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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-

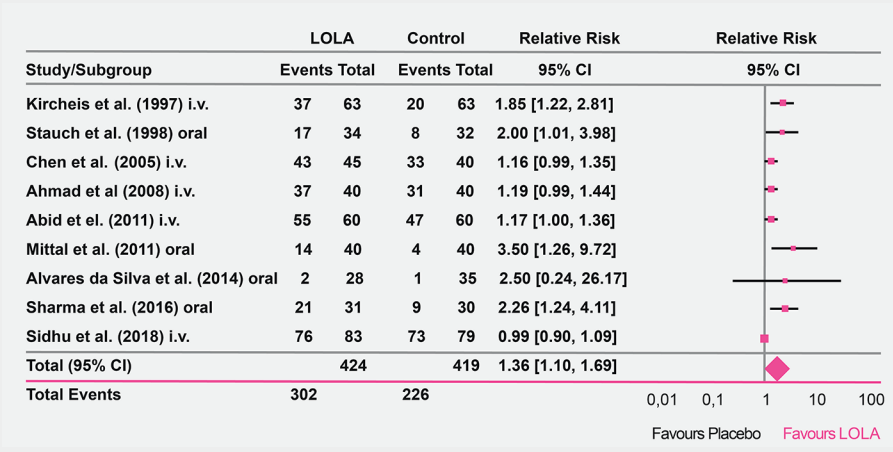

FIGURE 1: Meta-analysis for efficacy of LOLA across all stages of HE, mod. acc.[1]

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

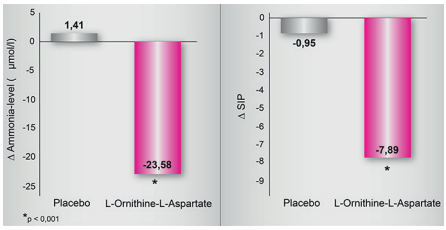

FIGURE 2: Significant reduction in the ammonia levels and SIP score when compared with the placebo after 6 months' treatment with LOLA (N=150), mod. acc.[2]

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).

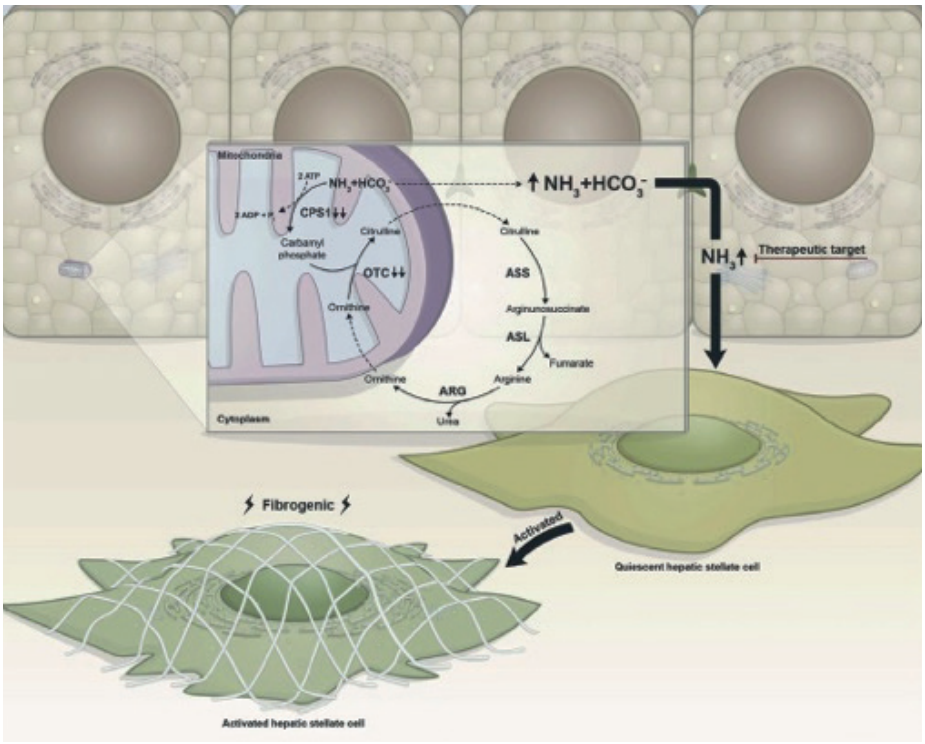

FIGURE 3: The early applied ammonia synthesis with NASH leads to the activation of the hepatic stellate cell and as a result to the development of a fibrosis, source:[3]

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).

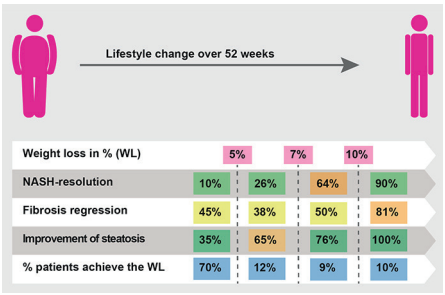

FIGURE 4: Probability of a NASH resolution, a fibrosis regression (at least one stage) and a steatosis improvement in patients with NASH where there is lifestyle intervention and in conjunction with percentage weight loss, mod. acc.[4]

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.