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EDITORIAL

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Dear Readers,

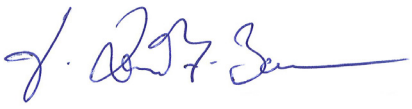
The focus of a satellite symposium, which took place virtually during this year's DGIM Congress, was on questions regarding patients' prognostic situation for liver diseases. How can the prognosis be improved? What is the prognostic significance of complications for liver cirrhosis or what is the significance of a fibrosis for NAFLD? In our focus topic, we have summarized the interesting contributions made by the renowned speakers on this matter.

In the expert's interview, Dr. Henning Pflugrad of the Medizinische Hochschule Hannover answers questions on the clinical significance of hepatic encephalopathy.

This time, in the section from research & literature, we are presenting the most important statements from three current publications to you. Here, it is about the biomarkers for the hepatic encephalopathy , the role of anomalies of brain activity in the pathogenesis of HE, as well as possible causes of cognitive disorders in patients with fatty liver diseases.

You will find more information and download options on our website for specialist groups www.hepa-merz.com.

We hope you find this read both interesting and informative.



Judith Lambert-Baumann

LIVER CIRRHOSIS

COMPLICATIONS ARE PROGNOSIS-RELEVANT

"Different to a heart attack, a chronic liver disease does not occur suddenly, but it develops over a long phase, which can be used for prevention and early detection. However, this is only too rarely the case nowadays", this is how Professor Peter R. Galle from Mainz began his presentation during an online satellite symposium at this year's German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin – DGIM) congress.

According to Galle, only a quarter of patients are free of complication when they are first diagnosed with liver cirrhosis. Complications such as ascites, hepatic encephalopathy (HE), gastroesophageal varices, hepatorenal syndrome and liver cancer develop in the later phases of the pathogenesis of a liver cirrhosis. At this point, the prognosis for the patient is substantially worse.

A diagnosis that comes too late can characterize the care situation of the patient with liver cirrhosis. An early diagnosis means better intervention options and accompanying this a better prognosis. Screening strategies that improve early detection would be relevant and would need to be specific, trans-sectoral and evidence-based. To date, medical check-ups, like the Check-up 35 do not contain a liver value screening. Specialists are requesting that a screening for an increase in alanine aminotransferase (ALT) is included within the program in conjunction with a non-invasive fibrosis-risk tool to increase the early-diagnosis share of treatable chronic liver diseases.

In the project SEAL by the Cirrhosis Center at the University of Mainz the ALT screening is a component of the Check-up 35 program. The aim is

IN THIS ISSUE YOU WILL FIND

to improve the care for patients with advanced liver cirrhosis by increasing the early-diagnosis share. Involved in the project are general practitioners, specialists and liver centers. F3 and F4 diagnoses, prevalence of liver value increase, detection of hepatopathies and the application of specific treatment approaches were determined at end-points.

HE), which are associated with very mild clinical indications. Diagnosis of covert HE is generally by way of psychometric tests that indicate the patient's cognitive performance.

During the course of the diagnosis, various differential diagnoses are of significance, like diabetes mellitus, electrolyte disorders, infections, alcohol, drug and medication intoxications; as well as neurological and psychiatric illness-

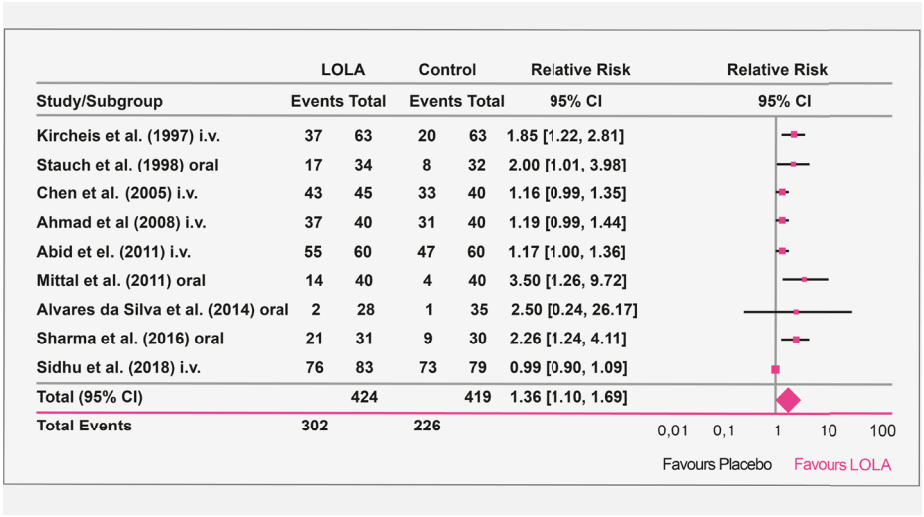


FIGURE 1: Meta-analysis for efficacy of LOLA across all stages of HE, mod. acc.[1]

HE SEVERE COMPLICATION WITH LIVER CIRRHOSIS

Hepatic encephalopathy (HE) is the second most frequent complication for liver cirrhosis, which impairs the patient's prognosis and affects quality of life already in the early stages. As Dr. Anton Gillessen from Münster explained at the symposium, HE is a potentially reversible, metabolically-determined dysfunction of the central nervous system, which appears as a complication for acute and chronic liver diseases. For HE in conjunction with liver cirrhosis, it is differentiated between episodic, persistent and minimal form. These three forms must be differentiated in principle, according to Gillessen. For that reason, a detailed anamnesis is allegedly important within the framework of diagnosis. The current DGVS guidelines recommend vigilance with regard to HE symptoms for all cirrhotic patients, both during the initial diagnosis and also during the course of the disease.

Not only the clinically advanced HE stages significantly affect the performance and quality of life of patients, however this is already the case for stages mHE (minimal HE) and HE 1 (covert

ses. Triggering factors of HE can, according to Gillessen, be infections, gastro-intestinal bleeding, medication, operations and protein-excess. A series of studies show that changes to the intestinal microbiota play a role in the pathogenesis of HE.

HE BARES THE HIGHEST MORTALITY RATE FOR LIVER CIRRHOSIS

Of all complications associated with liver cirrhosis, HE bares the highest risk of mortality and, in most cases, it is diagnosed too late. As a result, the possibilities for causal treatment is missed.

The aims of early treatment are the prevention of hospital admissions, maintaining or improving the psychomotor capabilities, as well as the disease-related life quality, and prevention of further HE episodes. HE treatment is generally a long-term treatment.

Management of HE is based on three pillars: exclusion of other causes of cognitive disorders, identification, elimination of the HE-triggering factors, and subsequently the empirical treatment. Nutrition plays an important role in the treatment of HE. Alongside sufficient energy

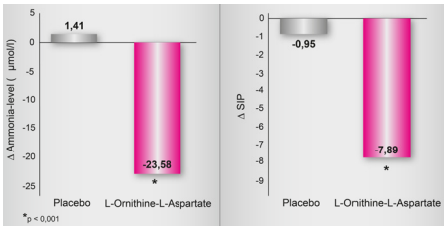


FIGURE 2: Significant reduction in the ammonia levels and SIP score when compared with the placebo after 6 months' treatment with LOLA (N=150), mod. acc.[2]

supply, the protein supply should not fall below 1.2 to 1.5 g/kg bodyweight. Food intake should be in small, frequent mealtimes to prevent longer phases with an empty stomach.

There are three substances available as a medicinal treatment. Lactulose, which prevents the transfer of ammonia from the intestine into the blood, is not always accepted by patients. Rifaximin is an intestinal-selective antibiotic for the prevention of recurrence of episodes of a manifesting hepatic encephalopathy.

"PATIENTS BRIGHTEN UP SHORTLY AFTER LOLA INFUSION"

L-Ornithine L-Aspartate (LOLA, Hepa-Merz®) stimulates the breakdown of ammonia by activating both the urea and the glutamine synthesis. LOLA is permitted for use in the treatment of latent and manifest HE. The medication is available orally and intravenously. According to Gillessen, the effect sets in very quickly after the infusion. "The patients brighten up shortly after and you can see how well it works in the advanced stage."

The efficacy of LOLA has been confirmed in a meta-analysis of 10 clinical controlled studies in all HE stages (Fig. 1).

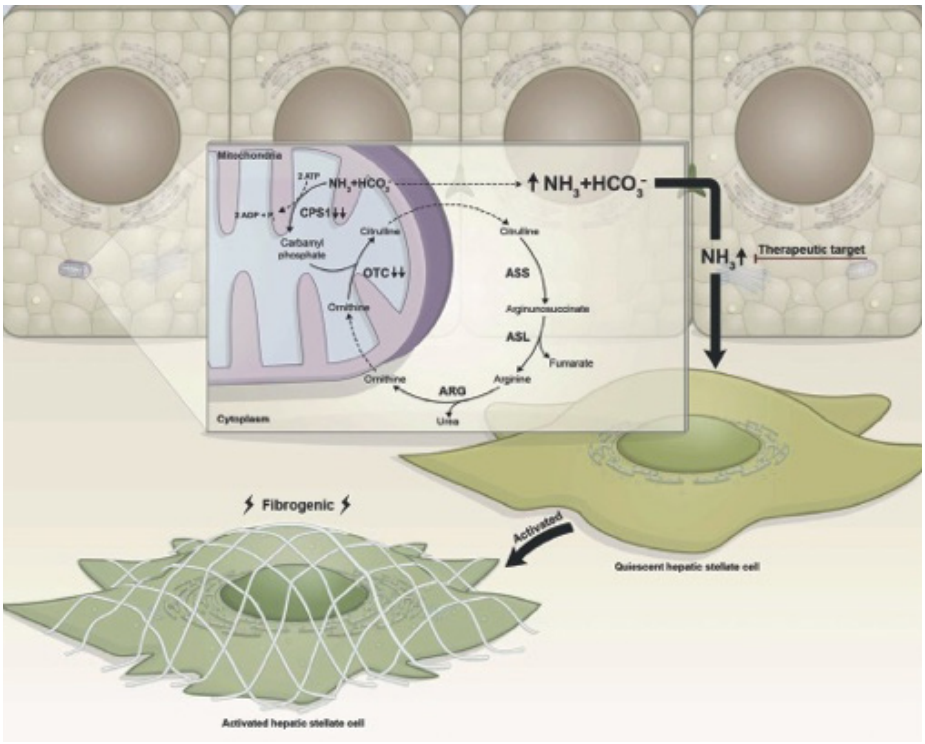


FIGURE 3: The early applied ammonia synthesis with NASH leads to the activation of the hepatic stellate cell and as a result to the development of a fibrosis, source:[3]

The efficacy could even be documented in the secondary prophylaxis of overt HE episodes. A study with cirrhosis patients after an HE episode shows a significantly lower chance of another HE episode in patients who were treated for six months with LOLA. Even the ammonia levels and SIP score (sickness impact profile) were significantly reduced when compared with the placebo (Fig. 2).

FIBROSIS PROGNOSIS-RELEVANT TO NASH AND ASH

There is still no medication for the treatment of NASH (non-alcoholic steatohepatitis) and ASH (alcoholic steatohepatitis), Professor Elke Roeb of Giessen clarified. It is therefore even more important to understand the pathopsychological basic principles and to correct the diagnosis.

"In Germany it is the opinion", said Roeb, "that fatty liver is detected among approx. 10 % of all hospitalized admissions." The majority of patients are between the ages of 60 and 80 years old. Among 10 % of them, NASH is already present.

For both NASH and ASH, fibrosis is prognosis-relevant. It is estimated that the number of F2 and/or F3 fibrosis patients needing treatment will increase three-fold by 2030. At the moment, the number of fibrosis patients with NASH is drastically increasing.

A compensated liver cirrhosis is not associated with a higher mortality. However, should complications arise, such as ascites, HE, icterus or gastro-intestinal bleeding, the patient's survival rate drastically decreases. According to Roeb, a decompensation would therefore absolutely be prevented. Where cirrhosis is alcohol-related, HE is linked to a clearly worse outcome.

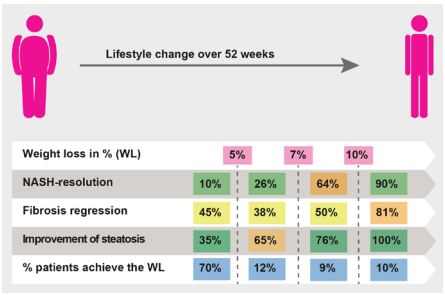
With the pathophysiology of NASH, unhealthy lifestyles, above all a lack of movement, but also a genetic predisposition play a role.

AMMONIA LEADS TO FIBROGENESIS WITH NASH

HE develops very early on for NASH patients, even before the onset of a fibrosis or cirrhosis. The cause is a very early onset of ammonia synthesis. Ammonia leads to the activation of hepatic stellate cells and thereby to fibrogenesis (Fig. 3).

The diagnosis of NAFLD initially occurs in the primary medical practice. According to DGVS guidelines, the fibrosis risk should subsequently be determined, for example with the FIB-4 score or the NFS (NAFLD fibrosis score). Where the risk is high, the patient is cared for by a specialist.

The most important treatment measure for NAFLD is changing lifestyle. At the forefront is a reduction in bodyweight by at least 10 %. It is in this way that a high resolution of NASH, fibrosis regression and an improvement in the steatosis can be achieved (Fig. 4).



Weight loss in % (WL)	5%	7%	10%	
NASH-resolution	10%	26%	64%	90%
Fibrosis regression	45%	38%	50%	81%
Improvement of steatosis	35%	65%	76%	100%
% patients achieve the WL	70%	12%	9%	10%

FIGURE 4: Probability of a NASH resolution, a fibrosis regression (at least one stage) and a steatosis improvement in patients with NASH where there is lifestyle intervention and in conjunction with percentage weight loss, mod. acc.[4]

Other than this, prompt HE treatment is important to improve the transaminase values, the gamma-glutamyl transferase and thereby the prognosis.

LITERATURE

1 Butterworth RF et al., J Clin Exp Hepatol. 2018; 8(3):301–313. **2** Varakanahalli, S. et al. Eur J Gastroenterol Hepatol 2018;30(8):951–958. **3** K.L. Thomsen et al., Medical Hypotheses 2018;113:91–97. **4** Romero-Gomez et al., J Hepatol. 2017; 67(4):829–846.

CLINICAL SIGNIFICANCE OF HEPATIC ENCEPHALOPATHY IS VERY HIGH

EXPERT INTERVIEW WITH DR. HENNING PFLUGRAD · CLINIC FOR NEUROLOGY AT THE HANNOVER MEDICAL SCHOOL (MEDIZINISCHE HOCHSCHULE HANNOVER)

Dr. Henning Pflugrad, Hannover Medical School
Photo: MHH

The hepatic encephalopathy is among the most frequent and severe complications for patients with liver failure. It makes the prognosis worse and affects the patient's quality of life. If diagnosed promptly, the neurological disorder can be treated well.

Dr. Pflugrad, what is the significance of hepatic encephalopathy (HE) today in medical practice? What role does minimal hepatic encephalopathy (mHE) play?

The clinical significance of hepatic encephalopathy is very high, because there are so many patients with chronic liver failure. It is estimated that approx. 35–45 % of these patients experience HE episodes. The frequency of minimal HE is estimated to be about 30-80 % among patients with chronic liver failure. The large range with mHE can be traced back to the impairments not being determinable in clinical investigation and therefore the psychometric test procedures are required. As a result, the estimated number of affected patients is definitely high. The significance of mHE is however, not to be underestimated because it can restrict the performance and health-related quality of life of the patient.

What influence do comorbidities, like metabolic disorders or neurological diseases often found with cirrhosis, have on the development of an HE?

Factors such as infections, medication, metabolic disorders, electrolyte lapses or traumas can trigger HE or substantially influence the course. Identification of these triggering or accompanying factors is a great challenge, but always of immense significance because the treatment or removal of these factors is the first step in treating HE.

How is HE diagnosed and treated?

HE is always a diagnosis by exclusion because there are no symptoms or biomarkers that unequivocally demonstrate HE. If a patient with liver cirrhosis develops cognitive disorders, the causes are initially sought after. The first steps consist of laboratory-chemistry diagnostics and cerebral imaging. The significance of the ammonia levels is controversially discussed. High ammonia levels can support the diagnosis of HE, however it does not exclude other causes of cognitive disorders, for example a bleed on the brain.

The best confirmation for the presence of an HE is the patient's response to an ammonia-lowering treatment.

The therapeutic concept for HE arises after the exclusion of other causes of a cognitive disorder, initially from the identification and treatment of precipitating factors. The pharmacological treatment targets the reduction of the ammonia levels. The most important medication is lactulose, which reduces the intestinal ammonia resorption and rifaximin, intestinal-selective antibiotics, as well as L-Ornithine-L-Aspartate, which supports the degradation of ammonia in the liver, brain and muscles.

Cognitive disorders often occur after a liver transplant. Until recently, it was believed that the transplant not only treated the underlying liver disease, but also the hepatic encephalopathy that developed from it. Are there any new findings today?

After the transplant, the cirrhosis is healed as the cause of HE, thus HE cannot arise anymore. Metabolic changes in the brain of patients with HE recede within months after a transplant. In the long term, we have seen that HE-related cognitive changes no longer play a significant role five years after the transplant. Therefore, approx. 30 % of patients exhibit neurological symptoms in the first few weeks after the transplant, which are frequently caused by metabolic changes. Here, we speak of a post-transplant encephalopathy. The causes are unclear. HE-related metabolic changes in the brain and neurotoxic side-effects of the immunosuppressive medication are being discussed.

MANY THANKS DR. PFLUGRAD FOR THIS INTERESTING INTERVIEW.

BASIC PRINCIPLES – REGULATION OF THE LIVER METABOLISM

THYROID GLAND HORMONES T_3 AND T_4

The thyroid gland hormones triiodothyronine (T_3) and tetraiodothyronine (T_4) are derivates of the amino acid tyrosine. Iodine is used for the synthesis of T_3 and T_4, which is absorbed with food as iodide, from which blood gets into the follicle cells, actively concentrates and is transferred through the thyroidal peroxidase in organic iodine (organification). The follicle cells surround a space that is filled with colloid, which consists of tyrosine-rich thyroglobulin, which contains tyrosine in its matrix. Tyrosine is iodized upon contact with the membrane of the follicle cells at one (monoiodotyrosine) or two (diiodotyrosine) points. It is then that respectively two molecules are combined with one another. Thus, the two thyroid hormones T_3 and T_4 arise. Due to their lipophiles in the blood, both are transported 75 % with the thyroid hormone binding protein (TBP) and 25 % with albumin and the thyroxine-binding prealbumin transthyretin.

Approximately 0.3 % of the total serum-T_3 and 0.03 % of the total seru-T_4 are present as free hormones in balance with bound hormones. Only free T_3 and T_4 can be effective in the periphery.

STANDARD VALUES

The height of the plasma concentrations for both thyroid hormones is dependent on the method. The free plasma concentration of T_3 amounts to approx. 5–10 pmol/l, the total 1.5–3.5 nmol/l. For T_4, the free plasma concentration is about 20–40 pmol/l. the total at 60-140 nmol/l. In the target tissue, the largest share of T_4 is converted into the activating T_3, which has a shorter half-life.

BREAKDOWN

The half-life and the duration of efficacy of the thyroid hormone is several hours for T_3, or several days for T_4. All iodothyronines are metabolized in the liver by glucuronidation and sulfation of the phenolic 4'-OH-group. As a result, they are water-soluble and partly eliminated renally, partly excreted with the bile. In the intestine, it is partially hydrolyzed and reabsorbed as intact hormones or in the form of fragments.

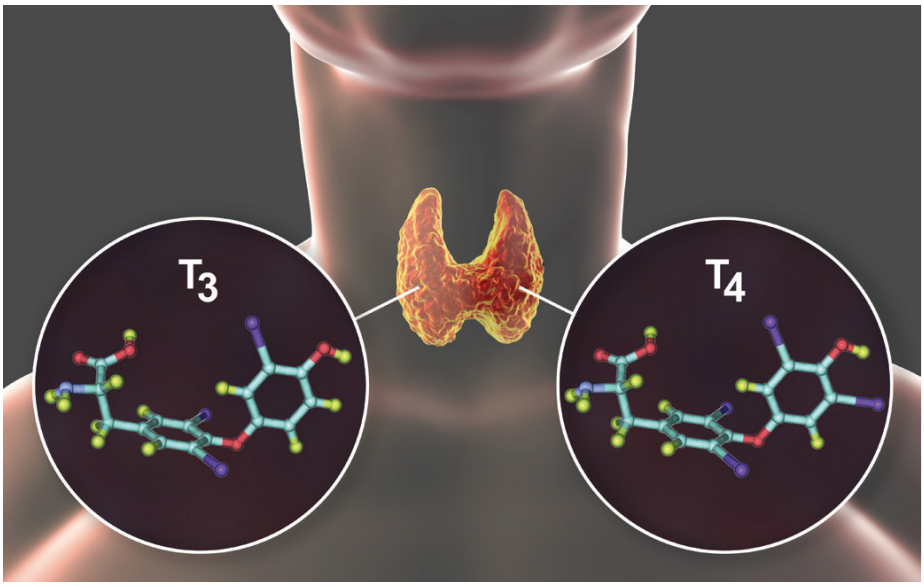


FIGURE: Molecules of the thyroid gland hormones T_3 and T_4 Source: Kateryna_Kon@Adobe_Stock

REGULATION OF RELEASE

The secretion of thyroid hormone is controlled by the hypothalamus and the hypophysis. The tripeptide thyroliberin (TRH, thyrotropin releasing hormone), which originates in the hypothalamus, activates the release of thyrotropin (TSH, thyroid stimulating hormone) from the hypophysis. The release of thyroliberin is primarily activated by cold.

In the thyroid gland TSH binds to the TSH receptors of the follicle epithelial cells. This stimulates the thyroid gland to absorb more iodine and stimulates the formation of the thyroid hormones T_3 and T_4, which are secreted into the bloodstream.

EFFECT

The effect of T_3 and T_4 is complex and affects not only the liver, but also the majority of the body. The thyroid gland hormone influences both the metabolic rate as well as the growth process and the differentiation. As a result, T_3 and T_4 play a significant role in the oxygen uptake and the thermogenesis in the tissue. In the liver, the capacity for oxygen uptake and for gluconeogenesis as well as glycolysis increases. They also facilitate the lipolysis and proteolysis in the fatty tissue and in the muscle.

Furthermore, the thyroid gland hormone supports bone growth and brain development. It increases the contractility of the heart muscle and the cardiac output and regulate the metabolism of connective tissue.

The series will be continued in the next issue of Hepa News®.

SOMATOSENSORY DISORDERS AS A MARKER FOR MINIMAL HEPATIC ENCEPHALOPATHY

ANOMALIES IN BRAIN ACTIVITY AMONG CIRRHOTIC PATIENTS PLAY A PATHOPHYSIOLOGICAL ROLE IN HE

In particular regions of the brain among people with liver cirrhosis and hepatic encephalopathy (HE) it is possible to see changes in the activity when compared with healthy people. This is confirmed by a current meta-analysis.[1] Another study shows a reduced sensory cognition among cirrhosis patients with minimal hepatic encephalopathy (mHE). Quantitative sensitivity disorders could also serve as biomarkers for the development of an mHE.[2]

A brain function disorder with neuropsychiatric deficits is identified as hepatic encephalopathy (HE), which develops as a result of a hepatic insufficiency and/or a portosystemic shunt. Classification occurs by way of clinical symptoms as overt (OHE) or covert HE (CHE). No clinical symptoms are yet detectable for covert or minimal HE (mHE). Up to 40 % of all patients with liver cirrhosis are affected by mHE. These patients will already exhibit attention deficits, psychomotor decelerations, and cognitive deficits, which impact life quality and reduce life expectancy. MHE is diagnosed with various psychometric tests, which together present the psychometric hepatic encephalopathy score (PHES).

HYPOSENSITIVITY AS INDICATION FOR MHE

However, not all mHE patients can be identified in this manner. According to a current study [2], there is a connection between the minimal brain function disorder and the changes in heat, vibration and/or heat pain feeling when compared with healthy subjects. According to this, cirrhotic patients exhibit a hyposensitivity, which is even stronger among patients with mHE. Both, the heat and cold feeling was clearly more strongly affected among these patients on their feet and distal than on the hands, and the reaction times were clearly increased when compared with patients without mHE. These hyposensitivities correlated with attention deficits, the speed of mental processing and the test of working memory of the mHE patients. Temperature feeling is the task of the autonomous nervous system. On the other hand, large nerve fibers react to vibrations. Quantitative sensitivity tests (QST) for cirrhotic patients could promptly diagnose disorders of thermal sensitivity and autonomous function, and be viewed as an early indication of pathophysiology of mHE, even before large nerve fibers are affected. An early diagnosis enables a corresponding treatment, and can improve the patient's quality of life and prognosis.[2]

CHANGES TO INTRINSIC ACTIVITY IN THE BRAIN AMONG HE PATIENTS

Studies show that the neuropsychiatric deficits among patients with liver cirrhosis and HE underly changes in brain activity. In one meta-analysis[1], it is now being investigated which of these changes in which brain region exhibits the highest consistency and whether liver transplant shows effects on brain activity.
In total, 19 studies with 419 liver cirrhosis patients and 349 healthy volunteers fulfilled the requirements for the meta-analysis. Brain activity was measured in a state of rest with the help of function magnetic resonance imaging (fMRI).

The analysis produced increased activity in the fronto-striatal neuronal network among cirrhotic patients when compared with healthy people. With this increase in activity, there appeared to be a compensatory process of neuronal reorganization. Contrary to this, there was less activity in the visuo-sensorimotor network and in the gyrus cinguli among these patients. These changes remained significant in a sub-group analysis for cirrhotic patients with mHE or OHE. OHE patients also exhibited functional deficits in the default mode network (DMN). The ammonia concentrations correlated positively with the activity in the right gyrus temporalis, while the time requirement for the number connection test A(NCT-A) were negatively associated with the brain activity in the left anterior gyrus cinguli (Fig.).

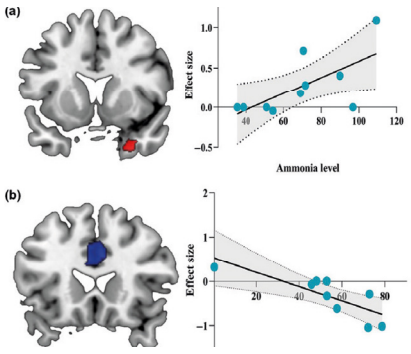


FIGURE: The meta-regression exhibits a positive correlation between the ammonia values and brain activity in the right, central gyrus temporalis (MTG) **a**, as well as a negative correlation between the results of the number connection test A (NCT-A) and brain activity in the left anterior gyrus cinguli **b**. The increase in meta-regression signed differential mapping is presented as a straight line. Red: activation; blue: deactivation. L, left; R, right mod. acc.[1]

These results pointed towards disorders in the fronto-striato-cerebral and visuo-sensorimotor networks being part of the pathophysiology of HE. The left anterior cingular cortex appears to be the most vulnerable region for cognitive impairments with HE. Disorders in the DMN indicate HE progression.

A liver transplant appears to improve brain activity in the visuo-sensorimotor quality of life again.[1]

LITERATURE

1 Cao Y et al. J Neurosci Res. 2021 May;99(5):1337-1353. **2** Rega D et al., J. Clin. Med. 2021;10:239.

NAFLD – COGNITIVE DYSFUNCTION THROUGH METABOLIC AND HEPATIC DISORDERS

The Non-alcoholic fatty liver disease (NAFLD) is gaining increasingly more significance as a hepatic component of the metabolic syndrome. NAFLD is associated with a series of intra- and extra-hepatic complications, among which is also cognitive dysfunction. In a current study, the evidence of underlying mechanisms was investigated in corresponding publications.[1]

NAFLD is one of the largest health problems worldwide. It is assumed that around a quarter of the world's population is affected. Fatty liver disease itself, as well as the extra-hepatic complications linked to it and the metabolic syndrome increase the patient's risk of morbidity and mortality. The cognitive dysfunction with NAFLD is gaining Increasing awareness as a risk factor, which is indicated by memory problems, awareness and concentration disorders, forgetfulness, and confusion. It is assumed that approx. 70 % of NAFLD patients are affected by it, and that their everyday life and quality of life are affected by it.

TIGHT CORRELATION BETWEEN THE SEVERITY OF NAFLD AND COGNITIVE DISORDERS

A current study analysis provides indication of a correlation between the severity of the fatty liver disease and cognitive restrictions. Systemic and neuroinflammation, vascular dysfunction, and sleep apnea are being discussed as possible mechanisms, which are observed with both a metabolic syndrome and also NAFLD.

More recent investigations indicate that NAFLD itself could be an independent risk factor for the development of a cognitive dysfunction. Alongside the indicated risk factors, there is also a dysbiosis of the intestinal microbiota and an impaired function of the urea cycle, which is the primary path to ammonia poisoning, among NAFLD patients. As a result, a systemic ammonia accumulation favored, and system inflammations are further triggered.

AMMONIA AS THE KEY TO NEUROINFLAMMATION

The neurotoxin ammonia can break down the blood-brain barrier and is applicable as a significant pathogenetic factor of hepatic encephalopathy (HE). Studies have shown that the cognitive dysfunctions caused by ammonia are worse in an inflammatory environment, and that ammonia is the key, which opens the blood-brain barrier to the systemic inflammation. A reduction in ammonia levels or an anti-inflammatory treatment can lead to an improvement of cognitive disorders and neuroinflammation.

Arteriosclerosis and cerebrovascular dysfunction are also connected with the cognitive disorders in NAFLD. Accumulation of fat in the liver appears to cause a microvascular hemodynamic dysfunction with endothelial dysfunction, which reduced cerebral blood-flow and thus leads to cerebrovascular dysfunction. It is possible that neurodegenerative developments are induced in the brain as a result of this, like dementia and Alzheimer's.

DIAGNOSTIC PROCEDURE MUST BE EXTENDED

The current studies indicate that NAFLD patients develop a cognitive dysfunction, which is a multi-factorial, metabolic encephalopathy with characteristics of both, hepatic and diabetic encephalopathy. Furthermore, with these patients there are also unspecific mental and physical symptoms, which can indirectly impair the cognitive functions. The cognitive phenotype of NAFLD is not yet specified in sufficient measure. Therefore, the psychometric and neuropsychological test methods used in previous studies cannot adequately address the extensive metabolic encephalopathy implied by the current evidence. To record the whole spectrum of cognitive dysfunction for NAFLD diagnostically, the validated test for diagnosis of hepatic encephalopathy must be complemented by at least one test for the learning and/or working memory.

INTENSIFICATION OF RESEARCH OF PATHOLOGY REQUIRED

In addition to improvements in diagnostic procedures, further research on the pathological basis of cognitive disorders in NAFLD is urgently required.

Treatment is currently essentially supported by a change in lifestyle and the bariatric operations, which lead to a reduction in weight, and thereby potentially improving the described neurological disorders.

The cognitive and functional restrictions as a result of NAFLD will have increasing social effects, and be lined with a cost increase for healthcare systems. People's quality of life gets worse, work productivity decreases, while the need for care increases. All of this illustrates an urgent need for medicative treatments for the treatment of patients with NAFLD.

LITERATURE

1 Kjaergaard K et al., J. Clin. Med. 2021;10:673. https://doi.org/10.3390/jcm10040673.

AS VALUABLE AS GOLD

Today's sought-after mineral is absolutely vital for humans, as it also is to all animals. It is therefore no surprise, that in earlier times, it was occasionally as valuable as gold, or even served as money. Even the language reveals the age-old meaning, because all Indo-Germanic languages, even Finnish and Hungarian, use the same stem for the sought-after commodity.

Although it is present on earth in tremendous volumes, it is unfortunately unevenly distributed. Where the climate permits it, people enjoyed settling there where the valuable substance could be found – in Europe there is even a culture named after a famous location. Only rarely can the mineral be easily lifted from the ground, and it is not always in its pure form. Then people are subjected to a lot of effort and work to get the substance in its transportable form. However, it is the at least durable and storable.

In the middle-ages, large trading towns, like Venice, would gladly buy and sell this commodity, but the trade had a hack. Because the substance was so valuable, many rulers placed high taxes on it, and unfortunately that substantially reduced the profits.

FIGURE: The sought-after, once very valuable mineral. Source: Creative Commons Attribution-Share Alike 4.0 International

Very early on, people recognized an essential characteristic of the mineral and used it for medical and some other purposes. In many religions the clear crystals symbolize purity.

Depending on the place of origin, the cubic crystals are light and transparent, or shimmer gray, red, or in different colors. For a long time, it was unbeknown to the natural scientists what the mineral was actually made up of. It was only in 1810 that the Brit, Sir Humphry Davy, discovered that it was not one element, however a combination. Chemists knew that the substance melted at 801 degrees.

Thanks to industrialization, the mineral is no longer a "white gold", however is available in excess. In the meantime, industry uses the majority share. A person required about five grams per day. What is the mineral known as?

From: Signe Seiler: Natur Rätsel, 1999, insel Taschenbuch

OUR OBLIGATION

Hepa-Merz® Granules. Composition: One sachet with 5 g of Granules contains: **Active substance:** 3 g L-ornithine- L-aspartate. **Excipients:** citric acid, aspartame (E951), povidone 25, fructose, flavorings, orange yellow S (E110). Note for diabetics: One sachet of Hepa-Merz® Granules contains 1.13 g of fructose (corresponds to approx. 0.11 BU). **Therapeutic indications:** Treatment of concomitant disease and sequelae due to impaired detoxification activity (e.g. in cirrhosis of the liver) with the symptoms of latent and manifest hepatic encephalopathy. **Contraindications:** Absolute: Hypersensitivity to L-ornithine-L-aspartate, orange yellow S or any of the other excipients. Severely impaired renal function (renal insufficiency). A serum creatinine value over 3 mg/100 ml can be used as a guideline value. Relative: Pregnancy and lactation: No clinical data are available relating to intake of Hepa-Merz® Granules in children and during pregnancy. No exhaustive animal studies have been performed for L-ornithine-L-aspartate, to investigate its toxicity in relation to reproduction. Administration of Hepa-Merz® Granules during pregnancy should therefore be avoided. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. It is not known whether L-ornithine-L-aspartate is excreted into the breast milk. Administration of Hepa-Merz® Granules should therefore be avoided during lactation. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. No data regarding fertility. **Undesirable effects:** Uncommon (≥ 1/1,000 to < 1/100): Nausea, vomiting, stomach ache, flatulence, diarrhea. Very rare (< 1/10,000): Pain in the limbs. These undesirable effects are usually transient and do not require withdrawal of the medicine. Orange yellow S (E110) can trigger allergic reactions. **Warnings:** Hepa-Merz® Granules contain fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Aspartame (E951): Contains a source of phenylalanine. May be harmful for people with phenylketonuria. **Further precautions:** As a result of the disease, the ability to drive and operate machinery may be impaired during treatment with L-ornithine-L-aspartate.

Hepa-Merz® Granules. Composition: One sachet with 5 g of Granules contains: **Active substance:** 3 g L-ornithine- L-aspartate. **Excipients:** citric acid, saccharin sodium, sodium cyclamate, povidone 25, fructose, flavorings, orange yellow S (E110). Note for diabetics: One sachet of Hepa-Merz® Granules contains 1.13 g of fructose (corresponds to approx. 0.11 BU). **Therapeutic indications**: Treatment of concomitant disease and sequelae due to impaired detoxification activity (e.g. in cirrhosis of the liver) with the symptoms of latent and manifest hepatic encephalopathy. **Contraindications:** Absolute: Hypersensitivity to L-ornithine-L-aspartate, orange yellow S or any of the other excipients. Severely impaired renal function (renal insufficiency). A serum creatinine value over 3 mg/100 ml can be used as a guideline value. Relative: Pregnancy and lactation: No clinical data are available relating to intake of Hepa-Merz® Granules in children and during pregnancy. No exhaustive animal studies have been performed for L-ornithine-L-aspartate, to investigate its toxicity in relation to reproduction. Administration of Hepa-Merz® Granules during pregnancy should therefore be avoided. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. It is not known whether L-ornithine-L-aspartate is excreted into the breast milk. Administration of Hepa-Merz® Granules should therefore be avoided during lactation. If, however, treatment with Hepa-Merz® Granules is considered necessary, careful consideration should be given to the benefit versus risk ratio. No data regarding fertility. **Undesirable effects:** Uncommon (≥ 1/1,000 to < 1/100): Nausea, vomiting, stomach ache, flatulence, diarrhea. Very rare (< 1/10,000): Pain in the limbs. These undesirable effects are usually transient and do not require withdrawal of the medicine. Orange yellow S (E110) can trigger allergic reactions. **Warnings:** Hepa-Merz® Granules contain fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicine. **Further precautions:** As a result of the disease, the ability to drive and operate machinery may be impaired during treatment with L-ornithine-L-aspartate.

Hepa-Merz® Infusion concentrate. Composition: One ampoule of 10 ml contains: **Active substance:** 5 g L-ornithine-L-aspartate. **Excipients:** Water for injections. **Therapeutic indications:** Latent and manifest hepatic encephalopathy. **Contraindications:** Absolute: Hypersensitivity to L-ornithine-L-aspartate. Severe renal impairment (renal failure). A serum creatinine level in excess of 3 mg/100 ml can be taken as a guide. Relative: Pregnancy and lactation: There are no clinical data available on the use of Hepa-Merz® Infusion concentrate in children and during pregnancy. L-ornithine L-aspartate has been investigated for reproduction toxicity only to a limited extent in experimental animal studies. The administration of Hepa-Merz® Infusion concentrate in pregnancy should therefore be avoided. If treatment with Hepa-Merz® is nevertheless thought to be necessary, the benefits and risks should be carefully assessed. It is not known whether L-ornithine-L-aspartate passes into breast milk. Administration of Hepa-Merz® should therefore be avoided during lactation. If treatment with Hepa-Merz® is nevertheless thought to be necessary, the benefits and risks should be carefully assessed. No data regarding fertility. **Undesirable effects:** Uncommon (≥ 1/1,000 to < 1/100): Nausea. Rare (≥ 1/10,000 to < 1/1000): vomiting. Frequency not known (frequency cannot be estimated from the available data): hypersensitivity, anaphylactic reaction. Generally however, the gastrointestinal symptoms are transient, and do not necessitate discontinuation of treatment. They disappear on reduction of the dose or the infusion rate. **Further precautions:** Hepa-Merz concentrate for solution for infusion can be mixed with the usual infusion solutions. So far, no peculiarities have been observed with regard to miscibility. However, the ampoules should be admixed to the infusion solution only immediately before application. At high doses of Hepa-Merz® Infusion concentrate, serum and urine urea levels should be monitored. If liver function is substantially impaired, the infusion rate must be adjusted to the individual patient in order to prevent nausea and vomiting. Depending on the underlying disease, the ability to drive and operate machines may also be impaired on treatment with L-ornithine L-aspartate. Hepa-Merz® Infusion concentrate must not be injected into an artery.

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