily ammonia-driven entity, as our counterparts did in the later part of the 20th century, and begin to characterise the fragile gut–liver–brain axis that leads to gut dysbiosis, bacterial translocation and immune dysfunction. We must make a concerted effort to focus on therapies that modulate the disrupted microbiome or alleviate its downstream consequences that may not only reduce the development of HE but also potentially reduce other complications that are often inevitable in those with advanced cirrhosis, including spontaneous bacterial peritonitis, variceal bleeding and the susceptibility to sepsis.

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