Pathogenesis of Hepatic Encephalopathy: Role of Ammonia and Systemic Inflammation

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The syndrome we refer to as Hepatic Encephalopathy (HE) was first characterized by a team of Nobel Prize winning physiologists led by Pavlov and Nencki at the Imperial Institute of Experimental Medicine in Russia in the 1890's. This focused upon the key observation that performing a portocaval shunt, which bypassed nitrogen-rich blood away from the liver, induced elevated blood and brain ammonia concentrations in association with profound neurobehavioral changes. There exists however a spectrum of metabolic encephalopathies attributable to a variety (or even absence) of liver hepatocellular dysfunctions and it is this spectrum rather than a single disease entity that has come to be defined as HE. Differences in the underlying pathophysiology, treatment responses and outcomes can therefore be highly variable between acute and chronic HE. The term also fails to articulate quite how systemic the syndrome of HE can be and how it can be influenced by the gastrointestinal, renal, nervous, or immune systems without any change in background liver function. The pathogenesis of HE therefore encapsulates a complex network of interdependent organ systems which as yet remain poorly characterized. There is nonetheless a growing recognition that there is a complex but influential synergistic relationship between ammonia, inflammation (sterile and non-sterile) and oxidative stress in the pathogenesis HE which develops in an environment of functional immunoparesis in patients with liver dysfunction. Therapeutic strategies are thus moving further away from the traditional specialty of hepatology and more towards novel immune and inflammatory targets which will be discussed in this review. (J Clin Exp Hepatol 2015;5:S7–S20)

Pathogenesis

Hepatic encephalopathy (HE) is the term used to encapsulate the broad spectrum of neuropsychiatric disturbances associated with both acute and chronic liver failure (ALF and CLF, respectively), as well as porto-systemic bypass in the absence of hepatocellular disease. The clinical manifestations of HE can be extremely heterogeneous in nature, with symptoms presenting anywhere on a continuum spanning from seemingly normal cognitive performance, right the way through to states of confusion, stupor and coma. In between these extremes, patients with HE may exhibit signs such as inattentiveness, blunted affect, impairment of memory or reversal of the sleep–wake cycle, as well as physical manifestations such as tremor, myoclonus, asterixis and deep tendon hyperreflexia.

ALF is defined by the onset of coagulopathy alongside any degree of encephalopathy in patients with no evidence of pre-existing liver disease.[1] The presence of HE in those with ALF is prognostic, with up to a quarter of cases developing raised intracranial pressure.[2] Patients presenting with ALF are at risk of developing its cardinal, life-threatening feature, cerebral edema. Left untreated, cerebral edema can rapidly progress to cause herniation of the uncus through the falx cerebri, leading to compression of the brainstem and, ultimately, death. Historically, cerebral edema was believed to develop in up to 80% of patients with ALF and be the most common cause of death.[3] However, recent data following a review of 3300 patients presenting to a single tertiary liver center has shown that the proportion of patients with intracranial hypertension (ICH) fell from 76% in 1984–88 to 20% in 2004–08 ($P < 0.0001$). In those who developed ICH, mortality fell from 95% to 55% ($P < 0.0001$). This mirrored a fall in the markers of disease severity on intensive care admission reflecting earlier recognition, improved care, and use of salvage emergency liver transplantation.[4]

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Abbreviations: HE: hepatic encephalopathy; ICH: intracranial hypertension; AoCLF: acute-on-chronic liver failure; MHE: minimal hepatic encephalopathy; GS: glutamine synthetase; CNS: central nervous system; BBB: blood–brain barrier; PAG: phosphate-activated glutaminase; CBF: cerebral blood flow; iNOS: inducible nitric oxide synthase; PTP: permeability transition pore; MPT: mitochondrial permeability transition; ATP: adenosine triphosphate; TLR: toll-like receptor
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In patients with CLF, the symptoms of HE tend to be far less severe and occur insidiously in keeping with the chronic nature of this disease. Factors such as sepsis, upper gastrointestinal bleeding, constipation or electrolyte disturbances, can precipitate the clinical decompensation of pre-existing cirrhosis and may lead to the development of organ dysfunction; a state sometimes referred to as acute-on-chronic liver failure (AoCLF). Phenotypically, AoCLF may be indistinct from ALF, and in some cases patients may even develop cerebral edema, although this is generally considered to be rare.[5] Great emphasis is put on actively seeking out and treating any precipitating factors in patients with cirrhosis presenting with overt HE, so as to minimize their risk of developing potentially fatal complications.[6]

Minimal hepatic encephalopathy (MHE) cannot, by definition, be detected by the clinician alone, and its diagnosis therefore hinges on detailed assessment of the patient's history and comprehensive examination of the neurologic system, as well as formal psychometric testing.[7] It has therefore recently been redefined as covert HE.[8] The prevalence of MHE in patients with cirrhosis has been estimated to lie between 30% and 84%, with variations in the diagnostic criteria thought to be responsible for this wide range.[9]

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THE ROLE OF AMMONIA IN THE SYNDROME OF HEPATIC ENCEPHALOPATHY

Ammonia was first implicated in the pathogenesis of HE by a team of Nobel Prize winning physiologists led by Pavlov and Nencki at the Imperial Institute of Experimental Medicine in Russia in the 1890's. Hahn and colleagues demonstrated the induction of an encephalopathic state in dogs following the formation of a surgical shunt, known as Eck's fistula, which served to divert nitrogen-rich blood from the portal vein directly to the inferior vena cava, therein bypassing the liver. Six weeks post-operatively, the dogs began to exhibit increased levels of aggression, irritability, ataxia, as well as experiencing seizures and eventually lapsing into coma especially following ingestion of an ammonia-rich meal.[10] Two years later, in another canine study with surgical portocaval fistulas, it was discovered that the urinary concentration of ammonia salts was elevated, leading to the logical first suggestion that ammonia may be key in the development of this neurobehavioural syndrome.[11] The ingestion of ammonium salts was subsequently shown to exacerbate the neurobehavioural symptoms in these dogs, causing them to become comatose and die. This causally implicated the inability of the bypassed liver to convert the neurotoxic ammonia into urea and its subsequent accumulation in the brain, in the syndrome which was later termed HE.[12,13]

Some years later, Gabuzda and colleagues[14] performed a therapeutic trial in 12 cirrhotic subjects which aimed to assess the efficacy of three different cation-exchange resins in the treatment of ascites; this followed reports that cation-exchange resins were effective in treating the fluid overload state associated with congestive cardiac failure. Whilst results from this study indicated that the resins were indeed effective diuretics, significantly reducing ascites and edema, almost all of the cirrhotic subjects receiving the ammonium-containing cation-exchange resins developed marked neurological and behavioral disturbances. Patients became drowsy, apathetic, weak, confused and disorientated to time and place, and exhibited various inappropriate behaviors. These neurocognitive changes presented within a few days of the administration of the ammonium-containing cation-exchange resins and resolved soon after their discontinuation, therein illustrating the generally reversible nature of HE. This prompted further investigation by Phillips and colleagues later on in the same year.[15] In this study, patients with advanced cirrhosis were administered ammonium chloride, urea, protein or di-ammonium citrate, and observed. These substances precipitated the development of a syndrome identical to that of impending hepatic coma and lay the foundations of our understanding that ammonia is central in the pathogenesis of HE.

Beginning in mid-1950s, studies began to focus on whether or not it was possible to establish a quantitative relationship between blood ammonia concentration and the severity of neurocognitive impairment in HE in cirrhosis. Broadly speaking, those patients who were experiencing significant neurological disturbances had elevated blood ammonia levels[16,17] but whilst blood ammonia levels were generally higher in cirrhotic patients with either past or present neurological disturbances, blood ammonia concentration was not predictive or consistent with severity HE.[18,19] This finding has been replicated with one such study showing that 69% of individuals with no overt signs of HE had elevated blood ammonia levels, whilst a number of patients with more significant grade 3 or 4 HE had either normal or only slightly elevated levels of ammonia in their blood.[20]

This is in contrast to ALF whereby the relationship between blood ammonia levels and the clinical severity of HE is more clear-cut. Bernal and colleagues demonstrated ammonia to be an independent risk factor for the development of both HE and ICH, with the latter occurring in 55% of patients with blood ammonia concentrations >200 μmol/L.[2] Blood ammonia levels $\geq$150 μmol/L have also been shown to predict a greater likelihood of cerebral herniation and death in patients presenting with ALF.[21] Persistent arterial hyperammonaemia for 3 days following hospital admission predicts a greater likelihood of complications and death in individuals with ALF.[22]

Discrepancies in the direct correlation between ammonia concentration and the severity of HE in patients with cirrhosis, have contributed to the general consensus

