

Comparative Evaluation of Signal Hyperintensity in Pallidal Structures of Patients with Liver Cirrhosis

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ABSTRACT

Clinical, laboratorial, morphologic and magnetic resonance imaging (MRI) observations indicate accumulation of paramagnetic substance (manganese - Mn and/or copper - Cu) in the brain of patients with hepatoencephalopathy (HE). Pallidal index (PI) - semi-quantitative indicator of brain manganese concentration in vivo is calculated as a ratio of globus pallidus to subcortical frontal white matter signal intensity in sagittal T1-weighted MRI planes multiplied by 100. Signal intensity in other regions of the brain (putamen, subthalamic area, amygdala etc.) also represents an area of interest. Significant correlations have been shown between blood Mn content, liver enzyme activity, brain MRI changes and signs of parkinsonism in cirrhotic patients. Recently it has been showed that in the diagnostics of HE psychometric tests are as valuable as neuroimaging. The goal of our study was to reveal correlations between signal intensity and severity of HE measured by number connection test part - A. The signal intensity was defined in the areas of globus pallidus, putamen and prefrontal white matter. Some correlations were calculated between PI, HE degree and in blood and 24 hour urine manganese and copper contents. The study covered 17 patients suffering from HE. Hyperintense T1 signal was revealed in all 17 cases. Maximal signal intensity was obtained in the pallidal area, less - in putamen and very low - in the prefrontal white matter. The brain manganese deposition is explained by the following hypothesis: hyperammonemia and lack of substrate - glutamate leads to the saturation and decrease of glutamatesynthetase activity. Imbalance in the distribution of metal co-enzyme Mn ions in mitochondria and cytosol occurs. Needless and thus unused free manganese ions released from mitochondria in cytosol, accumulate and create paramagnetic deposits.

KEYWORDS: *liver cirrhosis, hepatoencephalopathy, paramagnetic substances, manganese, copper, pallidal index*

Hepatoencephalopathy (HE) presents partially reversible neuro-psychiatric syndrome which develops in the patients with damaged liver function. Etiopathogenetic factors and mechanisms have not been defined yet, though recently two toxic substances have been detected: ammonium and manganese metabolic abnormality of which is considered to be the cause of HE [5,10]. The disturbance of ammonia metabolism in inflicted by decreased detoxifying function of liver and bile secretion. Resulted hyperammonemia contributes to the entrance of ammonium to the brain where it will be converted into glutamate due to the glutamatesynthetase. This process takes place only in astrocytes. They are mainly located in the basal ganglia. After the introduction of magnetic resonance imaging it become known that liver disfunction leads to the T1-signal hyperintensity in the brain, particularly, in pallidal area in 50-75% of patients [4,11,12]. The same can be noticed in the brain MRI of patients chronically intoxicated by Mn [13], long-term parenteral nutrition [14], and among manganic mine workers [15]. Excess amount of Mn and Cu was defined in the brain, pallidal area, putamen and white-matter areas of the patients who died from HE.

On the bases of the above-mentioned data, it was proposed that disturbances in the metabolism of Mn plays significant role in HE pathogenesis. The aim of our study was to tie up the given theories with the view to explain pathogenesis of HE (ammonia, Mn, edema etc.).

MATERIALS AND METHODS

17 patients suffering from chronic He (12 men and 5 women aged 22-53) were investigated in the developed chronic hepatoencephalopathy, among them were people with alcho-cirrhosis - 5, Wilson disease - 2, the rest cases of cirrhosis were of combined etiology (alcoholic, viral). Patients with cirrhosis gave written consent. Those having III-IV degree hepatoencephalopathy, acute gastrointestinal hemorrhage and spontaneous bacterial

peritonitis, were excluded during the period of 7 last days; non-liver acute diseases such as heart failure, pulmonary insufficiency, decompensated diabetes mellitus and also the patients treated with narcotics, sedative anesthetics and antidepressants, - during the period of 7 last days, were excluded.

Control group consisted of 15 practically healthy people, who did not suffer from liver disease and from all the above-mentioned pathologies (in most cases students and workers of Radiology Institute). All study subjects had consultations with a physician and a neurologist, had laboratory biochemical analysis (urine, glucose, coagulogram, creatinin, C-peptide, bilirubin, ALT, AST, GGT, protein, albumin, globulin, cholesterin, high and low density lipoproteins, K and Na). We detected manganese and copper in blood serum and 24 hour urine, performed ultrasonographic and dopplerographic examinations of abdominal cavity, fibrogastroscopy and CT (determined severity of cirrhosis by examination of oesophageal veins), Brain MRT, phsychometric tests, number connection test - A, mental status evaluation by West-Haven criterion.

RESULTS AND DISCUSSION

1. Maximal signal intensity is noted in pallidal area (max, min, average), less in putamen and the lowest in the prefrontal white matter.
2. The degree of HE severity, defined by means of number connection test - A, correlates with pallidal hyperintensity and blood manganese and 24 hour urine Cu content.
3. In two cases of umbilical vein recanalization, the intensity remains unchanged or even increases gradually. Thus Proceedings from our study, maximal intensity of signal (accordingly, accumulation of Mn) is detected in pallidal area [2,16], then in putamen and finally in prefrontal white matter.

The HE degree of severity, defined on the bases of number connection test - A, reveals correlation with pallidal signal hyperintensity with the concentration of Mn in blood and Cu in 24 hour urine.

These indications are in conformity with data given by other scientists [1,4,5,17], prove the central role of pallidal area in toxin metabolism. Our data coincide with the results of H. Ihara who has determined the presence of Mn, Cu and other paramagnetic substances in the brain tissue obtained from the patients who died due to cirrhosis. Pallidal area of the brain is mostly affected by Mn intoxication [15]. The absence of hemato-encephalic barrier in those areas [18] greatly contributes to the accumulation of excito-toxins in basal ganglia. Glutaminsynthetase in the brain is placed only in astrocytes, located between cerebral capillaries and neurons. They act as metabolic trap for catching ammonia in the blood and convert it into non-toxic glutamine [19]. Metal co-enzyme manganese is needed for this reaction.

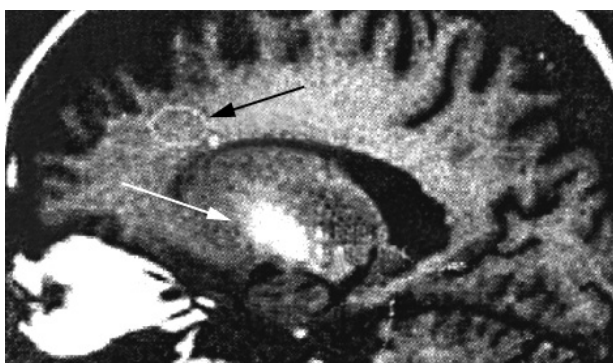


Fig.1 Maximal signal intensity in pallidal area, less - in putamen and the lowest in the pre-frontal white matter.

Hyperammoniemia increases activity of glutamate synthetase (when concentration of ammonia in blood reaches 0,4-0,9 mml/g) at the same time concentration of ammonia in blood increases. However, when concentration of ammonia in blood exceeds 0,9 mml/g, activity of

enzyme is completely saturated, and further increase of ammonia concentration to 1,3 mml/g causes complete inhibition of enzyme [19]. There seems to be an impression that major cause of decrease of glutamine synthetase activity is hyperammoniemia, which varies in range of 0,9 - 1,3 mml/g. According to Michaelis-Menten law, activity of glutamine synthetase by this time should be 79-84% of its maximal activity. However, we found out that, even when concentration of substrate ammonia reaches the level necessary for the enzyme saturation, in vivo activity of glutamine synthetase is only 2% of similar indicator in vitro [20]. Accordingly, the inhibition of glutamine synthetase in vivo is caused not only by hyperammoniemia but also because of other factors. These factors are: the decreased concentration of glutamate in astrocyte, sub-saturation level of ATP in situ and modulator activity of metal - ion - cofactor Mn (II) [21]. Regulation of glutamine synthetase activity in brain is not regulated by negative feedback mechanism (inhibition by product), like in every other tissue [22,23], but by the Mn(II) ion saturation level (Meister A. 1974). In mammalian cells, manganese is in micromolar amount. It actively binds to glutamine synthetase and activates it in vivo and this bond is rapidly reversible [24]. In normal conditions, Mn(II) ion concentration in cytoplasm and mitochondria of astrocyte is 30-40% and 60-70% respectively. Concentration of Mn(II) ions in cytoplasm corresponds to level needed for half saturation of glutamine synthetase, which is ideal condition for that, slight change in Mn(II) ion concentration will cause directly proportional change of glutamine synthetase activity [25]. In cytoplasm, change of Mn(II) ion concentration is caused by neurochemical signal, which are free Ca(II) ions [25]. Intracellular concentration of the latest, increases by release from deposits that is stimulated by increase in extracellular L-glutamate concentration. Stimulation occurs by ATP and is dose related. ATP stimulates release of excitatory amino acid (L-glutamate) from astrocyte in the way of Ca(II) dependant transport and sensitive to anion (Cl) transportation [26].

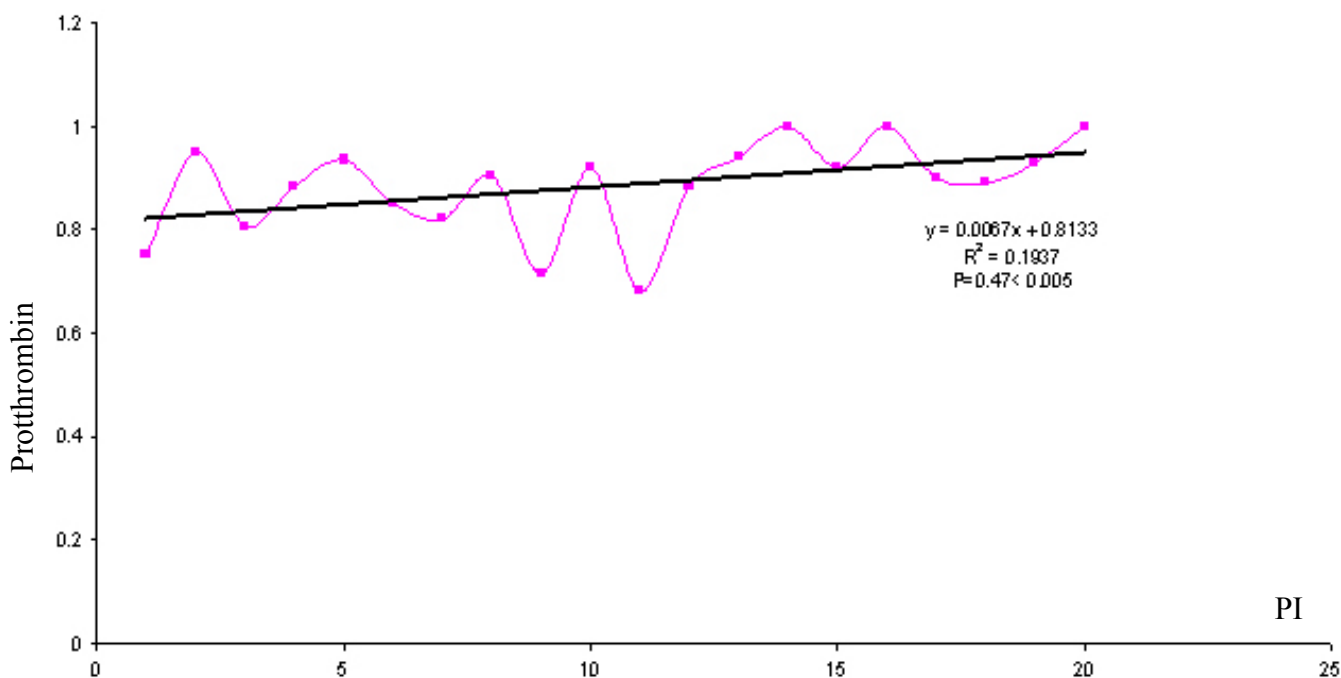


Fig.2 Correlation of PI to prothrombin.

To sum, Pathologic processes in the cytoplasm of astrocytes, which cause accumulation of Mn(II) and Mn(III) their product) are represented in the following way: hyperammonemia, caused by increased superficial permeability of blood brain barrier to ammonia, provides entry of high concentrations of ammonia into astrocytes. In response, glutamine-synthetase is activated: high concentration of L-glutamate outside the cell stimulated by ATP and by Ca(II) dependent way, because of effecting glutamate receptors on plasma membrane, causes stimulation of Ca(II) ion release into cytoplasm of astrocyte that provides transport of Mn(II) free ions from mitochondria into cytoplasm. As a result, glutamate synthetase is activated and big amount of glutamine is produced. The later attracts water - and osmotic homeostasis is disturbed. To regain homeostasis osmolites (myo-inositol and choline) are released from astrocytes. On the other hand, release of Ca(II) ions increases further release of L-glutamate from the cell. Because of lack of substrate glutamate, activity of glutamine synthetase decreases significantly. In response to Ca(II) ion signal, movement of Mn(II) ions from mitochondria to cytoplasm

continues. Deposit of manganese is produced, which clinically manifests with manganese accumulation symptoms, and on T1-weighted image of MRI is expressed as hyperactive signal.

CONCLUSIONS

1. Ammonia stops functioning in the brain owing to glutamate-synthetase enzyme in astrocytes. Mn-component is necessary to make glutamate operate. Having hyperammonia in the brain the increased amount of ammonia transits. This makes ammonia's affect less active. As a result of this, released ions of Mn locate in astrocytes and inflict T1 signal hyperintensity.
2. T1 signal intensity is maximal in the pallidal area, then in cortex and finally in the white matter of brain.
3. For the diagnosis of hepatoencephalopathy psychometric test's cost (value) is equal to MRT test. Number connection test - A is in correlation with the severe degree of hepatoencephalopathy and with the signal intensity in the pallidal area.

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Сравнительная оценка гиперинтенсивности сигнала в палидарных структурах больных циррозом печени

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РЕЗЮМЕ

Клинико-лабораторные, морфологические и магнитно-резонансные (МР) исследования указывают на наличие депозитов парамагнетических веществ (марганца - Mn и/или меди - Cu) в головном мозге больных гепатозэнцефалопатией (ГЭ). Соотношение интенсивности палидарного сигнала с интенсивностью сигнала белого вещества префронтальной области, умноженное на 100, является палидарным индексом (ПИ), который одновременно является полуколичественным показателем содержания марганца в мозге. Гиперинтенсивность сигнала отмечается во всех областях мозга (скорлупа, субталамическая область, миндалевидный шар, и др.) и соответствует экстрапирамидным нарушениям, наблюдаемым у больных циррозом и манганизмом. Выявлена корреляция между содержанием марганца в крови, активностью печеночных ферментов, МРТ изменениями и признаками паркинсонизма у больных циррозом. Доказано, что чувствительность психометрических тестов в выявлении ГЭ равноценна методам нейровизуализации. Цель работы - выявить корреляцию между интенсивностью сигнала и степенью тяжести ГЭ с помощью теста соединения цифр (часть А). Гиперинтенсивность сигнала фиксировали в трех областях: бледного шара, скорлупы и префронтальной части белого вещества. Учитывали корреляции между ПИ, степенью ГЭ, содержанием марганца и меди в крови и суточной моче. Было обследовано 17 больных ГЭ. Гиперинтенсивность сигнала T1 была во всех 17 случаях. Максимальная интенсивность отмечалась в области бледного шара, сравнительно меньшая в скорлупе и очень низкая - в префронтальной части белого вещества. Сформулирована гипотеза, объясняющая образование депозитов марганца в мозге больных ГЭ: в условиях гипераммониемии и дефицита субстрата - глутамата происходит сатурация и понижение активности глутаминсинтетазы. Нарушается баланс распределения ионов ко-фермента - марганца в митохондри и цитозоле астроцитов. Свободные ионы Mn²⁺ аккумулируются и создают парамагнитные депозиты.

Ключевые слова: цирроз печени, гепатозэнцефалопатия, парамагнетические вещества, марганец, медь, палидарный индекс