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NUTRITIVE THERAPY OF HEPATIC ENCEPHALOPATHY AS A COMPLICATION OF LIVER CIRRHOSIS

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Hepatic encephalopathy is a complication of liver cirrhosis and is defined as a neuropsychiatric disease, with a reversibile character. Besides classical ways of therapy, an increasing importance is attached to nutritional therapy that is an effective prevention of the onset and leads to an ease of symptoms in hepathic encephalopathy that already exists. After the patient's nutritional status evaluation, the prescription of diet that includes adequate protein, calories and vitamins is assessed. The greatest importance is attached to the zinc intake as well as branched chain amino acids (BCAA therapy) supplementation. It is believed that further development of science in terms of nutrigenomics and nutrigenetics will give detailed guidance on further developments since the possibility of clinical investigation in these patients is limited. *Acta Medica Medianae 2012;51(2):39-44.*

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Introduction

Changes in nutrition, as well as changes in metabolism of amino acids have an important role in the onset of liver cirrhosis complications. Again, malnutrition as a common complication of the end stage liver failure (the prevalence of malnutrition in liver cirrhosis is estimated to range from 65 % to 100%) is an important prognostic factor in terms of survival rate, hospitalization rate, posttransplantational morbidity as well as quality of life. The importance of malnutrition is obvious if one consideres that patient's nutritional status used to be a part of calculationg the Child-Turcotte index. However, the index was later reduced to the parameters that are easier to assess (clinical signs of ascites, encephalopathy and laboratory parameters) (1,2).

However, there is an obvious connection between nutrition on the one side and liver cirrhosis complications onset on the other side, as well as the impact of these complications on the outcome of the underlying disease. As the most obvious example of this correlation we observed hepatic encefalopathy (HE) (3,4). HE is defined as a neurophychiatric disease, with a reversibile character, in which base lies the liver damage. It may be endogenous, ie. primarily hepatic (occuring as a result of fulminant liver damage) and exogenous or secondary hepatic (that develops as a consequence of portal-systemic shunts existence). There are also acute, subacute and chronic HE, and this division refers to the speed of the disease development (5,6).

The pathogenesis of HE is multifactorial, but in its base lies the damage of metabolic liver function and consequent presence of excess toxic materies which impact CNS function. HE can manifest with the whole specter of psychoneurological changes, from barely detectable ones to those which dominate in clinical picture (e.g. flapping tremor). Mental changes are reflected in changes of speech, personality and consciousness. HE evolution passes through four stadia: prodromal stadium (signs of a very severe liver disease, a consequent change of the general situation, changes of patient's personality and damage of mental function), threatening coma (with preceeding symptoms neurological symptomatology occurs with changes in EEG), stupor (uncertain orientation of the patient, and contact with the patient is not always possible) and coma. In most cases, HE diagnosis is assessed by eliminating other possibilities of mental status changes. Laboratory analyses indicate the existence of liver disease. Phychometric tests are also required. Also, the use of CT and NMR results can be very helpful in diagnostics (5,7-9).

Patient's nutritional status assessment

Patients with liver disease generally submit to normal diet, however, the modification of it, i.e. prescribing of a specific diet can have a positive impact on disease development and prevention of disease complications, especially HE (10,11). We have already stated that malnutrition which occurs in the clinical picture of liver cirrhosis can speed up the development of complications, including the possibility of HE rapid emergence.

Contributing factors to malnutrition development in liver cirrhosis are: inadequate diet (unintentionally or due to anorexia, nausea, taste change, etc.), unadequate synthesis or nutrient absorption (due to severe liver damage and its consequently reduced capacity, disturbed enterohepatic circle, pacreatic insufficiency, cholestasis, diarrhea caused by drug consumption), increased protein loss (due to complication of cirrhosis, e.g. bleeding from gastric or esophageal varices), hypermetabolic conditions and increased body requirements for energy and proteins, insulin resistence, bleeding in GIT, ascites and infection existence (the existence of negative correlation between proinflammatory cytokines and nutrient intake has been proved) (4).

Assessment of nutritional status of liver cirrhosis patients begins with a questionarre about diet habits. Total nutrient intake is assessed and a degree of recent weight loss is evaluated. In case of pre-existing liver cirrhosis and existing HE, mental status does not allow the use of the correct clinical history, so an interview with family members is recommended (4).

In addition to the questionarre, a physical examination is conducted, and these two factors together make the so-called Subjective Global Assessment (SGA). SGA is considered as the most valid method, since these parameters are minimally affected by fluid retention and ascites presence.

Anthropometric measurements and bioelectric impedanse measurements are even more difficult due to the possible ascites presence, while malnutrition biomarkers are abnormal due to impaired metabolism. However, there are anthropometric parameters independent of ascites presence and these are: mid-thigh circumference, mid upper arm muscle circumference and skinfold thickness (12).

Certain nutrients' effects on the onset of hepatic encephalopathy

Former research in the field of dietetics concluded that protein intake (from animals and plants), branched chain amino-acids, dietary fiber, probiotics, vitamins and antioxidants, minerals (zinc and magnesium) and L-carnitine have the greatest impact on HE (4, 13-15).

Proteins

Clinical studies conducted worldwide have shown that the incidence of HE is increased with severity of resulting protein malnutrition. Thus, in case of a mild protein malnutrition occurrence, encephalopathy occurs in about 61% of patients, while in severe protein malnutrition it occurs in 67% of cases (16).

The conclusion is: if there exists a tolerance of protein intake higher that 70 g/day without the disturbance of mental status, a diet modification is not needed. If patients have a threshold intolerance to proteins (60-70 g/day), a diet rich in vegetables or fibers is recomended with the aim of HE prevention (17).

Only in patients without tolerance to amount of proteins larger than 1g/kg/day, a diet that includes only vegetable proteins must be included, besides optimal pharmacological therapy, and if necessary BCAA (branched chain amino acids-leucine, isoleucine, valine) enriched formula. However, it is important to note that even short term complete protein restrictions are strictly contraindicated in patients with liver cirrhosis (3).

Oral BCAA supplementation makes it possible for protein-intolerant patients with cirrhosis to maintain a positive nitrogen balance without an increased risk for encephalopathy onset. However, although a somewhat positive impact of supplementation with high levels of BCAA (40-45%) and decreased amount of amino acids and methionine on patients with HE has been proved, it has no impact on nutritional status (17).

When it comes to heavy protein supplementation, clinical research and practice have proved that even patients with severe forms of liver cirrhosis tolerate the diet without worsening of HE. In theory, protein supplementation represents a problem because proteins are being broken down to ammonia in the intestinal system, and in a normal organism it should be converted to urea. Since liver function is damaged, ammonia acts as a neurotoxin (11, 18). In brain nerve cells, ammonia converts locally to toxic glutamin. Recent research has shown that it is possible that glutamin acts as a neurotoxin (12, 19, 20). Research on laboratory rats has shown that liver failure results in boosting levels of ammonia, which entails the production of glutamine by skeletal muscle. This shows that muscle preservation through proper nutrition is crucial in preventing the development of HE (10).

Zinc

Zinc is an element with a very small concentration in the body, but it plays an important role in the regulation of protein and nitrogen metabolism as well as in organism's antioxidative defense. In patients with liver cirrhosis, a reduced amount of zinc is common. It should be noted that the level of zinc in the body cannot be determined solely by measuring its concentration in patients' serum since it binds to albumin (4).

Reduced zinc level correlates with lower activity of ornitin transcarbamylase and higher level of ammonia in the blood. Also, zinc deficiency leads to an impairment of neurotransmiters like gamma amino-butiric acid and norepinefrine (21).

The causes of zinc deficiency in patients with cirrhosis may include: reduced intake through food, reduced level of its absorption, reduced hepato-intestinal extraction, porto-systemic shunt and altered protein and amino acids metabolism. Deficiency of zinc can damage the activity of urea cycle enzymes as well as the activity of glutamine synthetase, which results in increased brain circulation. Ammonia has an easier penetration into brain tissue, causing further damage and eventual emergence or worsening of HE. Zinc deficiency results in appetite reduction, immune system dysfunction altered taste and smell, anorexia and altered patients metabolism (4, 21).

However, despite the fact that zinc supplementation has a positive influence on zinc deficiency in liver cirrhosis, the same therapy did not have obvious results in case of already existing HE. These results could be the consequence of a very scarce research in this area. Besides, different dosage and nature of zinc salts were used in the conducted research, and also the lenght of supplementation varied (4).

Vitamin A

Vitamin A is known as a hepatotoxin when given in doses greater than 100 000 IU/day. Besides, it is known that alcohol increases the toxicity of vitamin A. Patients with chronic liver disease surely need the limitation in vitamin A intake (20).

Iron

Patients with fulminant liver disease need an advice on iron intake. With iron overintake, it concentrates in liver parenchyma instead of being eliminated through GIT. About 30% of patients with chronic hepatitis C or alcoholic cirrhosis have a tendency of secondary chemochromatosis development.

Iron also induces an increased production of free radicals and an increased lipid peroxidation which leads to organele disfunction, lysosome fragility, mitochondrion dysfunction and it all eventually leads to cell death. That is why the intake of multivitamins without iron is recommended (20).

L- carnitine

Liver is the main site of kethone body production which are the products of fatty acids oxidation. Fatty acids cannot pass through mitochondrial membrane if they are not carried by the means of transportational system which includes L-carnitine (3-hydroxy-4-threemethylaminebutanoate). Carnitine is a cofactor of mitochondrial oxidation and it prevents the usage of fats with the aim of energy production except in case of starvation (4). L-carnitine has a protective role in the organism since it is connected with a significant reduction of ammoni concentration in blood and brain (22). Carnitine deficiency can result in letargy, somnolence, confusion and encephalopathy. Studies which examined the carnitine status in patients with cirrhosis gave different results depending on cirrhosis etiology and the severity of liver disease (4, 22).

Vitamin B (Thyamine)

The cause of vitamin B1 deficiency in cirrhosis includes the decreased intake of supplements, low absorbtion and loss of hepatic depoes of vitamins. That is how the vitamin B supplementation is very important in patients with end stage of liver failure, both caused by alcohol, or having other etiology (4).

Other supplements

In patients with liver cirrhosis a decreased selenium level is noticed, however, a clear connection between this fact and pathogenesis of cirrhosis complications has not been found yet (5).

An impaired hepatobiliary function and porto-systemic shunt have a consequence of increased manganium concentration in blood as well as increased deposition of the same supplement in basal structures of the brain, especially in globus pallidus. It is considered that manganium toxic efects on CNS are connected with the effects of glycolytic enzyme glycealdehide-3-phosphate dehydrogenase (GAPDH). Researches have shown that these effects of manganium are connected with the induction of perripheral type of besodyasepine receptors. Manganium is connected with the increased levels of glutamine and changes in dopamine metabolism and it can be connected also with other changes in patients with HE, like characteristic morphologic changes in astrocytes (4, 10).

Subclinical encephalopathy is present in about 75% of patients with liver cirrhosis. It influences the way of life and its quality, so it has to be treated in the right moment. Research has proved that nutritive therapy could be used with the aim of alleviating the symptoms and prevention as well.

Patients with HE usually need changes in diet with the therapeutic aims, but their optimal nutritions needs an adequate intake of proteins, calories and vitamins. Patient should be provided with nutrients by oral intake or by the nasogastic sond, and if it is not possible then with infusion (10, 11).

„Mild" encephalopathy is treated by removing the ammonia from the guts. Lactulosis has a key role in prevention of HE as well as in the therapy of the same condition. Lactulosis per os is still the primary therapy in patients with HE, since it decreases the level of ammonia in blood (15-45ml, per os, 3-4 times a day). A few oral antibiothics can be used in the therapy – neomicyn (3-6g/day), methronidasole (250 mg/day) or ryphampicine (1-2 g/day). They decrease the level of gut bacteria which produce ammonia. However, they should not

be used for a long period of time, because in that way they show their toxic effects. It is useful to intake bacteria which do not produce ammonia, like Lactobacillus acidophilus and Enterococcus faecium (11).

Replacement of zinc, if it is deficient in an organism, is a good choice (3). The connection between the onset of encephalopathy and zinc deficiency is already proven, however, clinical trials with oral supplementation of zinc (600 mg of zinc per day) did not yield specific results. Results have shown that the influence of zinc on the improvement of liver function is positive, but not to what extent and with the help of which mechanism (23, 24).

Besides pharmacological methods of therapy, it has been shown that for now the safest way of nutrition therapy with the aim of improving the mental status is protein supplementation with BCAA. In patients with stable liver cirrhosis there was the improvement in their mental status in phychometric tests when it came to normal diet with oral BCAA supplementation (0.25 g/kg/day). It has been shown that this kind of therapy lead to the improvement of patients' every day functions and that phychometric tests were normal. Patients who are intolerant to daily intake of proteins (1 g/kg/day) should be adviced to decrease the intake of proteins, but these measures should be delayed. In situations when proteins have to be decreased in the diet, a nitrogen should be supplemented by BCAA oral supplementation (0.25 g/kg/day), with further permanent clinical monitoring of the patient. Before planning a diet with decreased level of proteins we should first have in mind that protein intolerance can occur as a transient symptome. It is because of these phenomena that protein restriction should be advised as soon as possible (12).

There are also special dilutions (the so called „comma dilution") which besides other components include BCAA. These are not balanced dilutions and they are not recomended as the source of nitrogen for parenteral nutrition (14). Justification of BCAA use in HE therapy has not been proved yet because the worldwide studies have yielded conflicting results. Differences resulted from the fact that the effects of BCAA therapy are not the same if there are different complications of fulminant liver cirrhosis (like GI bleeding, sepsis or kidney failure). Meta analyses showed that there is a positive effect of the usage of BCAA enriched fluids in patients with HE, but further and better designed studies are needed in order to prove this (12).

Nutritive therapy application, which includes amino acids and nitrogen is well tolerated, with no major side effects when it comes to patients suffering from cirrhosis. Also, there is no risk of HE deterioration, regardless of whether the food is administered orally or by tube. Even patients in severe stages of alcoholic liver disease tolerate plenty of proteins in diet without the appearance or worsening of existing HE (12).

It has not been proven yet what effects the nutrients like phosphatidilcholine, S-adenosyl methionine (SAM) and saturated fat have on the development of complications in the same patient, although it is known that they are well tolerated after ingestion (10, 11).

It is believed that further science development (nutrigenomics and nutrigenetics) will give more detailed guidlines about future therapy development (25).

Conclusion

Nutrition modification in patients with cirrhosis plays an extremely important role, especially in patients with complications such as HE. The possibility of following diet in prevention of HE should be especially considered, since it is obvious that important developments in this field are obtained. If it were possible to achieve control over the development of such serious liver cirrhosis complications using a relatively simple diet manipulation, the benefit would be multiple for both patients and therapy progress.

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NUTRITIVNA TERAPIJA HEPATIČNE ENCEFALOPATIJE KAO KOMPLIKACIJE CIROZE JETRE

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Hepatična encefalopatija predstavlja komplikaciju ciroze jetre a definiše se kao neuropsihijatrijsko oboljenje, reverzibilnog karaktera. Pored klasičnih načina terapije, sve veći značaj se pridaje nutritivnoj terapiji, kojom se vrši efikasna prevencija nastanka, kao i ublažavanje simptoma kod već postojeće hepatične encefalopatije. Nakon procene nutritivnog statusa bolesnika, pristupa se propisivanju dijete, koja podrazumeva adekvatan unos proteina, kalorija i vitamina. Najveći značaj se pridaje unosu cinka, kao i suplementaciji amino kiselinama kratkog lanca (BCAA terapija). Veruje se da će dalji razvoj nauke, u smislu nutrigenomike i nutrigenetike, dati detaljnije smernice o daljim kretanjima, jer je mogućnost kliničkih ispitivanja u slučaju ovakvih bolesnika ograničena. *Acta Medica Medianae 2012;51(2):39-44.*

***Ključne reči**: hepatična encefalopatija, nutritivni status, nutritivna terapija, ciroza jetre*