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• *BRIEF REPORTS* •

Multidimensional assessment of neuro-psychiatric symptoms in patients with low-grade hepatic encephalopathy: A clinical rating scale

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Abstract

AIM: To evaluate the feasibility of a new clinical rating scale for a standardized assessment of cirrhosis-associated neuro-psychiatric symptoms.

METHODS: Forty patients with liver cirrhosis (LC, with or without low-grade hepatic encephalopathy) were investigated using a clinical neuro-psychiatric rating scale based on a comprehensive list of neurological, psychomotor, cognitive, affective, behavioral symptoms, and symptoms of disturbed bioregulation.

RESULTS: The analysis revealed that the majority of cirrhotic patients showed, besides characteristic neurological symptoms of hepatic encephalopathy, various psychomotor, affective and bioregulatory symptoms (disturbed sleep and sexual dysfunction). Patients were impaired in the following subscales: sleep and biorhythm disorder (75.0% of patients), Parkinsonoid symptoms (25.0%), affective symptoms (17.5%), and psychomotor retardation (12.5%). The increase of total neuro-psychiatric clinical score was significantly associated with the degree of hepatic encephalopathy.

CONCLUSION: This study suggests that a substantial number of patients with LC and low-grade hepatic encephalopathy manifest various clinical neuro-psychiatric symptoms. The use of a rating scale, which explores clinical dimensions of hepatic encephalopathy, would improve the management of patients with LC.

Key words: Liver cirrhosis; Hepatic encephalopathy; Neuro-psychiatric symptoms; Clinical neuro-psychiatric rating; Bradykinesia

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INTRODUCTION

Patients with liver cirrhosis (LC) and hepatic encephalopathy frequently demonstrate various neuro-psychiatric symptoms and deficits[1-3]. The pathophysiology, natural history, and prognosis of cirrhosis-associated neuro-psychiatric deficits are not completely established and the data on this issue are controversial[4-7]. Recent studies have shown that these deficits are associated with changes in metabolic brain patterns[8-11] and can fluctuate correspondingly to the current ammonia level. On the other hand, long-term persistence of these symptoms after liver transplantation has been reported[12-14] and the neurodegenerative nature of this disorder has been suggested[15].

Mild forms of cirrhosis-associated encephalopathy include minimal hepatic encephalopathy (MHE) and grade I hepatic encephalopathy (grade I HE). Patients with grade I HE manifest minor symptoms of motor dysfunction and with attention and concentration deficits[16-18]. MHE is diagnosed in patients who demonstrate deficits in attention and visuomotor coordination[1,4,7,17], but otherwise show no evident or only transient neuro-psychiatric symptoms. Besides, cirrhosis-associated neurological symptoms, such as asterixis, tremor, Parkinsonoid symptoms and bradykinesia, patients with low-grade hepatic encephalopathy frequently demonstrate bioregulative (disturbed sleep and sexual dysfunction), behavioral and affective symptoms[2,18,19]. The adequate clinical neuro-psychiatric evaluation of patients with LC remains difficult, because, in part, neuro-psychiatric symptoms associated with LC are multiform and sometimes subtle and also because, in part, there are no available clinical diagnostic tools adjusted to investigate this group of patients. The previously used Brief Psychiatric Rating Scale[18], which was initially designed for the monitoring of chronic psychiatric patients does not allow sufficient assessment of slight and moderate symptoms and does not include specific cirrhosis-

associated neurological, psychomotor, and cognitive symptoms. Combination of several available clinical rating scales adjusted for other clinical disorders would inevitably lead to unreasonable extension of the investigation procedure, which is not always possible in patients with LC.

The purpose of this study was to explore the feasibility of a comprehensive clinical rating scale for the evaluation of frequency and severity of neuro-psychiatric symptoms in patients with low-grade hepatic encephalopathy. A multidimensional clinical neuro-psychiatric rating scale was developed based on previous findings and clinical experience. The scale includes neurological, psychomotor, affective, behavioral, and bioregulatory symptoms and allows a global evaluation of the neuro-psychiatric state of the patients with emphasis on symptoms characteristic of LC.

MATERIALS AND METHODS

Patients

Forty patients with LC at the out-patient clinic of the Department of Gastroenterology of Innsbruck Medical University, who were listed for liver transplantation, were considered to be eligible for this study. Prior to inclusion, patients underwent a comprehensive hepatologic work-up and gave informed consent. The following exclusion criteria were applied in this study: (1) clinical or laboratory signs of inflammation, gastrointestinal bleeding, anemia, electrolyte abnormalities, or renal insufficiency; (2) overt hepatic encephalopathy (persistent or episodic, clinical grades II-IV); (3) abuse of psychotropic substances; (4) known major psychiatric disorders, as defined by DSM-IV classification; and (5) less than 6 mo of complete alcohol abstinence. The severity of cirrhosis was assessed as follows: Child A (n = 6); Child B (n = 30); and Child C (n = 4). Table 1 shows clinical and demographic data of the patients.

Table 1 Clinical and demographic characteristics of patients with LC

	No. of patients	Percent
Age (mean±SD)	54.77±10.06	
Men/women	28/12	70.0/30.0
Etiology		
Hepatitis C	14	35.0
Alcohol-associated	16	40.0
Autoimmune	4	7.5
Cryptogenic	2	5.0
Hepatitis B	2	5.0
Hepatitis C and hepatocellular carcinoma	1	2.5
Polycystic liver disease	1	2.5

Clinical neuro-psychiatric rating ACIND and psychometric tests

The clinical neuro-psychiatric examination focuses on the symptoms frequently found in patients with LC[2,21] and contains the following clusters of symptoms: neurological symptoms, symptoms of psychomotor retardation, cognitive symptoms, affective symptoms, behavioral alterations, symptoms of sleep, and bioregulatory disorder.

Neurological symptoms, such as asterixis, postural tremor, adiadochokinesia (pronation-supination of both forearms), upper limb dysmetria, dysarthria, oculomotor deficits (nystagmus and altered smooth gaze pursuit) and gait ataxia, are assessed using a standard neurological investigation. The evaluation of psychomotor retardation is based on the assessment of psychomotor change (non-interactiveness and retardation parts)[21]. Cognitive deficits and affective symptoms as well as behavioral changes and bioregulatory deficits (disturbed sleep and sexual dysfunction) are assessed using a semi-structured clinical interview based on the AMDP system[22]. Depending on the nature of symptoms, the evaluation is based either on patient's reporting or rater's clinical assessment (Table 2, Appendix 1). The intensity of symptoms, defined as a combination of frequency and severity, is uniformly assessed as follows: absent (0); slight (1 score point); moderate (2 score points); and severe (3 score points). This rating scale was arbitrarily named as assessment of cirrhosis-associated neuro-psychiatric deficits (ACIND).

The ACIND rating scale was designed in order to evaluate several possible syndromes by combining the symptoms into subscales as follows: Parkinsonoid syndrome (rigidity [obligatory symptom]; facial and head hypomobility, bradykinesia and adiadochokinesia); ataxia (dysmetria, dysartria, adiadochokinesia, gait ataxia, oculomotor deficits [without muscular rigidity]); cognitive impairment (memory decline, attention deficits, concentration deficits, as well as apperception and acalculia); psychomotor retardation (bradykinesia, facial and head hypomobility, delayed verbal responses, reduced speech velocity [without muscular rigidity]); affective symptoms (depressive mood [obligatory symptoms], loss of interest, anhedonia, feeling of loss of feeling, energy deficit, affective lability); as well as sleep and biorhythm disorder (recurrent drowsiness, impaired sleep initiation, increased daily sleep, interrupted sleep). The diagnosis of the impairment on a subscale is based on a cut-off average score point (ASP, Appendix 1). The calculation of the ASP is performed as follows: $ASP = \Sigma / n$ (Σ, sum of all score points; n, the number of symptoms within a subscale). Patients with the ASP 1.0 and higher are arbitrarily assessed as being impaired in the corresponding subscale. The total clinical neuro-psychiatric score is calculated as a sum of score points in all symptoms with a possible maximum of 96 score points. The clinical investigation based on the ACIND rating scale (duration 10-20 min) was performed by a trained neuropsychiatrist and was applied prior to the administration of psychometric tests.

The psychometric test battery included trail-making tests A and B (TMT A and TMT B[23,24]) as well as the digit symbol test (DST). The age-adjusted percentile scores based on a large population data were used in order to calculate a cumulative visuomotor index defined as the sum of percentile scores for TMT A, TMT B, and DST. Visuomotor impairment was assessed using 1.5 z-score cut-off (visuomotor index <10.57), based on age-adjusted control group of 34 healthy subjects (mean visuomotor index 19.95, SD = 6.25). Patients without obvious symptoms of grade I hepatic encephalopathy and regular psychometric performance (visuomotor index >10.57) were assigned with absent HE (grade 0 HE; n = 14). Patients without clinical symptoms but with reduced psychometric performance (cumulative index below 10.57) were diagnosed with MHE (n = 11). Patients with apparent

Table 2 Frequency of neuro-psychiatric symptoms in patients with LC

	Neuro-psychiatric symptoms	Mode of assessment	Cumulative percent of patients showing slight, moderate, or severe symptoms		Percent of slight symptoms
			%	95%CI	
	Adiadochokinesia	r	72.5	56.11-85.40	45.0
Neurological and	Bradykinesia	r	75.0	58.8-87.31	50.0
psychomotor symptoms	Dysmetria of upper extremities	r	47.5	31.53-63-87	22.5
	Asterixis	r	30.0	16.56-46.53	20.0
	Facial and head hypomobility	r	60.0	43.33-75.14	50.0
	Postural tremor	r	32.5	18.57-49.13	30.0
	Increased tendon reflexes	r	45.0	29.26-61.51	35.0
	Dysarthria	r	20.0	9.05-35.65	10.0
	Rigidity	r	25.0	12.69-41.20	22.5
	Gait ataxia	r	37.5	22.73-54.50	27.5
	Oculomotor deficits	r	22.5	10.84-38.45	17.5
	Delay in responding verbally	r	35.0	20.63-51.68	32.5
	Reduced speech velocity	r	22.5	10.84-38.45	20.0
	Reduced modulation of voice	r	40.0	24.86-56.67	37.5
Cognitive symptoms	Memory decline	s/r	57.5	40.89-72.96	35.0
	Attention deficits	s/r	47.5	31.51-63.87	32.5
	Concentration deficits	s/r	45.0	29.26-61.51	30.0
	Impaired apperception	s/r	25.0	12.69-41.20	20.0
	Impaired calculation	r	22.5	10.84-38.45	10.0
Affective symptoms	Energy deficit (lack of drive)	s	65.0	48.32-79.37	30.0
	Affective lability	s/r	52.5	36.13-68.49	25.0
	Depressive mood	s/r	40.0	24.86-56.67	27.5
	Interest deficits	s	32.5	18.57-49.13	12.5
	Anhedonia	s	20.0	9.05-35.65	12.5
	Feeling of loss of feeling	s	25.0	12.69-41.20	25.0
Behavioral symptoms	Reduction of working ability	s	87.5	73.20-95.81	25.0
	Social withdrawal	s	50.0	33.80-66.20	15.0
Bioregulatory symptoms	Recurrent drowsiness	s	82.5	67.22-92.66	15.0
	Impaired sleep initiation	s	62.5	45.80-77.27	25.0
	Increased daily sleep	s	72.5	56.11-85.40	27.5
	Interrupted sleep	s	60.0	43.33-75.14	17.5
	Sexual dysfunction (total)	s	72.5	56.11-85.40	5.0
	Women (n = 12)		66.6	34.89-90.08	16.7
	Men (n = 28)		75.0	55.13-89.21	0.0

CI: confidence interval; r: evaluation by rater; s: assessment based on patient's self-report.

clinical symptoms of cerebral dysfunction but without somnolence and disorientation were diagnosed with grade I hepatic encephalopathy (grade I HE; n = 15).

Statistical analysis

The comparison between the subgroups of patients (grade 0 HE, MHE and grade I HE) with regard to the total ACIND score was performed using non-parametric statistics (Mann-Whitney U test and Wilcoxon matched-pairs test) and one-way ANOVA. The confidence intervals of the frequency of neuro-psychiatric symptoms were analyzed using the statistical assumption of standard binomial distribution. For data processing and statistical analysis, the SPSS 11.5 software package was applied.

RESULTS

The analysis of neuro-psychiatric findings showed a high rate of different neuro-psychiatric symptoms in patients with LC. Table 2 presents the frequency of neuro-psychiatric symptoms expressed as the percentage of patients showing a corresponding symptom, as well as the 95% confidence intervals (CI). Adiadochokinesia, bradykinesia, memory and attention deficits as well as recurrent drowsiness, energy deficit (lack of drive), reduction of working ability, sexual dysfunction and impaired sleep were the most frequent symptoms in this study, although these symptoms were only slightly pronounced in a majority of patients. Recurrent drowsiness, reduction of working ability and sexual dysfunction were in some patients reported as moderate or severe (Table 2).

Patients with LC showed various intensities of neuro-psychiatric symptoms and ranged in total ACIND scores from 0 to 56. For the whole group of patients, the mean ACIND score was 22.95 score points (SD = 12.43). Figure 1A presents the percentage of LC patients in respect with different ranges of the total ACIND score and shows that LC patients most frequently ranged between 21 and 30 total ACIND score points and that 77.5% of patients in this study ranged between 10 and 40 score points.

The frequency of symptoms in different ACIND subscales is presented in Table 3. The percentages of the LC patients demonstrating in average one or more score points per symptom in a particular subscale are listed. Symptoms of biorhythm and sleep disorder were the most

Table 3 Percentage of patients impaired on different ACIND subscales

Subscales	Symptoms	Percentage of impaired patients (95% CIs)
Sleep and biorhythm	Recurrent drowsiness, impaired sleep initiation, interrupted sleep, increased daily sleep	75.0 (58.80-87.31)
Parkinsonoid	Rigidity[1], bradykinesia, adiadochokinesia, facial and head hypomobility	25.0[3] (12.69-41.20)
Cognitive	Memory decline, impaired apperception, concentration deficits, impaired calculation, attention deficits	25.0 (12.69-41.20)
Affective	Depressive mood[1], loss of interest, anhedonia, feeling of loss of feeling, energy deficits, affective lability	17.5 (7.34-32.78)
Psychomotor[2]	Bradykinesia, facial and head hypomobility, reduced speech velocity, delayed verbal responses	12.5 (4.19-26.80)
Ataxia[2]	Dysmetria of upper extremities, oculomotor deficits, adiadochokinesia, dysarthria, gait ataxia	12.5 (4.19-26.80)

[1]Obligatory symptom; [2]patients showing muscular rigidity are excluded; [3]patients with average 0.75 or more score points per symptom are included.

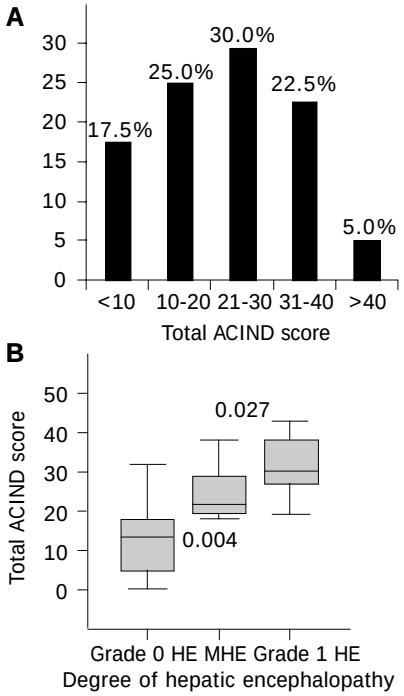

Figure 1 A: Clinical neuro-psychiatric symptoms in patients with LC; B: Box plot and Mann-Whitney *U* test with *P*-values showing the association between total ACIND score and the degree of hepatic encephalopathy (grade 0 hepatic encephalopathy, MHE, and grade I hepatic encephalopathy).

frequent (75.0%). Parkinsonoid syndrome, with rigidity as an obligatory symptom, was diagnosed in 10 patients out of 40 (25%). Cognitive impairment was found in 25% of patients. The average score on this subscale correlated significantly with the cumulative visuomotor index (Spearman's correlation: $r = 0.400$, $P = 0.021$). Depressive symptoms were found in 17.5% of patients. Both ataxia and psychomotor retardation scores were increased in 12.5% of patients.

The increase of the total ACIND score was significantly correlated with the degree of hepatic encephalopathy (Figure 1B). We observed a mean total ACIND score of 12.5 (SD = 9.1) in patients with grade 0 HE, 23.3 (SD = 9.0) in patients with MHE and 32.4 (the highest score, SD = 9.4) in patients with grade 1 HE. One-way ANOVA test demonstrated a highly significant ($P<0.001$) difference among the three subgroups of patients according to the degree of HE (grade 0 HE, MHE, and grade I). Also, the differences between the subgroups were found to be statistically significant, as proven by Mann-Whitney *U* test: grade 0 *vs* MHE ($P = 0.004$) and MHE *vs* grade I ($P = 0.027$).

DISCUSSION

This study provides a systematic description of the neuropsychiatric profile of patients with LC, including affective, behavioral, and bioregulatory symptoms and continues the investigation line of previous studies reporting various neurological, cognitive and psychomotor symptoms associated with LC[4,25-28]. A new clinical rating scale, i.e. ACIND, is proposed for the systematic assessment of the neuropsychiatric state of patients with LC. ACIND uniformly assesses a wide range of neuro-psychiatric symptoms and, due to retrospective evaluation of symptoms, is particularly sensitive for transient and subtle symptoms associated with LC. Since ACIND directly explores clinical dimensions of hepatic encephalopathy, there is a particular advantage in comparison to psychometric tests, which merely measure psychomotor performance.

Our data have shown that patients with LC frequently manifest mild neurological and psychomotor symptoms, such as adiadochokinesia, bradykinesia, and dysmetria of upper limb movements, which are consistent with previous reports on movement disorder in patients with LC[13,29,30]. Although, patients with hepatic encephalopathy grade II were not included in this study, a high rate of minor clinical symptoms of movement disorder was detected. Dysfunctions of basal ganglia, cerebellar pathways as well as in different cortical regions have been recently found to underlie neurological and psychomotor abnormalities in patients with LC and low-grade hepatic encephalopathy[9,30-35]. In our study, a bradykinetic syndrome was associated with Parkinsonoid symptoms in 25% patients (10/40). These findings support previous suggestions on the importance of Parkinsonoid syndrome in cirrhotic patients[13,30,36]. Some patients in our sample (12.5%) showed psychomotor slowing, which was associated with ataxia symptoms and not with crucial Parkinsonoid symptoms. This finding supports the suggestion of multifactorial genesis of bradykinesia in patients with low-grade hepatic encephalopathy[29].

A substantial number of our patients demonstrated a variety of affective symptoms. Depressive mood, energy deficits, loss of interest, feeling of loss of feeling, anhedonia, and social withdrawal were frequent, although in most cases slightly pronounced. These findings are in agreement with those recent reports that found affective symptoms in patients with LC[2,18,38]. Several factors may cause the occurrence of affective symptoms in patients with LC. First, a chronic disease, such as LC, is possibly associated with a high degree of impairment and might be *per se* a factor leading to the

development of a depressive syndrome. On the other hand, all patients in this study suffered from advanced LC and were challenged by indispensability of liver transplantation during several weeks or months prior to the neuro-psychiatric investigation. The inclusion in the liver transplantation waiting list requires substantial adjustment of everyday life and includes the possibility of being called for transplantation at any time. These conditions may also lead to the development of chronic adjustment disorder associated with the up-coming liver transplantation. Recent data supporting this assumption have shown manifest symptoms of post-traumatic stress disorder in a substantial number of LC patients after liver transplantation[39]. Furthermore, specific cirrhosis-associated biological mechanisms might also be responsible for the development of affective symptoms in patients with LC. Recent animal studies as well as investigations in humans have shown that acute and chronic hyperammoniemia can alter brain monoamine metabolism and cause disturbances of dopamine and serotonin neurotransmission[40-42]. Although current data on this issue are not sufficient and, to some degree, controversial, it can be assumed that metabolic brain dysfunction could lead to increased vulnerability for the development of affective symptoms in patients with LC. The high prevalence of depressive symptoms in our sample underlines the substantial demand on systematic screening of patients with LC with respect to affective symptoms.

Various cognitive symptoms, such as attention and memory deficits, have been previously reported in LC patients[37]. Our data were consistent with these findings and showed that 25% of LC patients reported increasing impairment of cognitive functions during the course of their illness.

Sleep and biorhythm dysfunction is an important clinical finding in our sample and has been reported earlier[19,43]. Disturbances of vigilance regulation have been supposed to be associated with a direct toxic effect of increased ammonia concentration, as well as with alterations in glutamine, dopamine, and serotonin neurotransmission occurring in low-grade hepatic encephalopathy[44].

Seventy-five percent of our patients reported sexual dysfunction. Previous reports suggest that an altered metabolism of steroid hormones in patients with LC could be responsible for sexual dysfunction in both men and women suffering from LC[45,46].

Our data demonstrate that clinical rating scale ACIND shows considerable sensitivity with respect to the degree of hepatic encephalopathy, which points toward its validity of clinical assessment of neuro-psychiatric deficits in patients with LC. Follow-up investigations of patients with LC after liver transplantation as well as further investigations including neuroimaging methods are needed to clarify the mechanisms underlying clinical neuro-psychiatric symptoms in LC.

Taking into account that the application of ACIND was not intended to substitute the established methods of investigation of cerebral dysfunction in LC, we suggest that the systematic use of a multidimensional clinical rating would profoundly improve the management of patients with LC.

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REFERENCES

1 **Li YY**, Nie YQ, Sha WH, Zeng Z, Yang FY, Ping L, Jia L. Prevalence of subclinical hepatic encephalopathy in cirrhotic patients in China. *World J Gastroenterol* 2004; **10**: 2397-2340
2 **Wiltfang J**, Nolte W, Weissenborn K, Kornhuber J, Ruther E. Psychiatric aspects of portal-systemic encephalopathy. *Metab Brain Dis* 1998; **13**: 379-389
3 **Ferenci P**, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002; **35**: 716-271
4 **Das A**, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J Gastroenterol Hepatol* 2001; **16**: 531-535
5 **Hartmann IJ**, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, Schalm SW. The prognostic significance of subclinical hepatic encephalopathy. *Am J Gastroenterol* 2000; **95**: 2029-2034
6 **Weissenborn K**. Minimal hepatic encephalopathy: a permanent source of discussion. *Hepatology* 2002; **35**: 494-496
7 **Duseja A**, Dhiman RK, Saraswat VA, Chawla Y. Minimal hepatic encephalopathy: natural history, impact on daily functioning, and role of treatment. *Indian J Gastroenterol* 2003; **22**: S42-44
8 **Thomas MA**, Huda A, Guze B, Curran J, Bugbee M, Fairbanks L, Ke Y, Oshiro T, Martin P, Fawzy F. Cerebral 1H MR spectroscopy and neuropsychologic status of patients with hepatic encephalopathy. *Am J Roentgenol* 1998; **171**: 1123-1130
9 **Huda A**, Guze BH, Thomas A, Bugbee M, Fairbanks L, Strouse T, Fawzy FI. Clinical correlation of neuropsychological tests with 1H magnetic resonance spectroscopy in hepatic encephalopathy. *Psychosom Med* 1998; **60**: 550-556
10 **Naegele T**, Grodd W, Viebahn R, Seeger U, Klose U, Seitz D, Kaiser S, Mader I, Mayer J, Lauchart W, Gregor M, Voigt K. MR imaging and (1) H spectroscopy of brain metabolites in hepatic encephalopathy: time-course of renormalization after liver transplantation. *Radiology* 2000; **216**: 683-689
11 **Mechtcheriakov S**, Schocke M, Kugener A, Graziadei I, Mattedi M, Hinterhuber H, Vogel W, Marksteiner J. Chemical shift magnetic resonance spectroscopy of cingulate gray matter in patients with minimal hepatic encephalopathy. *Neuroradiology* 2005; **47**: 27-34
12 **Tarter RE**, Switala JA, Arria A, Plail J, Van Thiel DH. Subclinical hepatic encephalopathy. Comparison before and after orthotopic liver transplantation. *Transplantation* 1990; **50**: 632-637
13 **Lazeyras F**, Spahr L, DuPasquier R, Delavelle J, Burkhard P, Hadengue A, Hochstrasser D, Mentha G, Giostra E, Terrier F, Vingerhoets F. Persistence of mild parkinsonism 4 mo after liver transplantation in patients with preoperative minimal hepatic encephalopathy: a study on neuroradiological and blood manganese changes. *Transpl Int* 2002; **15**: 188-195
14 **Mechtcheriakov S**, Graziadei IW, Mattedi M, Bodner T, Kugener A, Hinterhuber HH, Marksteiner J, Vogel W. Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation. *Liver Transpl* 2004; **10**: 77-83
15 **Rose C**, Jalan R. Is minimal hepatic encephalopathy completely reversible following liver transplantation? *Liver Transpl* 2004; **10**: 84-87
16 **Weissenborn K**, Heidenreich S, Ennen J, Ruckert N, Hecker H. Attention deficits in minimal hepatic encephalopathy. *Metab Brain Dis* 2001; **16**: 13-19
17 **Kharbanda PS**, Saraswat VA, Dhiman RK. Minimal hepatic encephalopathy: diagnosis by neuropsychological and neurophysiologic methods. Indian. *J Gastroenterol* 2003; **22**: S37-41
18 **Krieger S**, Jauss M, Jansen O, Theilmann L, Geissler M, Krieger D. Neuropsychiatric profile and hyperintense globus pallidus

on T1- weighted magnetic resonance images in liver cirrhosis. *Gastroenterology* 1996; **111**: 147-155
19 **Wiltfang J**, Nolte W, von Heppe J, Bahn E, Pilz J, Hajak G, Ruther E, Ramadori G. Sleep disorders and portal-systemic encephalopathy following transjugular intrahepatic portosystemic stent shunt in patients with liver cirrhosis. Relation to plasma tryptophan. *Adv Exp Med Biol* 1999; **467**: 169-176
20 **Collis I**, Lloyd G. Psychiatric aspects of liver disease. *Br J Psychiatry* 1992; **161**: 12-22
21 **Parker G**, Hadzi-Pavlovic D. Melancholia: A Disorder of Movement and Mood. *New York: Cambridge University Press* 1996
22 **Fändrich E**, Stiegltz RD. Das AMDP-System. Manual zur Dokumentation psychiatrischer Befunde. Göttingen: Hogrefe-Verlag GmbH, 2000
23 Hamburg-Wechsler Intelligenztest für Erwachsene Rev. Bern, Stuttgart, Toronto: Verlag Hans Huber, 1991
24 **Lezak DL**. Neuropsychological Assessment, Second Edition ed. New York: Oxford University Press, 1983
25 **Gerber T**, Schomerus H. Hepatic encephalopathy in liver cirrhosis: pathogenesis, diagnosis and management. *Drugs* 2000; **60**: 1353-1370
26 **Groeneweg M**, Moerland W, Quero JC, Hop WC, Krabbe PF, Schalm SW. Screening of subclinical hepatic encephalopathy. *J Hepatol* 2000; **32**: 748-753
27 **Lockwood AH**. Early detection and treatment of hepatic encephalopathy. *Curr Opin Neurol* 1998; **11**: 663-666
28 **Weissenborn K**, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. *J Hepatol* 2001; **34**: 768-773
29 **Joebges EM**, Heidemann M, Schimke N, Hecker H, Ennen JC, Weissenborn K. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. *J Hepatol* 2003; **38**: 273-280
30 **Spahr L**, Vingerhoets F, Lazeyras F, Delavelle J, DuPasquier R, Giostra E, Mentha G, Terrier F, Hadengue A. Magnetic resonance imaging and proton spectroscopic alterations correlate with parkinsonian signs in patients with cirrhosis. *Gastroenterology* 2000; **119**: 774-781
31 **Trzepacz PT**, Tarter RE, Shah A, Tringali R, Faett DG, Van Thiel DH. SPECT scan and cognitive findings in subclinical hepatic encephalopathy. *J Neuropsychiatry Clin Neurosci* 1994; **6**: 170-175
32 **Lockwood AH**. Positron emission tomography in the study of hepatic encephalopathy. *Metab Brain Dis* 1998; **13**: 303-309
33 **Montes S**, Alcaraz-Zubeldia M, Muriel P, Rios C. Striatal manganese accumulation induces changes in dopamine metabolism in the cirrhotic rat. *Brain Res* 2001; **891**: 123-129
34 **Timmermann L**, Gross J, Kircheis G, Haussinger D, Schnitzler A. Cortical origin of mini-asterixis in hepatic encephalopathy. *Neurology* 2002; **58**: 295-298
35 **Lockwood AH**, Weissenborn K, Bokemeyer M, Tietge U, Burchert W. Correlations between cerebral glucose metabolism and neuropsychological test performance in nonalcoholic cirrhotics. *Metab Brain Dis* 2002; **17**: 29-40
36 **Burkhard PR**, Delavelle J, Du Pasquier R, Spahr L. Chronic Parkinsonism associated with cirrhosis- A distinct subset of acquired hepatocerebral degeneration. *Archives Neurol* 2003; **60**: 521-528
37 **Weissenborn K**, Heidenreich S, Giewekemeyer K, Ruckert N, Hecker H. Memory function in early hepatic encephalopathy. *J Hepatol* 2003; **39**: 320-325
38 **Groeneweg M**, Quero JC, De Bruijn, I, Hartmann IJ, Essink-Bot ML, Hop WC, Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; **28**: 45-49
39 **Rothenhausler HB**, Ehrentraut S, Kapfhammer HP, Lang C, Zachoval R, Bilzer M, Schelling G, Gerbes AL. Psychiatric and psychosocial outcome of orthotopic liver transplantation. *Psychother Psychosom* 2002; **71**: 285-297
40 **Borkowska HD**, Albrecht J, Saransaari P, Oja SS. Ionotropic glutamate receptors and dopamine release in the frontal cortex in experimental hepatic encephalopathy. *Proc West Pharmacol Soc* 1998; **41**: 107-109
41 **Weissenborn K**, Berding G, Kostler H. Altered striatal dopamine D2 receptor density and dopamine transport in a patient with hepatic encephalopathy. *Metab Brain Dis* 2000; **15**: 173-178
42 **Jones EA**. Altered central serotoninergic neurotransmission: a potential mechanism for profound fatigue complicating chronic hepatitis C. *Med Hypotheses* 2001; **57**: 133-134
43 **Cordoba J**, Cabrera J, Lataif L, Penev P, Zee P, Blei AT. High prevalence of sleep disturbance in cirrhosis. *Hepatology* 1998; **27**: 339-345
44 **Jalan R**, Seery JP, Taylor-Robinson SD. Review article: pathogenesis and treatment of chronic hepatic encephalopathy. *Aliment Pharmacol Ther* 1996; **10**: 681-697
45 **Wang YJ**, Wu JC, Lee SD, Tsai YT, Lo KJ. Gonadal dysfunction and changes in sex hormones in postnecrotic cirrhotic men: a matched study with alcoholic cirrhotic men. *Hepatogastroenterology* 1991; **38**: 531-534
46 **Nolte W**, Schindler CG, Figulla HR, Wuttke W, Hufner M, Hartmann H, Ramadori G. Increase of serum estradiol in cirrhotic men treated by transjugular intrahepatic portosystemic stent shunt. *J Hepatol* 2001; **34**: 818-824

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