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Value of computerized inhibitory control test and blood tests in minimal hepatic encephalopathy diagnosis

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Background. Minimal hepatic encephalopathy (MHE) can be diagnosed by "paper-pencil" tests, computerised inhibitory control or critical flicker frequency tests, but for clinical practice more convenient methods of diagnosis are being searched.

The aim of the study was to assess the value of inhibitory control test (ICT) and laboratory blood tests (leucocytes, platelets, hemoglobin, AST, ALT, ALP, GGT, bilirubin, albumin, SPA, INR, glucose, ammonia, IL-6) for MHE diagnosis.

Materials and methods. 62 cirrhotic patients without overt hepatic encephalopathy were enrolled in the study. The control group consisted of 53 volunteers without chronic liver diseases. Routine laboratory tests, IL-6 of venous blood samples and ammonia of the capillary blood were extracted after overnight fasting. Ammonia was measured by the micro-diffusion method. IL-6 concentration was detected using the solid phase chemiluminescence immunometer analysis. At the same day all participants performed the PHES (Psychometric Hepatic Encephalopathy Score) battery and ICT under recommended diagnostic standards.

Results. MHE was diagnosed in 44/71.0% out of 62 cirrhotic patients while 18/29.0% had no evidence of psychomotor or cognitive disturbances. There was not statistically significant difference in age, gender, education. Patients with MHE had statistically significant differences neither in leukocytes, platelets count nor in ALT, AST, ALP, GGT, IL-6, albumin, SPA, INR, bilirubin concentration in comparison with those without MHE. Patients with MHE perform ICT worse than those without MHE but the differences were not statistically significant.

Conclusions. In our study ICT was not approved as a good diagnostic tool for MHE. The IL-6 concentration in the peripheral blood as well as routine biochemical tests seem not useful for MHE diagnosis in cirrhotic patients.

Key words: minimal hepatic encephalopathy, IL-6, inhibitory control test, cirrhosis

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INTRODUCTION

The minimal hepatic encephalopathy is a condition, which raises many discussions and questions of its diagnosis and treatment. Several years ago it was called "subclinical", "early" or "latent". The current term was proposed in the 11th World Congress of Gastroenterology in Vienna in 1998. In the same Congress hepatic encephalopathy (HE) classification, West-Haven's criteria, were published, but minimal hepatic encephalopathy was not mentioned (1). According to clinical symptoms overt HE was graded just into 4 grades – from 1 to 4, the grade 0 was added later. Although cirrhotic patients with encephalopathy grade 0 do not have any clinical signs of HE, further studies revealed presence of cognitive disturbances, MHE, in part of them (2–4).

Namely this stage of HE is of particular interest in clinical practice. MHE manifestation in the cirrhotic patient may be an indicator of imminent HE, the worse quality of life, driving abilities and opportunity of retaining the job. MHE diagnosis is the challenging "paper-pencil" tests, inhbitory control test, critical flicker frequency test, P-300 event related evoked potentials, electroencephalography – all have advantages and disadvantages, are time and personal consuming. For more accurate results a combination of two methods is proposed. Predictive values of various blood analysis (IL-6, IL-18, cGMP, 3-nitro-tyrosine, citrulline, methionine) for MHE diagnosis are investigated.

Up to now a portosystemic encephalopathy syndrome test developed in Germany and known as psychometric hepatic encephalopathy score for MHE diagnosis is considered as "gold standard" (5). This test consists of five subtests: number connection test A, number connection test B, digit symbol test, line tracing test, serial dotting test. This battery examines motor speed and accuracy, visual perception, visuospatial orientation, visual construction, concentration, attention and to a lesser extent memory.

The PHES battery is relatively easy to perform and it has rather high specificity (97.5%) for MHE diagnosis (5). In order to use the PHES test in routine clinical practice it must be validated. Studies have shown that the PHES test results highly depend on the performance conditions as well as its normal rates vary depending on population (6–9). The PHES battery was already validated for some populations (10–13), but still it is hardly possible to compare data about MHE prevalence in cirrhotic patients of various populations.

Scientists are still looking for other, more appropriate and more easily standardized methods for routine MHE diagnosis (14, 15). From the clinician point of view, computerized tests such as an inhibitory control test or a critical flickers frequency test can be among perspective MHE diagnostic tools (8, 16–20).

Also detection of some compounds in the cirrhotic patient blood can provide more objective information about presence or absence of cognitive disorders in such patients. As potential markers of MHE researches list routine markers of liver inflammation and fibrosis as well as pro-inflammatory cytokines – TNF-α, IL-1, IL-6 (4, 8, 21–25). Most recent studies are concentrated on IL-6 and IL-18 role in MHE pathogenesis (26–28). Those cytokines were also confirmed as potential MHE markers in small clinical studies (29, 30).

In Lithuanian population there were not any studies performed on topic of MHE, neither its pathogenesis nor prevalence in cirrhotic patients was investigated. The aim of the presented study was to evaluate the computerized inhibitory control test, routine liver biochemical tests and IL-6 as potential diagnostic tools for MHE in cirrhotic patients.

PATIENTS AND METHODS

Subject recruitment

This research project was approved by the Vilnius Regional Research Ethics Committee (7 June 2011, No. 158200-07-372-99). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All participants enrolled into this study were informed about the purpose of this investigation and the signed informal consent. This study was conducted between 2011 October and 2013 April in the Clinic of Gastroenterology, Nephrourology and Surgery of Vilnius University Hospital Santariškių Clinics, Lithuania.

62 cirrhotic patients (41 males, 21 females of 50.05 ± 7.99 years) without overt hepatic encephalopathy were enrolled. According to etiology, most of patients had viral C cirrhosis (30 subjects),

7 patients had mixed (viral C and alcoholic) cirrhosis, 7 had viral B cirrhosis, 8 had only alcoholic cirrhosis, 6 patients had primary biliary cirrhosis, 2 patients had cryptogenic cirrhosis, 1 patient had cirrhosis of autoimmune origin and 1 had steatocirrhosis. All patients were observed and treated in out-patient and in-patient departments of the Clinic. The control group consisted of 53 volunteers without chronic liver diseases.

The patient's inclusion criteria: 18–65 years old patients with different etiology liver cirrhosis, without overt hepatic encephalopathy, other neurological or psychiatric disorders, no history of psychiatric drugs, lactulose, L-ornithine L-aspartate, antibiotics, hepatitis C treatment with pegylated interferon regimen or recent alcohol abuse (<3 months), without acute or chronic infections (except chronic hepatitis B or C), compliance.

The exclusion criteria: patients with cancer, serious decompensated cardiac, pulmonary, renal diseases, acute or chronic infections, poor vision, uncompliance, history of transjugular intrahepatic portosystemic shunt or portosystemic shunt surgical procedures, psychoneurological diseases, illiteracy.

Laboratory tests

Liver cirrhosis was confirmed by clinical symptoms, laboratory tests, ultrasound and/or endoscopic procedures, transient liver elastography or biopsy results.

Routine laboratory tests (WBC, Hgb, Plt (hematological analysators Sysmex XE-5000, Coulter LH-780), SPA, INR (STA Compact), albumins, total bilirubin, fasting glucose, AST, ALT, ALP, GGT (Architect c8200, Abbott, USA), IL-6 of venous blood samples and ammonia of capillary blood were extracted after overnight fasting. Ammonia was measured by micro-diffusion method using a blood ammonia meter (PocketChem BA, Arkray, Japan) and an ammonia reagent kit (Ammonia Test Kit II, Arkray, Kyoto, Japan). 20 µl of blood was collected from the finger by a capillary tube (with a pipette) at room temperature, the drop was applied on the sample-receiving layer for 180 seconds, after that the base film and the spacer were peeled off and the reagent was placed on the optical unit. Ammonia measurement (µmol/l) was finished in 20 seconds. According to manufacturers, the normal value of ammonia in the peripheral blood is 54 µmol/l.

IL-6 concentration was detected using the solid phase chemiluminescence immunometer analysis (Immulite 1 000 Immunoassay System, Siemens, Japan). According to manufacturers, the normal value of IL-6 in the peripheral blood is <5.9 ng/l. The centrifugated serum was frozen to –80 °C until the analysis was performed.

MHE diagnosis using PHES battery

At the day of blood sampling for laboratory tests all participants performed the PHES (Psychometric Hepatic Encephalopathy Score) battery, which includes five paper-pencil tests: digit symbol test, number connection test A, number connection test B, line tracing test, serial dotting test. The PHES battery and instruction of use were kindly provided by the inventors (5). PHES battery tests were performed by all subjects (control and enrolled patients) under the same conditions (a silent, well lighted room) and instructions. All participants were asked to wear glasses if needed. The results of the tests were calculated in points according to the inventors' methodology. The value of PHES <–4 was considered pathological.

Computerized inhibitory control test (ICT)

The inhibitory control test was used with a kind permission from the authors (18). That is a computer program which provides tested subjects with flashing series of letters on the screen. Tested subjects should follow letters flashing across the computer screen at 500 ms intervals and react to the submitted letters properly according to the test instruction: press spacebar when X and Y are alternating (they are called targets) and inhibit response when X and Y are not alternating. After the test is finished, the program calculates the number of correct and incorrect reactions on the targets and lures: correct target responses, incorrect target misses, correct lures responses, incorrect lures responses. We have calculated the total number of errors (the sum of incorrect lures response and incorrect target misses). Patient's test results were compared with the results of the control group.

Statistical analysis

Data are presented as means with standard deviation (SD), the number of male and female patients is given as a ratio. The Fisher exact test was applied to evaluate differences in age, gender

distribution, education as well as in laboratory tests results and inhibitory tests data between groups of patients with and without MHE. The Spearman correlation coefficient was calculated for evaluation of correlation between inhibitory test results and routine laboratory tests, ammonia and IL-6 concentration. The sensitivity and specificity of the laboratory blood tests and inhibitory control test were calculated by the receiving operative curves (ROC). Data were computed with Microsoft Excel and SPSS 17.0. Both tests were two-tailed with the α risk set as 5% and the ρ value <0.05 or less was considered significant.

RESULTS

According to the PHES battery results MHE was diagnosed in 44/71.0% out of 62 cirrhotic patients while 18/29.0% had no evidence of psychomotor or cognitive disturbances. There was not statistically significant difference in age, gender and education between groups of patients with and without MHE. We noticed some difference in MHE prevalence depending on cirrhosis etiology. All patients with dual liver injury agents had cognitive disturbances. In patients with cirrhosis of HCV infection etiology MHE was detected less often than in cirrhosis of other etiologies (Table 1).

Patients with MHE had statistically significant differences neither in leukocytes, platelets count nor in ALT, AST, ALP, GGT, IL-6, albumin, SPA, INR, bilirubin concentration in comparison with those without MHE (Table 2).

Although the patients with MHE performed the inhibitory control test worse than those without MHE the differences were not statistically significant (Table 3).

There were no clinical valuable correlations between the inhibitory control test and laboratory blood tests in the cirrhotics group without

Table 1. Demografic data of patients with and without MHE

	Without MHE, n = 18	With MHE, n = 44	t/F	P
Years of education	14.05 ± 2.65	12.61 ± 2.97	1.886	0.067
Age, years	50.67 ± 11.74	49.43 ± 7.99	0.553	0.584
Males / females ratio	10/8	31/13	1.266	0.202
Viral C cirrhosis	14/46.7%	16/53.3%	9.588	0.048
Viral B cirrhosis	1/14.3%	6/85.7%		
Mixed (viral C and alcoholic cirrhosis)	0	7/100%		
Alcoholic cirrhosis	1/12.5%	7/87.5%		
Other etiology cirrhosis	2/20.0%	8/80.0%		

Table 2. Differences in laboratory test results between patients with and without MHE

	Without MHE		With MHE		F	p
	M	SD	M	SD		
Ammonia, μmol/l	95.06	44.15	104.71	55.46	0.428	0.515
ALT, U/l	104.31	77.08	85.51	73.62	0.731	0.396
AST, U/l	94.81	78.37	88.89	57.53	0.096	0.758
ALP, U/l	117.00	81.46	128.56	69.91	0.246	0.622
GGT, U/l	145.20	167.11	152.81	221.80	0.014	0.906
Bilirubin, μmol/l	25.49	17.29	30.66	25.41	0.427	0.517
Albumin, g/l	34.57	4.98	34.40	5.53	0.007	0.932
Glucose, mmol/l	6.35	1.71	5.69	1.73	0.438	0.519
SPA, %	71.85	27.96	66.41	20.86	0.561	0.457
INR	1.24	0.25	1.26	0.20	0.070	0.793
Hemoglobin, g/l	136.33	20.22	128.26	21.17	1.615	0.209
Wbc	5.10	2.03	5.20	2.89	0.017	0.897
Plt	133.48	104.33	101.82	55.85	2.084	0.155
IL-6, ng/l	3.36	2.48	9.35	15.25	2.567	0.115

Table 3. Differences in the inhibitory test results between groups of patients with and without minimal hepatic encephalopathy

	Without MHE, n = 18	With MHE, n = 44	F	P
Incorrect lures response	7.60 (6.00)	9.63 (6.75)	1.054	0.309
Correct lures response	32.40 (6.00)	30.37 (6.75)	1.054	0.309
Incorrect lures response, %	19.00 (14.99)	24.09 (16.88)	1.054	0.309
Correct lure response, %	81.00 (14.99)	75.91 (16.88)	1.054	0.309
Correct target response	201.87 (8.39)	194.22 (22.25)	1.668	0.202
Incorrect target misses	10.13 (8.39)	17.78 (22.25)	1.668	0.202
Correct target response, %	95.22 (3.96)	91.61 (10.50)	1.668	0.202
Incorrect target misses, %	4.78 (3.96)	8.39 (10.50)	1.668	0.202
Total number of errors	19.53 (14.06)	27.17 (22.34)	1.522	0.223
Random response	6.27 (4.56)	5.73 (4.43)	0.158	0.693

Table 4. Correlation between the results of inhibitory control test and laboratory tests ($p^* < 0.05$, $p^{**} < 0.01$)

	Ammonia	ALT	AST	ALP	GGT	Bili-rubin	Albu-min	Glucose	SPA	INR	Hgb	Wbc	Plt	IL-6
Incorrect lures response	–0.007	–0.212	–0.230	–0.092	0.015	–0.018	0.125	.608*	0.121	–0.141	0.025	0.182	0.101	0.157
Correct lures response	0.007	0.212	0.230	0.092	–0.015	0.018	–0.125	–.608*	–0.121	0.141	–0.025	–0.182	–0.101	–0.157
Incorrect lures response, %	0.001	–0.205	–0.223	–0.092	0.015	–0.010	0.109	.608*	0.118	–0.137	0.025	0.182	0.101	0.160
Correct lures response, %	–0.001	0.205	0.223	0.092	–0.015	0.010	–0.109	–.608*	–0.118	0.137	–0.025	–0.182	–0.101	–0.160
Correct target response	–0.127	–0.085	–0.123	–.460**	–.640**	–0.294	–0.059	0.256	–0.207	0.127	–0.119	–0.011	–0.222	–0.080
Incorrect target misses	0.127	0.085	0.123	.460**	.640**	0.294	0.059	–0.256	0.207	–0.127	0.119	0.011	0.222	0.080
Correct target response, %	–0.127	–0.085	–0.123	–.460**	–.640**	–0.294	–0.059	0.256	–0.207	0.127	–0.119	–0.011	–0.222	–0.080
Incorrect target misses, %	0.127	0.085	0.123	.460**	.640**	0.294	0.059	–0.256	0.207	–0.127	0.119	0.011	0.222	0.080
Total number of errors	0.124	0.016	0.058	.427*	.637**	0.296	0.095	–0.014	0.231	–0.157	0.115	0.058	0.230	0.135
Random response	–0.023	–.428**	–.349*	–0.113	0.019	–0.121	–0.042	0.450	0.010	–0.037	–.393*	0.140	–0.058	0.245

MHE. In the group with cognitive disturbances we found correlations between correct and incorrect lures responses and glycemia (the higher glucose, the more incorrect lures responses); correct and incorrect targets responses and ALP, GGT (Table 4).

We calculated the areas under the ROC of laboratory and ICT indicators for MHE diagnosis. The best results are just satisfactory: ALP AUC = 0.621, IL-6 AUC = 0.646, incorrect lures response AUC = 0.601, the total number of errors AUC = 0.611.

DISCUSSION

In 71% cirrhotic patients without overt sings of HE enrolled in our study minimal hepatic encephalopathy was diagnosed. This MHE prevalence does not differ from those reported in the literature – up to 70% (2, 31). The fact that MHE does not correlate with cirrhosis etiology has been found by other investigators we denied (32). In our cohort of patients we have found that those with cirrhosis due to C hepatitis infection suffered from MHE less often – only 53.3%. It would be useful to study a bigger cohort of such patients to elucidate the MHE prevalence more precisely. We found a correlation between dual etiology of liver disease and cognitive disturbances, which was noticed by other authors (38). Our results reaffirm the importance of early diagnosis of MHE, which is an indicator of threatening HE, and this threat is not associated with patients' age, education or gender.

The finding that ageing and education did not associate with MHE in our cohort may indicate accuracy of test performance conditions in our study, although other investigators have found such relationship. That is why they discuss the necessity of looking for more objective MHE diagnostic methods (20, 33, 34).

Biochemical blood tests in our patients with MHE were not significantly worse than in those without MHE. The liver synthetic function of patients without and with MHE was similar. Probably the study results may have been affected by the fact that most of the subjects were in the compensated cirrhosis condition (CHILD-PUGH class A). Patients with MHE had higher concentration of proinflammatory cytokine IL-6, but the results were not statistically reliable. These results oppose to other study results (30, 36, 37).

In our study the results of the inhibitory control test in the groups of patients with and without MHE did not have statistically significant differences. So, we did not confirm the results of previous investigators who proposed the ICT test for differential diagnosis of patients with and without MHE (19). The recent study was also in agreement with our findings (35).

CONCLUSIONS

The inhibitory control test was not proved as a good diagnostic tool for MHE in our study. The IL-6 concentration in the peripheral blood as well as the routine biochemical tests and blood formula seem not useful for MHE diagnosis in cirrhotic patients.

Our study confirms the necessity of looking for the serological markers of MHE, which can be more objective than tests for the evaluation of the psycho-motor function.

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KOMPIUTERIZUOTO INHIBICINIO KONTROLĖS TESTO IR KRAUJO TESTŲ VERTĖ NUSTATANT MINIMALIĄ HEPATINĘ ENCEFALOPATIJĄ

Santrauka

Įžanga. Minimaliai hepatinei encefalopatijai (MHE) nustatyti naudojami psichometriniai „popieriaus ir pieštuko“ testai, kompiuterizuotas inhibicinis kontrolės (IKT) ar kritinio mirgėjimo dažnio testai, tačiau nuolat ieškoma klinikiniame darbe lengviau pritaikomų diagnostikos metodų.

Mūsų tyrimo tikslas – nustatyti IKT, rutininių kraujo rodiklių (leukocitų, trombocitų, hemoglobino, AST, ALT, ŠF, GGT, bilirubino, albuminų, SPA, INR, gliukozės), amoniako, IL-6 vertę diagnozuojant MHE.

Tyrimo metodai. Į studiją įtraukti 62 ciroze sergantys pacientai, kuriems hepatinė encefalopatija nebuvo kliniškai išreikšta. Kontrolinę grupę sudarė 53 savanoriai, nesergantys lėtine kepenų liga. Nevalgiusiems pacientams buvo tirti rutininiai laboratoriniai kraujo tyrimai ir IL-6 veniniame kraujyje bei amoniakas kapiliariniame kraujyje. Amoniakas išmatuotas mikrodifuzijos metodu. IL-6 koncentracija tirta kietos fazės cheminės iliuminescencinės imunometrijos būdu. Tą pačią dieną studijos dalyviai atliko bakterijos testus PHES (*Psychometric Hepatic Encephalopathy Score*) ir IKT pagal rekomenduojamus diagnostikos standartus.

Rezultatai. MHE diagnozuota 44/71,0 % iš 62 ciroze sergančių pacientų, o 18/29,0 % neturėjo psichomotorinių ar kognityvinių sutrikimų. Neradome statistiškai reikšmingų skirtumų nei pagal amžių, nei pagal išsilavinimą ar lytį tarp MHE sergančių ir nesergančių ligonių. Taip pat tarp šių grupių nebuvo statistiškai patikimų nei leukocitų, trombocitų skaičiaus, nei AST, ALT, ŠF, GGT, IL-6, albuminų, bilirubino koncentracijos, SPA, INR skirtumų. Pacientai, sergantys MHE, IKT atliko blogiau, bet statistiškai nereikšmingai.

Išvados. Mūsų tyrimas nepatvirtino IKT kaip gero MHE diagnostikos būdo. IL-6, amoniakas, rutininiai laboratoriniai kraujo tyrimai taip pat nebuvo diagnostiškai vertingi nustatant MHE.

Raktažodžiai: minimali hepatinė encefalopatija, IL-6, inhibicinis kontrolės testas, cirozė