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The current concept in the pathogenesis and treatment of hepatic encephalopathy

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Abbreviations

Acute Liver Failure (ALF)

Adherens junctions (AJ)

Antigen presenting cells (APC)

Bacterial translocation (BT)

Blood Brain Barrier (BBB)

Central nervous system (CNS)

Dendritic cells (DC)

Endothelial cells (EC)

Gastrointestinal tract (G.I.T.)

Glyceryl phenylbutyrate (GPB)

Gut-associated lymphoid tissue (GALT)

Hepatic encephalopathy (HE)

Interferons (INF)

Interleukin (IL)

International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)

Intestinal permeability (IP)

Mesenteric lymph node (MLN)

Minimal HE (MHE)

Magnetic resonance imaging (MRI)

Myosin light chain kinase (MLCK)

N-methyl D-aspartate (NMDA)

Nitric oxide (NO)

Oro-cecal transit time (OCTT)

Pathogen-associated molecular patterns (PAMPs)

Pattern recognition receptor (PRR)

Phenylacetylglutamine (PAGN)

Portosystemic shunting (PSS)

Reactive oxygen species (ROS)

Reactive nitrogen species (RNS)

Small intestinal bacterial overgrowth (SIBO)

Spectrum of neurocognitive changes in cirrhosis (SONIC)

Spontaneous bacterial peritonitis (SBP)

Systemic inflammatory response syndrome (SIRS)

Tight junctions (TJ)

Tumor necrosis factor (TNF)

Urinary tract infection (UTI)

West Haven Criteria (WHC)

Introduction

Hepatic encephalopathy (HE) is a complex and sometimes life threatening neuropsychiatric condition caused by liver injury (Coltart, Tranah, & Shawcross, 2013). “It is characterized by the spectrum of neurocognitive changes in cirrhosis (SONIC) in the absence of other known brain diseases.” (Montgomery & Bajaj, 2011)

The liver is a vital organ that detoxifies most toxic compounds in the body. When the liver fails, these processes do not function correctly and toxic compounds may reach the brain and affect its function. (Felipo, 2013) The clinical signs vary greatly and can range from mild neuropsychological disturbances to coma. (Weiss, Jalan, & Thabut, 2018) These neuropsychological disturbances can include changes in personality, altered mood, decreased intellectual capacity, abnormal muscle tone, tremor and seizures. (Jayakumar, Rao, & Norenberg, 2015). HE is the term used to describe alterations in cerebral function that result from liver failure but it is not a single syndrome (Felipo, 2013).

Patients with liver cirrhosis are often found to have disturbances in intestinal flora. It has also been shown to increase intestinal permeability and intestinal barrier dysfunction. (Luo, Guo, & Cao, 2015). Infection can be the trigger for HE. Sepsis and systemic inflammation are seen as an indicator of the severity of cirrhosis (Weiss, Jalan, & Thabut, 2018). Elevated levels of circulating pro-inflammatory cytokines are seen in decompensated cirrhotic patients. Although these cytokines do not directly affect the brain recent studies have demonstrated that Tumor necrosis factor (TNF)-α and Interleukin (IL)-1β can influence the Blood Brain Barrier (BBB) (Luo, Guo, & Cao, 2015).

Although the pathogenesis is still not fully understood, gut derived ammonia is still considered to be a key factor but neuro-inflammation is now also believed to play an important role in the pathogenesis. (Wright, Swain, Annane, Saliba, & Samuel, Neuroinflammation in liver disease: sessional talks from ISHEN, 2016). Blood ammonia levels are not an accurate predictor of the severity of HE. Ammonia-lowering drugs are only partially effective in the treatment of HE. Recent studies show convincing evidence for the role of neuro-inflammation, including activation of microglia as well as activation of genes coding for pro-inflammatory molecules. (Butterworth, 2015) These findings form the basis of ‘synergism’. Ammonia appears to act in concert with inflammation and other factors, such as manganese, in the progression of HE (Wright, Swain, Annane, Saliba, & Samuel, Neuroinflammation in liver disease: sessional talks from ISHEN, 2016).

It is hypothesised that glutamine accumulation in the brain also plays a role in HE and Brain edema. (Buttorworth, 2015) Glutamine is taken up by the mitochondria of the astrocytes and then converted to glutamate and ammonia. This ammonia leads to the mitochondrial permeability transition which leads to loss of mitochondrial dysfunction and astrocytic swelling. This hypothesis is called the "*Trojan horse hypothesis"*. (Wright, et al., neuroinflammaton in liver disease; sessional talks from ISHEN, 2015).

Although the etiology of HE is not fully understood it is thought that multiple factors work together in the pathogenesis of HE in cirrhotic patients, this is reflected in the treatments used in HE. Combinations of medications are used, including gut modulators like rifaximin, probiotics and lactulose and anti-inflammatory drugs. (Luo, Guo, & Cao, 2015)

1. Epidemiology of hepatic encephalopathy

The liver has a key role in the body to neutralise many toxic chemicals absorbed in the gastrointestinal tract (G.I.T.) and other by-products of normal metabolism. (Bleibel & Al-Osaimi, 2012) Liver cirrhosis is an advanced stage of liver fibrosis with vascular remodelling. It is the end stage for chronic liver disease and severe liver damage. There are 2 types: compensated, usually showing no or mild clinical signs and decompensated cirrhosis, usually showing clinical complications. The only curative option at this stage is liver transplantation. (Pijls, Jonkers, Masclee, & Koek, 2013)

One of the most common and debilitating manifestations of liver disease is HE. (Vilstrup, et al., 2014) It is frequently seen in severe hepatic insufficiency. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003). When the liver does not function properly, these toxic compounds may reach the brain and affect cerebral function. (Felipo, 2013) The clinical spectrum of HE ranges from mild neuropsychological signs to coma. (Weiss, Jalan, & Thabut, 2018)
HE is a complex condition with many different grades, categories and subcategories. Type A is associated with acute liver failure, type B with portosystemic shunt, type C with liver disease. (Savlan, Liakina, & Valantinas, 2014) Different types of liver disease lead to different cerebral and neurological alterations, so therefore different forms of HE, which require different treatments. (Felipo, 2013)

There is a number of HE validation and classification methods. A commonly used scale is the west havens criteria; this recognises 4 grades of HE ranging from trivial lack of awareness, euphoria or anxiety and shortened attention span (grade 1) to coma (grade 4) (Savlan, Liakina, & Valantinas, 2014)

Overt HE, also called clinically apparent HE, is classified as a variety of mental and motor disorders due to liver disease where as patients with minimal HE (MHE) appear clinically normal but show abnormalities in neuropsychometric performance. (Gluud, Jeyaraj, & Morgan, 2019) (Shawcross, et al., 2016) MHE is the mildest form of HE and although patients are clinically normal they will show a subtle decline in attention, immediate memory, visual-spatial abilities and fine motor skills. (Montgomery & Bajaj, 2011)

The characteristic presentation is development of acute encephalopathy with a sharp decline in the level of consciousness, clinically seen as confusion or coma. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) This impairment of brain function is usually reversible if treated correctly. (Ferenci, 2017) Chronic encephalopathy can present as frequent episodes of acute encephalopathy or with persistent neurological signs. In patients with chronic recurrent encephalopathy the cause is commonly the result of constipation, improper dosage or termination of treatment. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003)

The mechanisms causing cerebral alterations and brain dysfunction are still not fully understood. Part of the reason for this is the limitations of studying the brain *in vivo.* (Ferenci, 2017) Ammonia has been well documented as a key factor in HE. It is known to be related to the swelling of astrocytes in the brain. (Guan-Huei, 2015) Ammonia is mainly derived from the gut flora in the colon. It is a by-product of catabolism of ingested protein and secreted urea and enterocytes from glutamine which is their main energy source. (Weiss, Jalan, & Thabut, 2018)

Although ammonia plays a central role in the pathogenesis there are many other factors which influence the appearance and severity of this condition. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) These include other neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, systemic inflammation and alterations of the BBB. A combination of a number of these factors may occur concurrently and affect the development of HE. (Ferenci, 2017)

Unless the underlying liver disease is identified and treated, HE has a high chance of reoccurrence, decreased quality of life and poor survival rate. (Ferenci, 2017) The most important factor determining the prognosis is the development of multi-organ failure. (Guan-Huei, 2015)

1.1. Classification system

HE can be classified under the 4 following headings:

1. According to the underlying disease:

    - Type A resulting from Acute Liver Failure (ALF)
    - Type B Predominantly from Portosystemic shunting (PSS)
    - Type C resulting from liver cirrhosis

    Clinically types B and C have similar presentation and are easily distinguishable from type A. (Vilstrup, et al., 2014)

2. According to the severity of manifestation using the West Haven Criteria (WHC) with clinical description:

    - Unimpaired- No Encephalopathy, no history of HE
    - Minimal- psychometric or neuropsychological alterations without clinical evidence of mental change.
    - Grade 1- trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm. Despite orientated in time and space the patient appears to have some cognitive or behavioural decay with regards to their standard on clinical examination.
    - Grade 2- lethargy or apathy, disorientation for time, obvious personality change, inappropriate behaviour, dyspraxia, asterixis. Will show disorientation for time, at least 3 of the following are wrong: day of the month, day of the week, month, season or year.
    - Grade 3-somnolence to semi stupor, responsive to stimuli, confused, gross disorientation, bizarre behaviour. Also disoriented for space, at least 3 of the following are wrong: country, state/region, city or place.
    - Grade 4- Coma, does not respond to painful stimuli.

    All conditions are to be related to liver insufficiency and/or PSS. Under the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) minimal and grade 1 HE are considered covert and grade 2-5 are considered overt as seen in *Figure.1*. (Ferenci, 2017)

3. According to its time course (Vilstrup, et al., 2014)

    - Episodic HE
    - Recurrent HE: recurring cases of HE with intervals or 6months or less
    - Persistent HE: a pattern of behavioural alterations that are always present with intermittent relapse of overt HE

4. According to the existence of precipitates:

    - Non precipitated
    - Precipitated

    In patients with previously stable cirrhosis, HE is usually a consequence of precipitating factors. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003)

HEPATIC ENCEPHALOPATHY (HE)

Patients can change between these states over time	COVERT HE ◄——► OVERT HE Includes minimal HE and grade 1 HE	Subdivided by **Time course:** episodic (one epidose/6 months), recurrent: >1/6 months, persistent—never resolved **Factor-associated:** precipitated (associated factors), spontaneous (none))
Diagnosis	• Cannot be diagnosed clinically • Needs combination of paper/pencil/ computerized/neurophysiological tests	• Exclusion of other causes of altered mental status • Obvious clinical manifestations ranging from disorientation through coma without focal deficits
Clinical relevance	• Overt HE development, impaired quality of life • Driving and socioeconomic status • Higher death and hospitalizations	In-hospital death, aspiration, recurrent episodes, disability, burden on caregivers and socioeconomic status, poor survival within 2 years of discharge, persistent cognitive impairment after multiple episodes
Treatment strategies	• Growing evidence base but not standard care • Can treat patients on an individual basis with lactulose, rifaximin, or probiotics	**Acute episode:** care of unconscious patient, identify/treat precipitating factors, and empiric treatment with lactulose, then rifaximin **To prevent recurrence:** after first episode, lactulose; after second episode, rifaximin **Overall:** consideration for liver transplantation

Figure 1. A table of the differences between overt and covert HE . (Bajaj, 2015)
Overview including diagnosis, clinical relevance and potential but the treatment plan is usually made on a case by case approach. These states can change over time depending on patient status.

1.2. Precipitates

In nearly all cases of type 3 HE precipitating factors can be found. They should actively be sought and treated when found. (Vilstrup, et al., 2014)

Nitrogen products:

- Gastrointestinal bleeding
- Hyperazoemia
- Constipation
- High protein diet
- H. Pylori
- Uremia

Metabolic disequilibrium:

- Hypokalemia
- Alkalosis
- Hypoxia
- Hyponatremia
- Hyperkalemia
- Dehydration

Drugs:

- Opiates
- Benzodiazepines
- Diuretics
- Sedatives
- Phenol

Other:

- Infections
- Surgery
- Hepatopaties
- Renal failure
- Short-fatty acids

The treatment of episodes is focused towards correction of the precipitating factor. Once this is resolved, the encephalopathy will usually disappear and the patient will recover to their previous state. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003)

If no precipitating factor can be found, a major consideration should be the presence of a significant spontaneous PSS. Occluding of such shunts may improve the condition but in some cases this has been shown to increase portal hypertension, ascites and increase incidences of esophageal viseral bleeding. (Bleibel & Al-Osaimi, 2012)

2. Pathogenesis

Although the pathogenesis of HE is not fully understood, it is obvious that there are many different factors which contribute to the occurrence and severity of this condition. The gut flora plays a major role, directly and indirectly, in the appearance and severity of HE.

2.1. Disturbance in gut integrity and microbiota

The G.I.T. is home to trillions of intestinal bacteria. Given its large surface area, the G.I.T. is constantly exposed to these bacteria. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014) The gut microbiota plays a pivotal role in many vital functions essential for normal nutrition and metabolism. These include digestion of complex carbohydrates, vitamin synthesis and secretion of biologically active compounds. Many of these compounds play a role in the balance of the gut flora and overall health of the patient by inhibiting pathogens and metabolising toxic compounds such as ammonia. (Rai, Saraswat, & Dhiman, 2015)

There is a very strong relationship between the liver and the gut. The portal veins carry blood from the intestines to the liver therefore its content can potentially affect the liver function but also the liver affects the intestinal function through bile secretion. (Dhiman, 2013) Patients with liver cirrhosis are seen to have a significant deviation from the normal gut flora. This is partially the result of a decrease in small intestinal motility resulting in a delayed oro-cecal transit time (OCTT). (Gupta, et al., 2010) This decrease in motility has been attributed to multiple factors including bowel wall edema, autonomic dysfunction, altered concentration of intestinal peptides and neurotransmitters and altered intestinal myoelectrical activity. (Rai, Saraswat, & Dhiman, 2015)

Bacterial translocation (BT) is a physiological process by which bacteria and/or bacterial products are translocated to the mesenteric lymphnodes (MLN). In cirrhosis this becomes pathological when there is a sustained increase in the quantity. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014) This pathological BT plays a major role in the development of complications in cirrhosis not only in infections but also by inducing an inflammatory state and exacerbating hemodynamic derangement. (Bellot, Frances, & Such, 2013)

The 3 main factors which have been implicated in the development of pathological BT are: overgrowth of intestinal bacteria, an increase of the intestinal permeability and impaired immunity. (Benjamin, Singla, Arora, & Sood, 2013) Small intestinal bacterial overgrowth (SIBO) has been demonstrated in a high number of patients with liver cirrhosis. (Clecko-Michalska, Szczepanek, Slowik, & Mach, 2012) Intestinal bacterial overgrowth is seen in many cirrhotic patients, with a higher prevalence being reported in more advanced cases of hepatic functional impairment. In these advanced cases, small intestinal hypomotility is especially common and is a major predisposing factor for SIBO. This is reversible and normal motility is seen to be restored after liver transplantation. (Riordan & Williams, 2006)

SIBO is associated with systemic endotoxemia. The decrease in intestinal motility facilitates not only the overgrowth of bacteria but also an increased absorption of gut toxins. (Lunia, Sharma, Sachdeva, & Srivastava, 2014) These bacterial endotoxins are absorbed in to the circulation and are categorised under the term Pathogen-associated molecular patterns (PAMPs). These PAMPs are recognised by Pattern recognition receptor (PRR) by the innate immune system. They consist of mainly lipopolysaccarides, flagellin, peptidoglycan and microbial nucleic acid. (Dhiman, 2013) Normally there is a low level of endotoxins in the circulation as the Kupffer cells of the liver are believed to clear endotoxins from the intestines as they reach the liver through the portal vein. In cirrhotic patients the number of endotoxins circulating in the body is greatly increased because of increased BT and reduced liver clearance capacity. Endotoxemia initiates liver damage due to the endotoxins interactions with Toll-like receptors. These changes in the body will lead to the activation of the immune system and an inflammatory response. (Dhiman, 2013) (Benten, et al., 2011)

These endotoxins and the subsequent inflammatory cytokines which are released will in turn lead to an increased production of nitric oxide (NO). The NO will cause vasodilation and a hyperdynamic circulatory state, which facilitates further complications in patients. (Benjamin, Singla, Arora, & Sood, 2013)

The basic role of the G.I.T. is to absorb nutrients but provide an effective barrier against absorption of intestinal bacteria to the systemic circulation. (Palma, Mihaljevic, Hasenberg, Keese, & Koeppel, 2007) Increased intestinal permeability (IP) in cirrhotic patients is potentially caused by changes in the intestinal mucosa because of portal hypertensive enteropathy. Other factors such as alterations in bile flow and composition, oxidative stress, inflammation and elevated nitric oxide levels may also lead to a disturbance in the integrity of the intestinal mucosa. (Benjamin, Singla, Arora, & Sood, 2013) (Pijls, Jonkers, Masclee, & Koek, 2013)

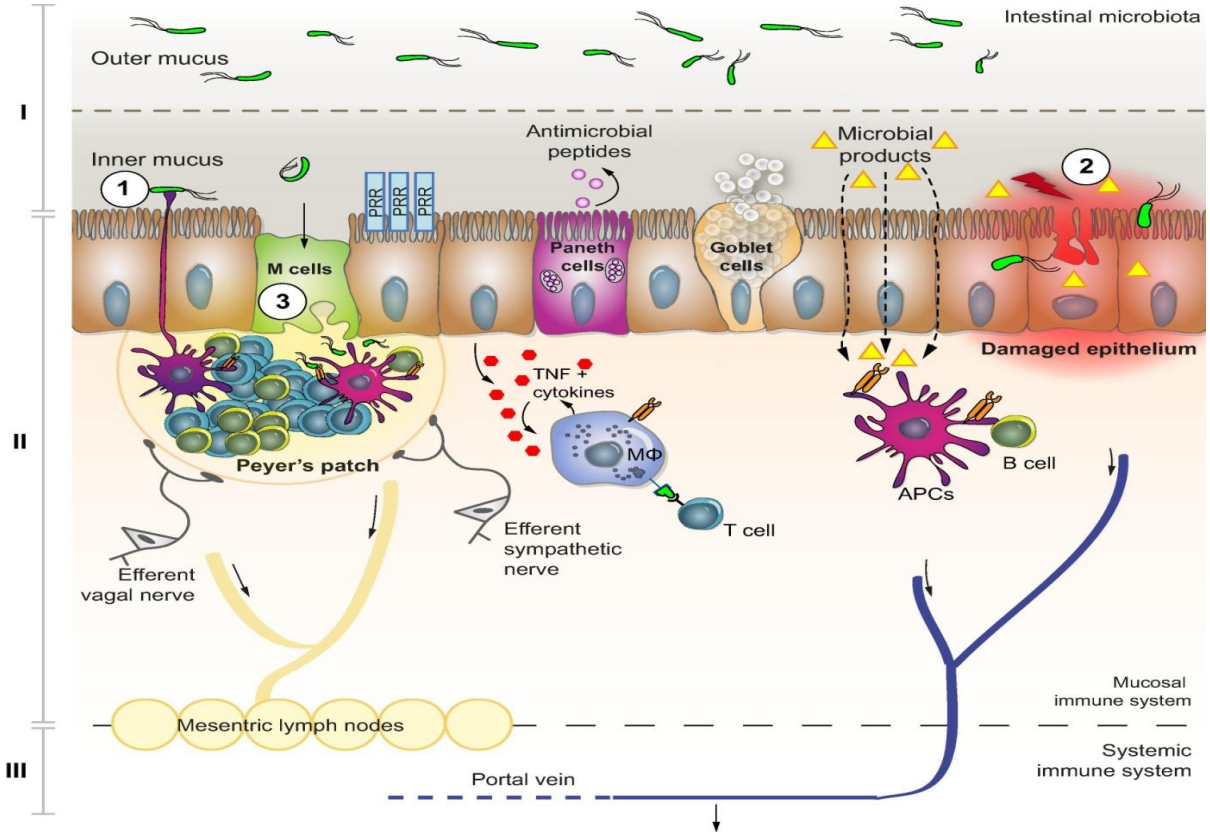

Figure 2. 'Compartments and key players involved in mediating pathological BT and the associated host response. There are three different routes of BT (1) direct sampling of luminal bacteria by DCs using long processes between epithelial cells 2) injured/inflamed epithelium where the epithelial barrier is no longer intact or is not functioning correctly and (3) M-cells overlying Peyer Patches are specialized cells that provide access of microbial products to APCs.
There are also three different layers that act as a barrier against BT: (I) lumen and secretory component (e.g., inner and outer mucus layer, antimicrobial peptides) of gut barrier; (II) mechanical epithelial barrier and the GALT beneath with response elements to BT (e.g., TNF and other pro-inflammatory cytokines) and autonomic nervous system; (III) systemic immune system as third barrier in case of spreading of bacteria and/or its products beyond MLN.' **(Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014)**

This intestinal barrier can be divided in to two distinct compartments; the mechanical (epithelial) barrier consisting of a mucus layer and the epithelial cells and the immunological barrier consisting of epithelial secretions and immune cells. The epithelial cells are connected to each other by junctional complexes, these are essential in the regulation of transport across the membrane. (Pijls, Jonkers, Masclee, & Koek, 2013) The paracellular transport is regulated by the tight junctions (TJ) and possibly the adherens junctions (AJ). The TJ form a selective barrier in the paracellular space. TJ will respond to a variety of stimuli and are highly dynamic; they are controlled by signalling molecules such as myosin light chain kinase (MLCK).

In cirrhotic patients a loosening of these TJ allows an increase in the paracellular transport of harmful bacteria and bacterial products. As the epithelial cells are put under stress the transcellular transport of commensal bacteria is also increased. This increased permeability will cause inflammation and in turn worsen the BT. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014) (Pijls, Jonkers, Masclee, & Koek, 2013)

The Mucus layer protects the microvillus from direct contact with the intestinal bacteria. There are two layers; the inner layer which is thought to trap immune exclusion molecules and the outer layer which is the location of the commensal bacteria. It is important to note the bacteria of the intestinal lumen are not the same as the bacteria in the mucus. In cirrhotic patients, especially those with HE, the mucosa-associated microbiome differs from stool flora. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014)

The Intestinal immune system, also called Gut-associated lymphoid tissue (GALT), is the largest immunological organ of the body. It comprises of 4 parts: Peyer's patches, lamina propria lymphocytes, intraepithelial lymphocytes and MLN. (Bellot, Frances, & Such, 2013) Bacteria can usually be detected in the intestinal tissue with no adverse reaction as the organisms are removed by phagocytosis in healthy patients. The GALT composition is influenced by the microbial colonisation of the gut. (Wiest & Garcia-Tsao, Bacterial translocation (BT) in cirrhosis, 2005)

The innate immunity is the nonspecific immune response of the body; it is considered the first line of defence. It recognises bacteria and/or bacterial products and releases chemokines and cytokines, leading to the destruction of the bacteria. Monocytes and dendritic cells (DC) are important cells in the innate immunity of the gut. The DCs, which are attracted by the chemokine release, will sample the microbial antigens and have the capacity to induce mucosal B and T cells, effectively shaping the mucosal adaptive immunity. In cirrhosis an increase in gram negative bacteria is seen, this will activate peripheral mononuclear cells with an increase in LPS-induced tumor necrosis factor (TNF) expression. Although there is activated mononuclear cell in advanced cirrhosis, the innate immunity is impaired as there is reduced phagocytic and killing capacity. Cytokines, particularly TNF-alpha, interleukins and NO enhances the damage caused to the intestinal mucosa. This will in turn increase the intestinal permeability, favouring BT as seen in *figure3*. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014) (Wiest & Garcia-Tsao, Bacterial translocation (BT) in cirrhosis, 2005) (Bellot, Frances, & Such, 2013)

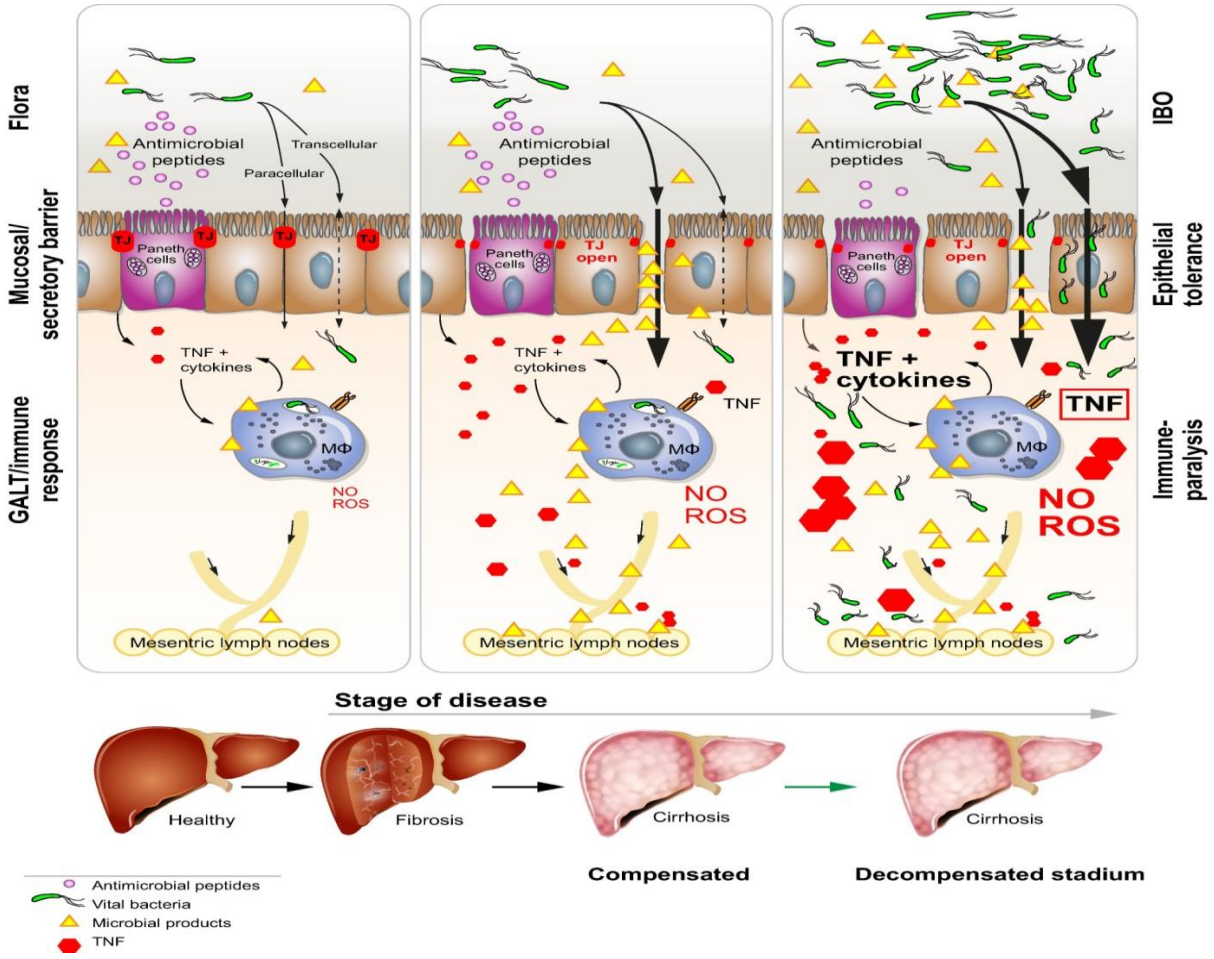

Figure 3. 'Stages of liver disease and hypothesis on development of pathological BT.
Left: normal healthy liver and gut wall integrity. With a normal physiological level of BT.
Middle: as the liver disease progresses an increase in paracellular BT is seen. This stimulates an increase in pro-inflammatory cytokine response and release of ROS and NOx within the GALT; these mediators impact on the mechanical and secretory barrier as well as most likely on the flora;
Right: in cirrhotic state the IBO and the decreased epithelial integrity of the G.I.T., enhanced transcytosis of viable bacteria, ultimately leading to immune paralysis in the GALT (which could lead to a vicious circle perpetuating BT by a relative lack of bacterial killing).' **(Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014)**

Adaptive immunity is an acquired and more specific immune response. There are two mechanisms in which intestinal bacteria are presented to the DCs. 1. M cells overlying lymphoid follicles endocytose antigens to local DC and Macrophages, both are antigen presenting cells (APC). (Wiest & Garcia-Tsao, Bacterial translocation (BT) in cirrhosis, 2005) 2. DCs under the epithelium send processes into the lumen and directly sample microbes. *See Figure 2.* These DCs will activate and prime B and T cells, when they mature they are released to the circulation and will travel back to the lamina propia due to homing markers

expressed on their surface. B-cells will then produce specific IgAs when presented with microbial antigens to help protect against BT. In cirrhosis both B and T cell number is reduced, leading to a negative effect on the immune system and facilitating BT to the systemic circulation, untimely leading to sepsis and death if untreated. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014) Bacterial infections in cirrhotic patients are associated with a poor prognosis and increased mortality rate. (Bellot, Frances, & Such, 2013)

These three main disorders (SIBO, Increased IP, and immune system disorders) play a large part in BT in cirrhosis and lead to more severe complications of liver disease.

2.2. Systemic inflammation

There is mounting evidence to show that systemic inflammation worsens the clinical symptoms of HE in cirrhotic patients (Dhiman, 2013) The mechanisms mentioned above exacerbate BT from the gut to the systemic circulation. This leads to a spontaneous bacterial peritonitis (SBP) and ultimately to systemic infection in cirrhotic patients. The most common infections are urinary tract infections (UTI), nosocomial pneumonia, sepsis and systemic inflammatory response syndrome (SIRS). (Luo, Guo, & Cao, 2015) When the gut derived bacteria and/or endotoxins reach the blood stream, they cause inflammation in the liver and spleen leading to a further decrease in their elimination. (Coltart, Tranah, & Shawcross, 2013) Sepsis and systemic inflammation are seen as a hallmark of the severity of liver cirrhosis and infection is a common trigger for HE. (Weiss, Jalan, & Thabut, 2018)

The liver is the 1st line of defence against bacteria translocating from the gut. Blood flows slowly through the liver parenchyma allowing most of the microbial agents from the portal system to be destroyed by the immune cells in the liver. In liver cirrhosis the hemodynamic is altered due to the increase in hepatic resistance and porto-systemic shunts (PSS), this causes the portal circulation to ‘by-pass’ the liver allowing these microbes to escape into the systemic circulation. This will lead to a chronic state of endotoxemia and inflammation. (Bleibel & Al-Osaimi, 2012)

Neutrophils are a key component of the innate immune response. They are recruited to the site of infection or inflammation and destroy the pathogens by generating reactive oxygen species (ROS) in a process called oxidative burst. The products of this process may damage surrounding tissue. This damage leads to an increase in the pro-inflammatory state of the patient. (Coltart, Tranah, & Shawcross, 2013) Ammonia induces neutrophil and macrophage swelling and dysfunction, decreasing their phagocyotic capacity. This can cause a sepsis-like immune paralysis. (Luo, Guo, & Cao, 2015) A similar neutrophil dysfunction is also seen in hyponatremia. This dysfunction causes a decrease in microbicidal activity. (Coltart, Tranah, &

Shawcross, 2013) The resulting immunosuppressed state leads to a higher prevelance of infection in cirrhotic patients. (Bleibel & Al-Osaimi, 2012)

SIRS is defined as the presence of at least 2 of the following factors: 1. Temperature above 38 or bellow 36 °C, 2. Heart rate above 90 beats/min, 3. Over 20 breaths/min, 4. White blood cell above 12,000/cu mm, below 4,000/cu mm or less than 10% neutrophils. It results in the release of pro-infammatory cytokines including TNF-α, IL-1β, IL-6, IL-8 and IL-12. (Coltart, Tranah, & Shawcross, 2013) These cytokine cannot directly affect the brain as they cannot cross the BBB but studies show that they exert their effect by other mechanisms discussed under neuroinflammation. (Luo, Guo, & Cao, 2015)

The presence and severity of HE have been shown to correlate positively with serum levels of inflammatory markers, not ammonia.

2.3. Neuroinflammation

The inflammatory response in the brain is called neuroinflammation. The brain parenchyma is made up of multiple cell types such as astrocytes, microglia, neurons and endothelial cells (EC) that have the ability to respond to and generate an inflammatory response. Although the BBB remains anatomically intact until the very late stages of HE, SIRS is able to exert its effects on the brain. (Wright, et al., neuroinflammaton in liver disease; sessional talks from ISHEN, 2015)

Neuroinflammation is closely related to systemic inflammation. Peripheral cytokines exert their effects on the brain, leading to the cerebral production of pro-inflammatory mediators, by 3 pathways: 1.activation of the vagus nerve's afferent neurons in target tissues, 2. Signals are sent by the brain vasculature through secondary messengers such as NO and prostanoids, which are produced in response to cytokines, 3.cytokines enter the brain at points where the BBB is lacking and exert effects on the brain parenchyma. (Luo, Guo, & Cao, 2015). IL-6, IL-1 and TNF-α are thought to be important for plasticity of synapses, long term potentiation, neurogenesis and memory consolidation. Increasing levels of these inflammatory cytokines can lead to disturbances in these processes and patients will show clinical signs.When they are decreased back to a normal level, patients preformed better in the psychometric tests than before the treatment. (Savlan, Liakina, & Valantinas, 2014)

Several studies have shown an increase in the severity of HE in cases of infection and systemic inflammation. There is a positive relationship between the brains production of cytokines and the severity of intracranial hypertension. This supports the activation of the inflammatory response in the brain in patients with advanced HE and cerebral oedema.

(Coltart, Tranah, & Shawcross, 2013) Brain oedema plays a major role in the neurological deterioration in acute HE. (Cudalbu & Taylor-Robinson, 2019)

The development of oxidative stress is also a contributing factor to the pro-inflammatory state of patients in both the peripheral circulation and CNS and is important in the pathogenesis of HE. Exposure of astrocytes to ammonia,cytokines, hyponatremia and benzodiazepines may produce ROS and reactive nitrogen species (RNS) in target tissues, leading to oxidative stress and induce a local and systemic inflammatory response. N-methyl D-aspartate (NMDA) receptors are important receptors for the production of free radicals. Oxidative stress can be avoided by administrating NMDA receptor antagonists. (Savlan, Liakina, & Valantinas, 2014) (Coltart, Tranah, & Shawcross, 2013)

2.4. Ammonia in the brain

Ammonia is considered to play a key role in the pathogenesis of HE. Ammonia is a neurotoxin, it impairs transport of electrolytes, water and amino acids through neuron membranes and astrocytes. It also disturbs metabolism of amino acids, energy consumption and nerve potentials transmission. (Savlan, Liakina, & Valantinas, 2014) The gut microbiota plays a key role in the pathogenesis of HE. Ammonia is predominantly derived from the gut, therefore many treatments are aimed at the reduction of harmful bacteria in the gut. (Dhiman, 2013) (Zhang, Feng, Cao, & Tian, 2015) Ammonia is produced by the enterocytes and as a by-product catabolism of ingested proteins by colonic bacteria. (Bleibel & Al-Osaimi, 2012)

In cirrhotic patients, systemic ammonia is increased, partially due to reduced urea cycle enzyme activity, which is linked to liver damage or liver shunting. This increased ammonia is converted to glutamine, through glutamine synthetase, in muscle cells and astrocytes. (Weiss, Jalan, & Thabut, 2018) Muscle wastage is common in these patients; this can predispose them to develop HE in cirrhosis as the ammonia and glutamine clearance is reduced further. This muscle wastage is not only linked to liver damage and decreased nutritional status but also elevation of some cytokines activate transcriptase factors like NK-a causing a reduction in myosin synthesis. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) (Ferenci, 2017) Ammonia affects the normal function of the central nervous system (CNS) in multiple ways. These include excitatory and inhibitory neurotransmissions, inhibition of glucose oxidation and stimulation of glycolysis, altered mitochondrial function and impairment of cellular transport systems. (Buttorworth, 2015)

Astrocytes are a type of glial cell in the CNS. They are particularly sensitive to ammonia as they contain glutamine synthetase. The role of this enzyme is to detoxify ammonia to glutamine in the brain; however the resulting accumulation of glutamine within the astrocytes causes osmotic stress and leads to cell swelling. (Coltart, Tranah, & Shawcross, 2013) One

hypothesis of the consequences of elevated glutamine is the '*Trojan horse hypothesis'.* This hypothesises that glutamine is taken up by the mitochondria in the astrocytes and converted to ammonia and glutamate. Here the ammonia then leads to the loss of mitochondrial function and astrocytic swelling. This hypothesis is not fully understood and further studies need to be undertaken to determine the exact mechanism. (Wright, et al., neuroinflammaton in liver disease; sessional talks from ISHEN, 2015)

Astrocytes are part of the macrophage lineage. They secrete cytokines and neurotrophic factors to neurons. They are also centrally involved in the formation of the BBB and in controlling the cerebrovascular tone. The purpose of the BBB is to provide a separation between the circulation and the brains extracellular fluid. Although the BBB remains anatomically intact in HE, studies show an increase in permeability to ammonia in more severe cases of liver disease. (Coltart, Tranah, & Shawcross, 2013)

Although ammonia is clearly a key factor in the development of HE, it is clear that it does not act alone in the development of the characteristic neurological and psychiatric abnormalities of HE (see *figure 4)*. Blood ammonia level is not a reliable indicator of the severity of HE in cirrhotic patients and ammonia lowering drugs are seen to be only partially effective in the treatment of HE. (Butterworth, 2015)

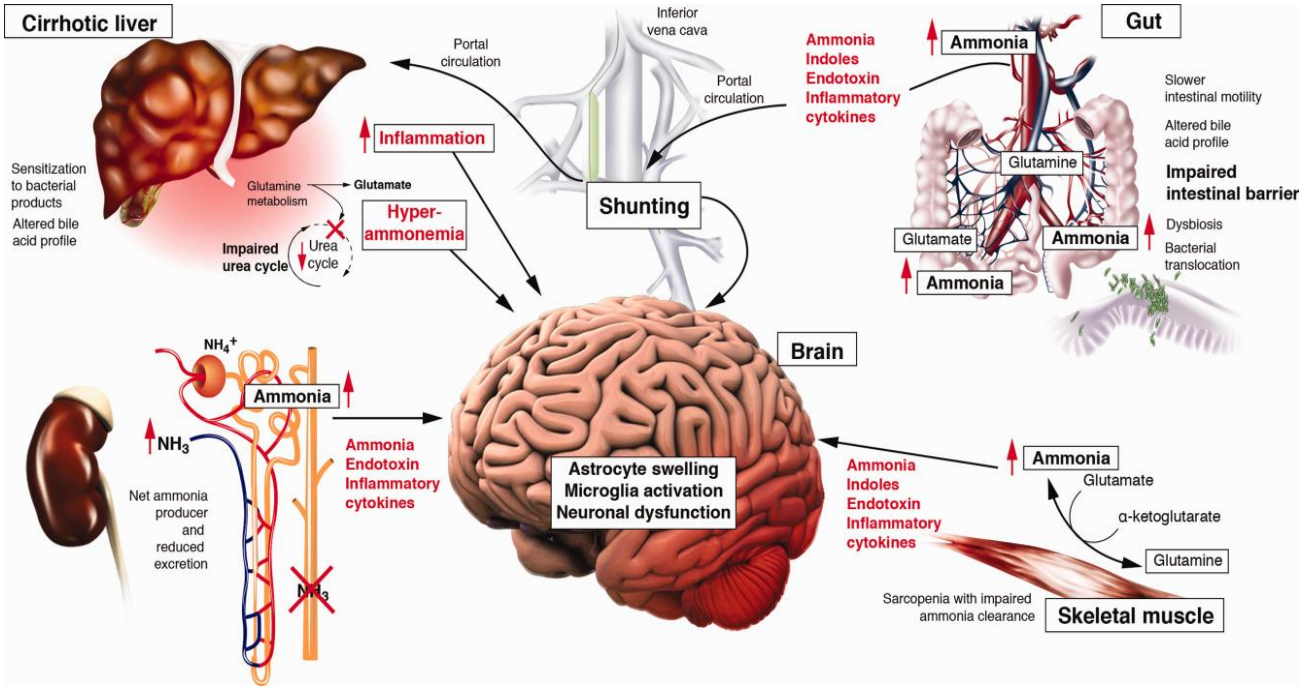

Figure 4. Multiple factors play a role in the pathogenesis of HE. (Bajaj, 2015)

2.5. Synergism

There is a synergestic effect of hyperammonemia and endotoxemia induced inflammatory response. (Rai, Saraswat, & Dhiman, 2015) Decompensated cirrhosis leads to both systemic inflammation and hyperammonemia. (Luo, Guo, & Cao, 2015) Inflammation exacerbates the effects of hyperammonemia on the brain, leading to cognitive deficits. (Felipo, 2013) Cytokines increase BBB permeability for ammonia and its passage into astrocytes. (Savlan, Liakina, & Valantinas, 2014) it has been shown that there is greater neuropsychological function following induced hyperammonemia in cirrhotic patients who have severe inflammation or infection. (Rai, Saraswat, & Dhiman, 2015)

TNF-α and IL-β have receptors on the endothelial cells. These endothelial cells, when activated by systemic inflammation and the pro-inflammatory mediators, will release different pro-inflammatory mediators or secondary messengers into the brain. The macrophages of the brain, also known as microglial cells, can also be activated by these pro-inflammatory mediators and release various types of inflammatory chemokines. (Luo, Guo, & Cao, 2015)

Endotoxins, produced by the intestinal bacteria can enter systemic circulation by BT and portosystemic shunting. It can cause activation of the immune system either through activation of toll-like receptors or by the production of pro-inflammatory cytokines. Like pro-inflammatory cytokines endotoxins cannot cross the BBB but can increase permeability of the BBB and act on the brain itself by the production of secondary messengers from endothelial cells.

Excess manganese is normally removed via the hepatobillary system. (Butterworth, 2015) Manganese is a neurotoxin, it accumulates only in the basal ganglia of the brain. Manganese is seen to normalise low striatal levels of dopamine. Some extra pyramidal symptoms in cirrhotic patients are thought to be due to altered dopaminergic function. This may explain the accumulation as an attempt of the brain to correct dopamine deficiency in liver disease. When liver function is restored manganese is eliminated. (Savlan, Liakina, & Valantinas, 2014) (Ferenci, 2017)

Manganese which is deposited at the sustantia nigra is most likely to cause the clinical condition called parkinsonism in cirrhosis. Not only does manganese interact with dopamine production it also has a detrimental effect on glutamatergic neurotransmitter system, It causes a decrease in the ability of astrocytes to accumulate glutamate. This process is necessary for the inactivation of glutamate's synaptic action. Ammonia has a similar effect and has been shown to have a synergistic effect with manganese. (Butterworth, 2015)

Increases of pro-inflammatory cytokines in the brain following activation of microglial cells may exeracebate the problem. Ammonia, manganese and pro-inflammatory are shown to work synergistically and lead to a nitrosative stress (see *Figure 5*.). (Buttorworth, 2015)

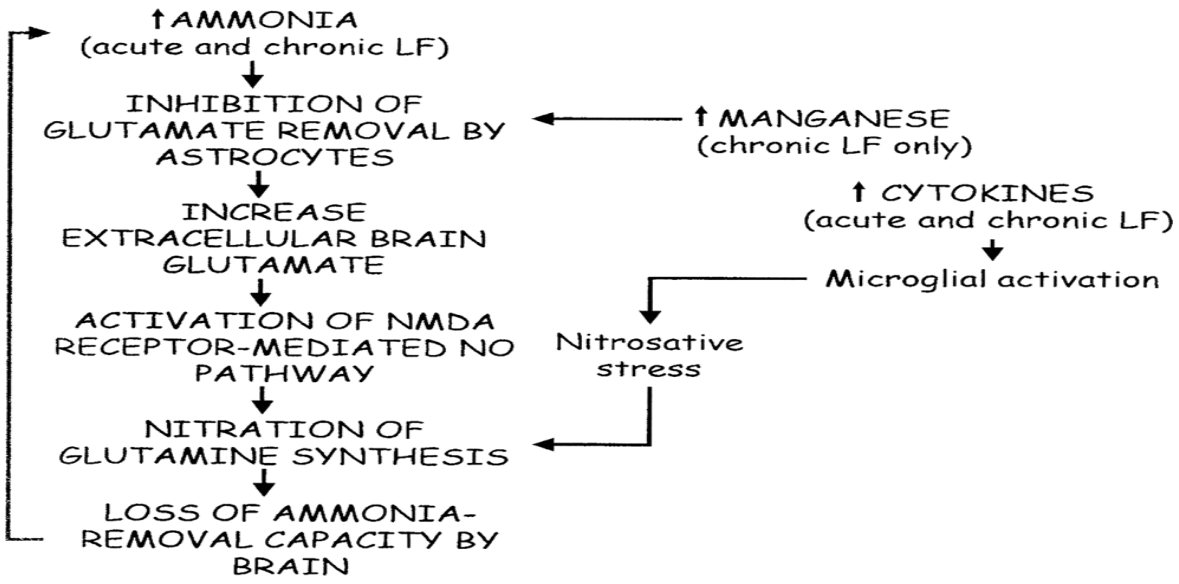

Figure 5. "Possible mechanisms implicated in the synergism between ammonia, manganese and proinflammatory cytokines related to the pathogenesis of HE in acute and chronic liver failure. Both ammonia and manganese inhibit high affinity glutamate transport by the astrocyte resulting in increased extracellular concentrations of glutamate leading to the activation of post-synaptic glutamate NMDA receptors, activation of the NO signal transduction pathway and nitration of glutamine synthetase protein. Glutamine synthetase is the only ammonia-detoxifying route in brain; this causes an increase in brain ammonia levels and will lead to a vicious cycle. Neuroinflammation which is caused by microglial activation occurs independently in nitrosative stress and the synergisticeffect of nitration of glutamine synthetase protein leads to a further loss of brain ammonia-removal capacity. The result of these processes is an increase of brain ammonia with stimulation of multiple mechanisms including ammonia-induced accumulation of lactate, impending brain energy failure and neurotransmitter imbalance, brain edema and encephalopathy". **(Butterworth, 2015)**

Glucose is the main energy source of the mammalian brain. Increasing evidence shows that the metabolism of glucose is altered early on the progression of HE, leading to abnormal CNS metabolism and function. Increased brain lactate has been linked to increased intracranial hypertension and poor out comes in dogs with ALF. (Buttorworth, 2015) Hyperammonemia leads to lactate accumulation in the brain. This will also cause an activation of microglial cells and production of TNF-α, IL-1β and IL-6.

Anti-inflammatory treatment reduced neuroinflammation and restores motor and cognitive function in hyperammonemic rats. This again indicated the inflammation has a synergistic effect and mediates the effect of ammonia on the brain. (Rodrigo, et al., 2010) Many studies have shown the synergistic effect of ammonia and systemic inflammation. Some show that there was no cognitive impairment with either ammonia or inflammation but when acting together resulted in significant cognitive impairments in cirrhotic patients with MHE. (Luo, Guo, & Cao, 2015)

Although it is not fully understood, many factors appear to work together to influence the severity and occurrence of HE. This is very important in terms of treatment as several aspects of the disease may need to be assessed and treated to improve clinical symptoms or to avoid the occurrence of HE.

3. Treatment and prevention

The main aim in treatment is to identify and treat the precipitating factors. Treatment of these factors can be used as a prevention of the development of HE. In the prevention of first time episodes it is called primary prophylaxis, for further episodes it is secondary prophylaxis. (Lunia, Sharma, Sachdeva, & Srivastava, 2014)

Precipitating factors can often be identified by a physical exam, lab and imaging tests including blood count, renal function test, serum electrolytes, chest x-ray, urinary analysis, blood cultures and ascetic fluid analysis. Infection is a very common precipitating factor in patients with HE. (Bleibel & Al-Osaimi, 2012) Another key part of the therapy is the removal of bacterial toxins and influencing the gut flora as can be seen in *figure 6*. (Cudalbu & Taylor-Robinson, 2019)

The treatment of HE should be combined with the treatment of other complications of cirrhosis. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) It is important to recognise that HE is mostly reversible if the precipitating factor is found and treated. (Bleibel & Al-Osaimi, 2012)

Each treatment plan should be altered to meet the specific requirements of each patient.

3.1. Nutrition

Modulation of nitrogen metabolism is a crucial aspect in the management of HE. (Ferenci, 2017) During an acute episode of HE nutrition is usually given parenterally. When the patient recovers oral feeding is resumed with low levels of protein which a gradually increased until the maximum tolerance amount is reached. A good nutritional status significantly improves the prognosis in HE. An increase in muscle mass can enhance the metabolism of ammonia. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003)

Long term protein restriction is seen to be detrimental to patients. In experimental models, it has also been noted that a free protein diet increases the ammonia level in the circulation due to a decrease in enzyme activity in the urea cycle. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) Their protein requirements are relatively greater than that of normal patients and they run the risk of accelerated fasting metabolism. This can lead to wasting of muscle which has a negative effect in the case of HE as spoke about above. (Ferenci, 2017)
In patients with a low tolerance to dietary proteins supplements rich in branch amino acids can be used. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) Another option, especially in patients with refractory HE, is to give a vegetable based protein diets.

3.2. Non-absorbable disaccharides

The non-absorbable disaccharides include lactulose (β-galactoside-fructose) and lactitol (β-galactoside-sorbitol). They are well known for their laxative effect but they also reduce colonic pH and decrease uptake of glutamine from the gut. This in turn reduces the synthesis and absorption of ammonia. (Cudalbu & Taylor-Robinson, 2019) Studies have shown that they not only reduce circulating ammonia but as reduce pro-inflammatory cytokines and endotoxins. This was shown to improve cognitive and motor function in HE patients. (Luo, Guo, & Cao, 2015)

The non-digestible disaccharides are broken down by the intestinal bacteria in the colon to short chain fatty acids which lower the colonic pH. This in turn causes NH3 to be converted into NH4, which is non absorbable. They may also decrease GI transit time, which is commonly increased in cirrhotic patients, further increasing nitrogen excretion in the feaces. (Bleibel & Al-Osaimi, 2012)

Both are taken orally and are metabolised in the colon by bacteria. They are not absorbed in the gut because of the absence of specific disaccacharidases. The dose should be given that results in 2 to 3 smooth bowel movements per day. It is usually administrated 2 to 3 times per day depending on the patient. The dosage can be adjusted over time to give the desired result. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) In severe clinical cases of HE, if the patient is at risk of aspiration of oral medication, Lactulose can be administered via a nasogastric tube after endotracheal intubation or can be given by rectal enema. (Bleibel & Al-Osaimi, 2012) Lactitol is similar to lactulose; it appears to be more effective but needs further research to confirm this. (Ferenci, 2017)

Adverse effects may include flatulence, diarrhea, abdominal pain and intestinal malabsorption. This often leads to noncompliance in cirrhotic patients. (Luo, Guo, & Cao, 2015) Care must also be taken to avoid dehydration and electrolyte imbalance, by increased bowel movements, with can lead to progression of HE. (Bleibel & Al-Osaimi, 2012)

3.3. Antibiotics

For patients that do not tolerate non-absorbable disaccharides or do not respond to them antibiotics can be used. Again their purpose in to reduce the ammonia produced by the bacteria in the gut. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) Antibiotics eliminate

pathogenic gram negative in the GIT, inhibit BT and therefore reduce pro-inflammatory cytokines and endotoxins. (Luo, Guo, & Cao, 2015)

Rifaximin is an oral antibiotic with minimal absorption and very few adverse affects. It has no known drug-drug interactions and a low risk of inducing bacterial resistance. (Cudalbu & Taylor-Robinson, 2019) In trials rifaximin shows a cognitive improvement and lower ammonia levels. (Ferenci, 2017) (Cudalbu & Taylor-Robinson, 2019) In cirrhotic patients with MHE it was shown that rifaximin can regulate the intestinal flora, reduce endotoxin and pro-inflammatory cytokines production and lead to an improvement in cognitive function. When compared with lactulose, rifaximin correlated with decreased hospitalisation and better clinical manifestations. (Luo, Guo, & Cao, 2015) Many studies undertaken have shown that rifaximin is more beneficial than non absorbable disaccharides and has been associated with a higher response rate, faster effects and less side effects. Patients show a better quality of life and a reduced recurrence rate of HE. (Bleibel & Al-Osaimi, 2012)

Neomycin is a known glutaminase inhibitor and was widely used in the past as part of the treatment plan of HE. Metronidazole can be used for short term treatment but has been shown to have ototoxic, nephrotoxic and neurotoxic properties in long term use. (Ferenci, 2017)

3.4. Medications affecting neurotransmission

Doperminergenic drugs are now used to conteract the deficit of domaminergenic function, resulting from the manganese, which is deposited on the basal ganglia. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) It is important to note that these drugs may cause constipation so the dose of non-absorbable disaccharides may need to be increased. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003)

The production of free radicals may be mediated by the activation of NMDA-receptors in hyperammonemia. NMDA-receptor antagonists have been shown to prevent oxidative stress in ammonia intoxication. Although they do not influence the ammonia concentrations they have been shown to improve EEG activity, clinical grading, intracranial pressure and water content of the brain. (Coltart, Tranah, & Shawcross, 2013) NMDA-receptors are a subclass of glutamate receptors which are located on both neuron and astrocyte membranes. Memantine, an NMDA-receptor inhibitor, reduced the clinical grade of HE. (Buttorworth, 2015)

The GABA receptor complex contributes to the inhibition of HE. It is the main inhibitory network in the CNS and consists of a GABA binding site, a chlorine channel and barbiturate and benzodiazepine receptor sites. Flumazenil, an antagonist of benzodiazepine receptor, has been proven to partially reverse HE but the effect is only for a short time. (Bleibel & Al-Osaimi, 2012)

3.5. Probiotics

As mentioned above, the abnormal function of the G.I.T. and the imbalance of gut flora play a key role in the development and severity of HE. Therefore it is important to stabilize and maintain the normal gut flora.
Probiotics are living beneficial bacteria, they are able to inhibit bacterial ureases, modulate pH and decrease ammonia absorption. (Luo, Guo, & Cao, 2015) Prebiotics are defined as non-digestable beneficial ingredients which either stimulate the growth or action of beneficial bacteria in the gut. Synbiotics are a combination of pro- and prebiotics. They improve dysbiosis by decreaseing pathogenic bacteria so have been shown to improve endotoxemia, HE and liver disease. (Dhiman, 2013)

Probiotics and synbiotics are safe, effective and widely available. Although their mechanism of action is not clear they have been shown to be effective in the treatment of HE. When administrated for prolonged periods of time it has been demonstrated that they reduce urease producing bacteria in the gut, acidify colonic secretions, decrease blood ammonia and reverse MHE in some cases. (Montgomery & Bajaj, 2011) They have also been shown to inhibit bacterial activators like TLRs, reduce IL-10 and TLR-4 expression and restore neutophil pahagocytosis activity in patients with cirrhosis. (Luo, Guo, & Cao, 2015)

3.6. Other treatments

Glyceryl phenylbutyrate (GPB) is a metabolic ammonia scavenger, clinical trials have been shown a decrease in the number of episodes and hospitalisation. A longer time before the first event occurred was also seen. (Ferenci, 2017) It has been used in treatment of urea cycle disorders by mediating the excretion of nitrogen waste. When taken a prolonged urinary exvcretion of phenylacetylglutamine (PAGN). Urinary PAGN enhances excretion of waste nitrogen and lowers ammonia levels. (Montgomery & Bajaj, 2011)

Ornthine-asparate provides substrates for the urea cycle and for the synthesis of glutamine and also diminished ammonia levels. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) It has successfully been used in the treatment of HE as an ammonia lowering agent. As well as stimulating urea formation it also muscle ammonia removal in the form of glutamine. (Buttorworth, 2015)

Sodium benzonate reduces ammonia levels by increasing urinary excretion levels. (Lizardi-cervera, Almeda, Guevara, & Uribe, 2003) It reacts with glycine to develop hippurate which is a nitrogen waste excreted in the urine. Results of studies indicated similar efficacy to lactulose. (Bleibel & Al-Osaimi, 2012)

Molecular adsorbant recirculating system (MARS), have been found to modulate the inflammatory response and result in a decrease in pro inflammatory mediators. This helps improve clinical cases of HE and delay progression of symptoms. This is a method of hemodiafiltration, to eliminate albumin bound and water soluble toxins, using an albumin containing solution and a high flux membrane. MARS decreases inflammatory mediator from the circulation like TNF-α, IL-6, IL-8 and Interferons (INF-γ), also a reduction in NO by both clearance and reduced production. HE patients showed improvements on this theraphy. (Luo, Guo, & Cao, 2015)

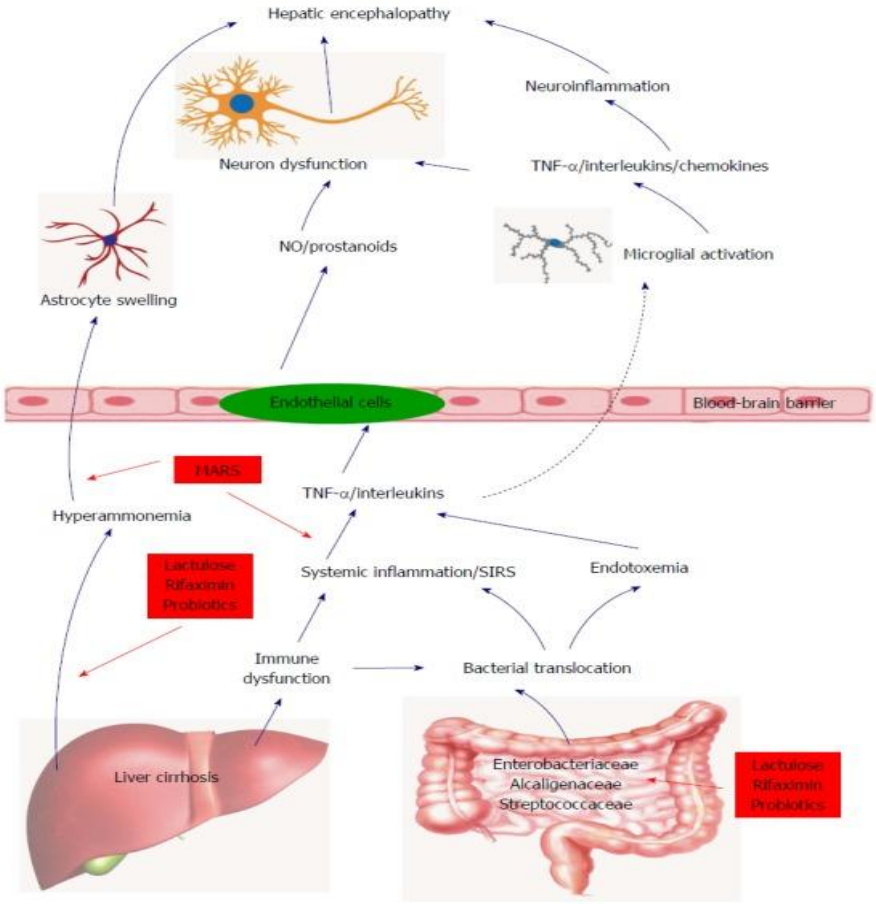

Figure 6 The inflammatory pathogenesis of hepatic encephalopathy in liver cirrhosis.
Lactulose, rifaximin, and probiotics not only reduce the circulating levels of ammonia but also modulate intestinal flora, lower the endotoxemia and inhibit the production of pro-inflammatory cytokines. MARS treatment also decreases the circulating levels of ammonia and pro-inflammatory cytokines**. (Luo, Guo, & Cao, 2015)**

Mild hypothermia (lowering temperature by two or three degrees) has been shown to decrease brain oedema and other complications in liver failure. The mechanism is not clear but it has been proposed that it may be caused by decrease blood brain ammonia transfer and/or decreased lactate production so an improvement in brain energy metabolism. It also possesses anti-inflammatory properties. (Buttorworth, 2015) When the temperature is dropped a decrease in free radical production occurs, there is also a decreased in cerebral blood flow, systemic inflammation and oxidative stress which will help lower cranial hypertension. (Coltart, Tranah, & Shawcross, 2013)

N-Acetyl Cysteine (NAC) antioxidant and central anti-inflammatory properties have been credited to its use. Improvements in both hepatic and neurological function have been observed after its administration. This is widely used in acetaminophen overdose but also shows to be beneficial in non- acetaminophen liver damage. (Buttorworth, 2015) It replenishes glutathione stores and prevents hepatic necrosis. It is shown to have a hemodynamic effect, improving cerebral perfusion pressure in liver failure patients.

Liver transplantation is known to greatly improve the clinical status of cirrhotic patients with HE. Although it is thought to reverse the effect caused by the liver damage to the brain and the mental status of the brain this is not strictly true. After each episode of overt HE, a residual neurological impairment will remain. Structural changes in the brain have been detected using Magnetic resonance imaging (MRI), the extent of this damage directly relates to the number of overt HE episodes the patient has had. (Bleibel & Al-Osaimi, 2012)

It is important after treatment that the patient is re-evaluated. If they still have some neurological dysfunctions it is important that they can be cared for appropriately and maintenance medication should be given if needed. Patients owners or carers should be educated on how avoid future episodes and reduce risks of precipitating factors (e.g. diet), how to administer the medication and why it is important to closely adhere to the treatment plan and how to identify a re-occurrence and what to do. (Vilstrup, et al., 2014)

4. Differential diagnosis

The neurological signs of HE are nonspecific. Other similar disorders must be considered in any patient with these signs and liver failure. If present, these concomitant diseases may be an additional source of neurological dysfunction. (Ferenci, 2017)

- Metabolic encephalopathy
- Hypoglycemia
- Hyponatremia

- Hypoxia
- Hypercarbia
- Uremia
- Ketoacidosis
- Heavy metal intoxication
- Intoxication: Alcohol, sedatives, narcotics, hypnotics, antidepressents, neuroleptics, and salicylates
- Alcohol withdrawal
- Wernicke encephalopathy

Hyperammonemia not related to liver failure or portosystemic shunts could be seen in:

- Renal failure
- Urinary tract infection with a urease-producing organism (e.g.Proteus mirabilis)
- Ureterosigmoidostomy
- Severe muscle exertion/heavy exercise
- Transient hyperammonemia in newborns
- Urea cycle defects
- Gastrointestinal bleeding
- Parenteral nutrition
- After high-dose chemotherapy
- Side effect of certain drugs: Valproic acid, Barbiturates, Salicylate intoxication

Organic CNS diseases:

- Intracranial lesions: Subdural hematoma, intracranial bleeding, stroke, tumor, or abscess infections like meningitis, encephalitis, or intracranial abscess
- Organic brain syndrome
- Traumatic brain injury
- Postseizure encephalopaty

(Bleibel & Al-Osaimi, 2012)

5. Summary

HE is a serious complication of liver cirrhosis causing neuropsychiatric signs. Ammonia has long been known to be a major factor in the pathogenesis but now inflammation has been shown to play a key role. In the majority of cases this inflammation is caused by BT and endotoxemia derived from the bacteria in the gut to the MLN and then to the systemic circulation. (Luo, Guo, & Cao, 2015) Multiple factors may be contributing to Pathological BT in cirrhotic patients. This can differ from case to case depending on type of translocating agent, genetic susceptibility of the host, environmental factors and the stage and etiology of the disease. (Wiest, Lawson, & Geuking, pathological bacteria translocation in liver cirrhosis, 2014)

One of the livers main roles in the body is to detoxify and neutralise many toxic chemicals which are absorbed from the gut and reach the liver through the portal vein. If the liver is damaged or not working correctly, this will lead to an increase in these un-metabolised toxins entering the systemic circulation, which will eventually reach the brain and other organs. (Bleibel & Al-Osaimi, 2012)

Liver failure is associated with IP of GIT leading to increased BT and activation of the innate immune system. In liver failure the innate immune response is diminished due to the effects on neutrophil phagocytic capacity, decrease hepatic antimicrobial products and reduced reticuloendothelial system. (Weiss, Jalan, & Thabut, 2018) Advanced cirrhosis acts like a chronic inflammatory disease. The immune system is continuously activated by bacteria and/or bacterial products of intestinal origin (BT). Most of the pro-inflammatory state seen in cirrhosis is owing to the BT to the systemic circulation. (Bellot, Frances, & Such, 2013)

The brain requires anatomical brain intergerity, sufficient energy and efficient synapse neurotransmission to function correctly. In HE all of these do not function correctly. (Bleibel & Al-Osaimi, 2012)

As the gut flora is clearly implicated in HE development, it is important to try to control the balance. It is a key treatment approach. If the gut flora can be controlled this will reduce BT and improvements the clinical signs of HE. (Rai, Saraswat, & Dhiman, 2015)

Inflammation, ammonia and many other factors play a synergistic role in the development of HE. (Jayakumar, Rao, & Norenberg, 2015) It is important to treat the underlying liver disease but also to treat the precipitating factors. The clinical signs of HE will usually decrease and/or disappear after the treatment of these precipitating factors. (Lunia, Sharma, Sachdeva, & Srivastava, 2014)

Combinations of medications are used, including gut modulators like rifaximin, probiotics and lactulose and anti inflammatory drugs. (Luo, Guo, & Cao, 2015) It is important that a treatment plan should be made on a case by case basis.
The only ‘curative’ option at this stage is liver transplantation. (Pijls, Jonkers, Masclee, & Koek, 2013)

There are many hypothesised mechanisms for HE but it is still not fully understood. Although many of the current treatments decrease the clinical signs and improve the quality of life, they are still quite limited. More research is required in this topic to fully understand both the pathogenesis and treatment of HE.

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I hereby confirm that I am familiar with the content of the thesis entitled THE CURRENT CONCEPT IN THE PATHOGENESIS AND TREATMENT OF HEPATIC ENCEPHALOPATHY written by LORRAINE CUNNINGHAM (student name) which I deem suitable for submission and defence.

Date: Budapest, 21 day 11 month 2019 year

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