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Inflammation and Hepatic Encephalopathy

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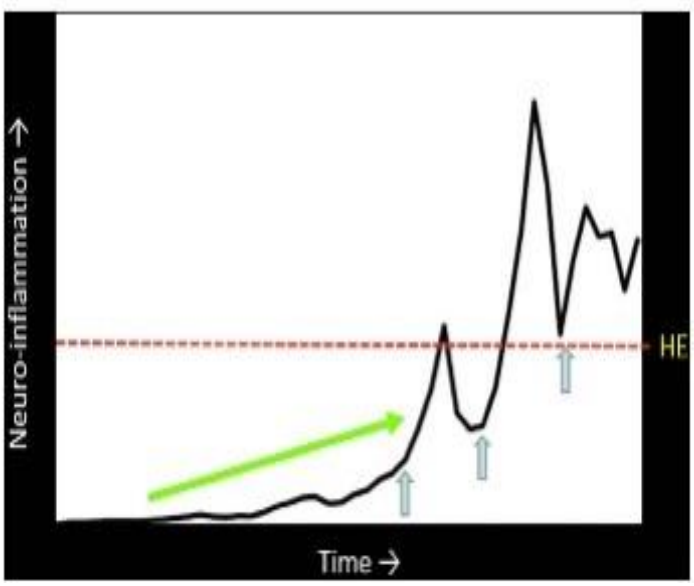
1.Introduction:

Hepatic Encephalopathy (HE) is a life-threatening and complicated neuropsychiatric syndrome which is associated with the presence of porto-systemic shunting, and/or with acute and chronic liver injury. Ammonia plays a central and incontrovertible role in pathogenesis of HE, however, a full-bodied evidence base is present indicating the major role played by inflammation in exacerbating the HE caused neurological effects. Research progressed showcasing the diverse face of HE and characterized the key roles of inflammation, infection, and oxidative stress along with other possible parameters. Inflammation is a very common and significant biological process which functions by generating a plethora of molecules, acting in response to tissue alterations. Such response is a result of tissues trying to maintain and restore their integrity and alter back the homeostasis by inducing various repair mechanisms. Regulation of these processes is essential to ensure the equilibrium and to avoid uncontrolled amplification of the response which might lead to disease progression further down the spectrum.

Various signalling processes initiate after sensing the damage associated molecular patterns, and/or pathogens in neuronal functioning. Via intracellular pathway immune response activates by an intricate cascade of different molecular events regulating the up and down regulation of a number of different immune cells such as chemokines, cytokines, various enzymes, regulation of growth factors and different tissue repair molecules (Wellen and Hotamisilgil,2005). Trigger to Inflammation can either be direct i.e. within the brain, as a result of over-expressed nitrogen or energy homeostasis, resulting in neuronal, glial cells as microglial, astrocytes dysfunctions. The other possible route to inflammation originates in peripheral circulation, that indirectly exerts different effects to the activity of brain, by the up-regulation of pro-inflammatory immunogenic mediators which signals the brain directly via vagus nerve.



The potential link in HE progression, Neuro-inflammation is apparent in this graph. The arrow indicates the proportional relation b/w liver disease progression and inflammation. Left side of the graph with lower inflammation indicates the covert stages while moving towards right is the overt stages in disease spectrum, showcased by azhari et al., 2018.

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2. "Meat In-toxification Syndrome" Hypothesis:

The causative role played by ammonia in the intoxication of liver and developing HE was described as "meat intoxication syndrome" by Nencki et al., during 1890s while other investigators proved the definitive role of ammonia in HE development. Indeed, there have been number of studies showcasing that single blood ammonium concentration test as a non- efficient method to assess HE.

Zieve et al. in 1974, changed the paradigm towards the possibility of involvement of some other factors in the pathologenic picture of HE. Though, the involvement of ammonia in the pathogenesis of HE can't be denied, it seems that there might be an involvement of other significant factors as well. The synergistic role of ammonia and inflammation has been demonstrated by the aid of animal models, clearly indicating that ammonia toxicity can expose brain to deleterious effects of inflammation (Shawcross et al., 2007, Wright et al., 2012). The extensive research showcased the role of different aspects of inflammatory responses to play a synergistic role in HE pathogenesis.

3. Astrocytes in HE:

A type of glial cell in the central nervous system (CNS) involved majorly in maintaining other cells within CNS as well to provide nutrition to neurons. The role of astrocytes is notable in HE because of the exclusive presence of enzyme glutamine synthase amongst the neuronal cells. The presence of capillaries at the end process of astrocytes makes them further significant in CNS functioning. HE is as well characterized by functional changes in astrocytes. Though, the blood brain barrier (BBB) stays anatomically intact (Dhandha,2013) in HE but several PET studies showcased the increased permeability to ammonia with increased severity to HE. The schematic diagram provided by Seyas et al., clearly showcases the role of astrocytes in HE by calling it "Two-hit hypothesis".

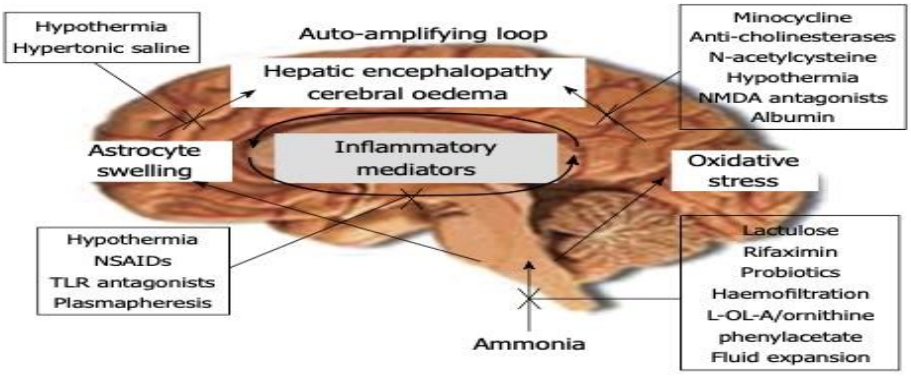

Figure 1 The "Two-hit" hypothesis. In a background of liver injury and hyperammonemia, a second "hit", such as an ammonia load following an upper gastrointestinal bleed, systemic inflammation/infection, or the development of hyponatremia can drive further astrocyte swelling, oxidative stress and lead to a rapid deterioration in neurocognitive function. The close relationship between astrocyte swelling and oxidative stress leads to an "auto-amplifying signalling loop". The sites of action of potential therapies are indicated on the Figure. L-OL-A: L-ornithine L aspartate; NMDA: N-methyl D-aspartate; NSAID: Non-steroidal anti-inflammatory; TLR: Toll-like receptor.

3.1 Proposed mechanisms leading to astrocytes dysfunctioning:

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1. Chronic liver induced HE patients are characterized neuropathologically by type-II astrocytosis. Ammonia taken up in brain might interact with astrocytes causing morphological changes like swollen nucleus, enlarged nucleolus, chromatin pattern changes. Evidence to this fall back to several animal model studies along with clinical experiments by norenberg et al.,1977.
2. Brain oedema is also found to be present by Kato et al., with pronounced swelling of astrocytes in acute liver failure patients. Glutamine synthetase catalyses the conversion of ammonia as well as of glutamate to glutamine. Because of the inactivity of enzyme, hyperammonemia can lead to excessive levels of glutamine within astrocytes, causing the cells to swell, and as a consequence leading to intracranial hypertension and oedema.
3. Cytokines as well might be involved directly in affecting astrocyte functioning, by, entering the CNS via sites with compromised BBB (like the circumventricular organs), and diffusing into brain parenchyma causing the activation of some transcription factors that increases pro-inflammatory cytokines in astrocytes.

Though, these are the mechanism available in the literature study, there is still a loop present to analyse and evolve several other ways by which astrocytes can undergo dysfunctioning. The area needs some sincere research as the astrocytes play an integral role in neuronal functioning.

4.Synergy b/w inflammation and other precipitating factors:

Traditional routes of communication between the periphery and the brain involve neural (i.e. vagal afferent nerves) and humoral (blood-borne) pathways, with increased circulating levels of endotoxin and cytokines (especially Tumour Necrosis Factor α, TNFα) that occur during systemic inflammatory responses, as being primarily implicated in mediating signalling via these pathways. Patients with liver failure gets pre-disposed to variety of infections and become immunocompromised (Butterworth, 2011). Liver is the first organ to encounter metabolic and other toxins along with pathogens. In such case, insufficiency of liver causes such antigens to reach blood and in turn activating immune response. The generated immune response can be both innate as well cellular. Innate comprise majorly of phagocytic cells like monocytes, neutrophils while cellular in turn increases the blood pro-inflammatory cytokines such as various interleukins (IL) like IL-6, IL-11, IL-1β as embarked by montalieu et al., 2009, along with tumor necrosis factor, TNF-α. Odeh et al.,2011 in his study formed a positive corelation in HE severity and TNF-α.

Fig 2 represents hyperammonemia and the development of immune dysregulation contribute to the propensity to develop hepatic encephalopathy and brain oedema in the context of acute and chronic liver failure (Colart et al., 2013). Though, during an episode of infection, cytokines cannot directly cross the blood brain barrier and are unable to have a direct effect. Nevertheless, the peripheral immune system can still signal the brain to elicit a response during infection and inflammation through the expression of pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6, both in the periphery and in the brain. Brain signalling may occur by direct transport of the cytokines across the BBB via an active transport mechanism, the interaction of the cytokine with circumventricular organs and activation of afferent neurons of the vagus nerve.

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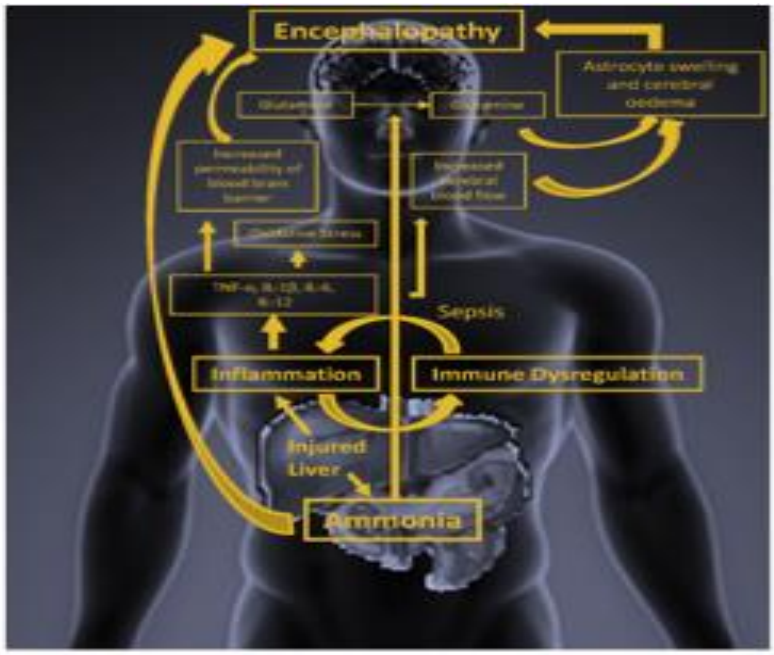

The rise of these pro-inflammatory mediators have the capacity to cause the activation of glial cells which themselves are pre-equipped with the capacity to produce a full repertoire of cytokines causing inflammation, thereby generating a positive feedback loop or “an auto-amplifying” loop.

5.Functioning mechanism of Immune cells:

The largest resident of macrophage population is the Liver, such macrophages are the Kupffer cell. Liver inflammation typically is associated with their activation and, thereby, cause the production of cytokines, including TNFα, IL-1β, and IL-6. Wu et al., 2016 described the functioning mechanism of different cytokines and their association with HE. The circulating cytokines like ILs, Interferons (IFN) such as IFN-17α, IFN-λ2, IFN-λ3 and others correlates with minimal form of HE.

Monocytes have the capacity to infiltrate liver and are a critical component of innate immune response. Such elevated number of monocytes in longer run can cause severe liver damage. In rodents, monocytes of two sub-kind are found: 1. A noninflammatory subtype, which can give rise to tissue resident macrophages, and 2. an inflammatory subtype, which expresses high levels of chemokine (C-C motif) receptor 2 (CCR2) and responds to MCP-1, a potent chemoattractant for monocytes. Similar monocyte subtypes have been characterized in humans, (Gordon S, Taylor PR, 2005). Experimental cholestasis was accompanied by an increase in circulating inflammatory monocytes, and a large proportion of them were activated and expressed TNFα.

Some studies also presents how peripheral cytokines can affect brain and cause systemic inflammation via indirect route. Moreover, the pro-inflammatory cytokines can cross BBB by active transport and thus alleviating cerebral inflammation. Via neural pathway, liver which is innervated by vagal afferents can directly activate cytokines, along with vagal nerve afferents, since they have been described to express cytokine receptors, such as the IL-1 receptor (IL-1R) (Ek m et al.,1998). In addition, macrophages interspersed between vagal fibers within the nerve could also respond to cytokines.

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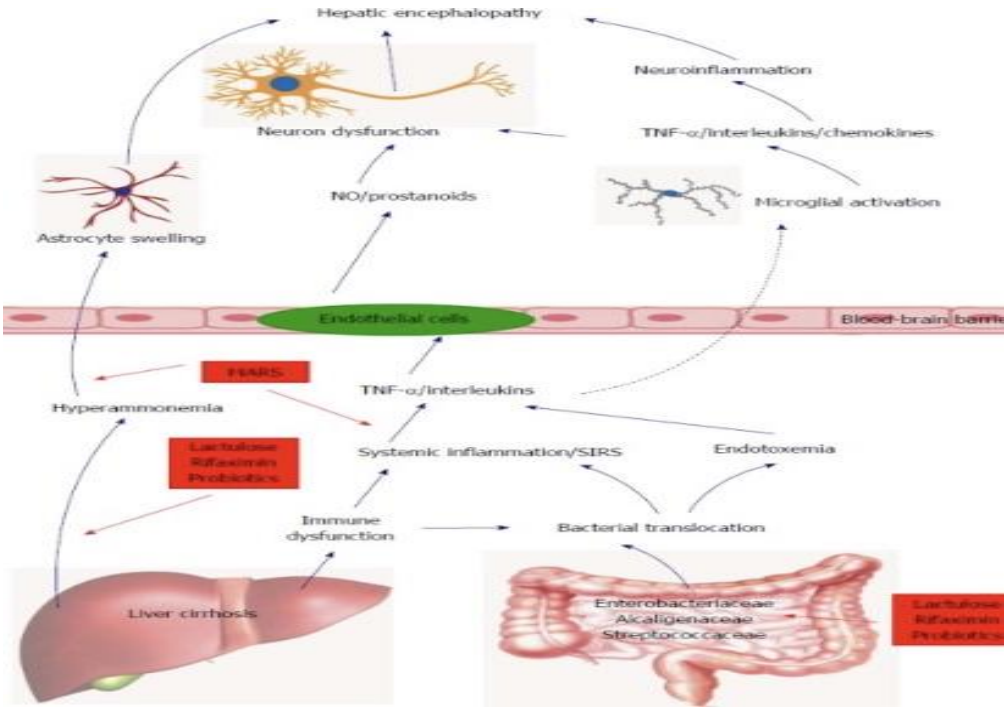
Secondary mediators are as well used by cytokines to mediate their effects on CNS activity such as PGE2 and NO, which further are competent of inducing de novo synthesis of cytokines within the brain, e.g. IL-1β was found to be upregulated in rodents after peripheral administration of TNFα and TNFα expression also alleviated within the brain (Qin et al.,2007).

The administration of anti-inflammatory drugs like ibuprofen has shown improved effects in rats learning ability (cauli et al., 2007).

The figure by Luo et al., 2015 clearly demonstrates how inflammation is involved in the HE and the mode of functioning of different immunogens in order to severe the HE. It provides a brief yet panoramic picture of all the possible routes by which inflammation can cause the HE and its associated disorders. The CNS is protected by a BBB, which largely consists of non-fenestrated endothelial cells with tight junctions between them. Cytokines are large, hydrophilic molecules that cannot readily cross the blood-brain barrier and thus uses different routes to communicate with the brain.



6. Conclusion:

In conclusion, Inflammation acting synergistically with all precipitating factors of HE plays a significant role in both pathogenesis as well as in progression of HE. The outcome has made a clear picture about the complex and multifaceted pathogenesis of HE. The number of upstream factors together lead to a variety of downstream influences ranging from blood serum changes to brain oedema and differed behavioural deficits. The under studied mechanism of HE requires further inspection, in wide areas like analysing the Hypothalamic-pituitary-adrenal axis. Though, ammonia and the downstream consequences of ammonia uptake by astrocytes remain fundamental to the process. The limited literature in establishing a link between all the precipitating factors thus demands more researchers to continue dwelling in this field in order to get a sound analysis of HE.

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