significant positive correlation with plasma phenylalanine and a negative correlation with the plasma levels of BCAA. D_2 receptor binding in the lenticular nuclei was correlated with prothrombin time.

Discussion

The present study is the first to describe, using PET, significant alterations of binding sites for ^{11}C-*N*-MSP in the brains of cirrhotic patients indicative of alterations of dopamine D_2 receptors in these patients. Binding site densities were found to be heterogeneous in distribution with up to five-fold differences observed between lenticular nuclei (known to be rich in D_2 receptors) and other cortical and subcortical structures. ^{11}C-*N*-MSP binding sites in thalamus and hippocampus of cirrhotic patients were significantly reduced compared to healthy controls. A previous study using SPECT and ^{123}I-iodobenzamide as ligand revealed decreased D_2 receptor sites in striatum of a cirrhotic patient (Weissenborn et al. 2000). However, in contrast to the patient population in the present study in which no patients had overt neurological symptoms, the patient studied by SPECT showed clear extrapyramidal symptoms. Earlier neurochemical studies in autopsied brain tissue from cirrhotic patients who died in hepatic coma also showed a significant loss of D_2 sites in globus pallidus/putamen (Mousseau et al. 1993) and it was suggested that loss of these sites could be the consequence of manganese deposition in the brains of these patients (Spahr et al. 1996). Manganese accumulation is the most likely cause of T_1-weighted signal hyper-intensities observed in pallidum by magnetic resonance imaging (Pomier-Layrargues et al. 1995) and such signal hyperintensities were observed in all patients enrolled in the present study. However, findings from the present study of a lack of decrease in D_2 sites in lenticular nuclei do not support the notion of a toxic effect of manganese on D_2 sites suggesting that the toxic effects of manganese occur at later stages of liver decompensation associated with overt encephalopathy. Findings from the present study of a selective loss of thalamic D_2 sites in cirrhotic patients could be expected to lead to altered levels of brain excitability and relate to previous PET findings of increased cerebral blood flow and glucose utilization in thalamus of similar patients (Lockwood et al. 1991).

Decreased D_2 binding site decreases were found to be more severe in alcoholic cirrhotic patients compared to non-alcoholic cirrhotics suggesting that alcohol (or one of its metabolites) could play a contributory role. A substantial body of evidence suggests that the brain dopamine system is implicated in the central nervous system effects of alcohol (Heinz et al. 2004) and results of a previous SPECT study suggest a role for decreased D_2 binding sites in alcohol dependence (Ebert et al. 2002). In the autopsy study of Mousseau et al. (1993), showing loss of D_2 sites, the etiology of cirrhosis was alcoholic in all cases. Taken together, these findings strongly suggest that exposure to alcohol (or its metabolites) in addition to liver-derived toxins contributes to the loss of D_2 sites in the brains of alcoholic cirrhotics.

In contrast to the apparent effects of alcohol, a previous history of overt HE did not result in greater decreases of D_2 sites. On the contrary, D_2 binding sites were significantly increased in lenticular nuclei, pericallosal area and hippocampus of patients who manifested previous episodes of HE compared to those patients who

did not. This apparently counter-intuitive finding might suggest the presence of an alternative or additional mechanism to explain the pathogenesis of HE in these patients. On the other hand, these finding could relate to decreased synaptic concentrations of dopamine resulting in upregulation of postsynaptic D_2 receptors in the brains of these patients. Studies in autopsied brain tissue from cirrhotic patients who died in hepatic coma provide evidence for a dopamine deficit; such evidence includes increased activities of monoamine oxidase (the enzyme responsible for dopamine degradation) (Mousseau et al. 1997) and increased brain concentrations of dopamine metabolites (Bergeron et al. 1989). The notion of dopaminergic deficit has clinical correlates in HE. Both the dopamine precursor amino acid and L-DOPA (Lunzer et al. 1974) and the dopamine receptor agonist bromocriptine (Morgan et al. 1980) improve the motor coordination and performance in speed-based psychometric tests in patients with chronic HE.

The magnitude of D_2 sites in thalamus of cirrhotic patients in the present study were significantly correlated with indices of severity of liver failure such as Child–Pugh scores, serum bilirubin and prothrombin times. No significant correlations were observed between D_2 site densities and serum ammonia, albumin or amino acids with the exception of phenylalanine (correlation $p<0.05$ with D_2 sites). Phenylalanine is a precursor amino acid for the synthesis of catecholamines. However, in the case of dopamine, the rate-limiting enzyme is tyrosine hydroxylase and results of the present study showed no correlation between D_2 sites and circulating levels of tyrosine. It is unlikely therefore that alterations of D_2 sites in the brain of cirrhotic patients is a consequence of altered availability of dopamine precursor amino acids.

D_2 binding sites in cirrhotic patients showed a clear correlation with patient age in both cortical and hippocampal structures, a finding that could relate to loss of cholinergic neurons in these brain structures that are known to express D_2 receptors (Finch and Roth 1999). A greater loss of D_2 sites from these neurons could explain the more severe cognitive dysfunction that is observed in older cirrhotic patients following portal decompression by TIPS or in aged portacaval-shunted animals (Audet and Butterworth 1998). If confirmed, these findings might indicate a potentially beneficial effect of D_2 receptor agonists in this population of patients.

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Diagnosis of sub-clinical hepatic encephalopathy by Neuropsychological Tests (NP-tests)

Akinobu Kato,[1] Yuki Watanabe,[2] Kei Sawara[2] and Kazuyuki Suzuki[2]

[1]*Morioka Municipal Hospital, Morioka, and* [2]*Iwate Medical University, Iwate, Japan*

Aim: At present, there are no generally accepted diagnostic criteria or methods for sub-clinical hepatic encephalopathy (SHE) associated with liver cirrhosis. We therefore developed an easily conducted computer-aided quantitative neuropsychological function test system for use in routine medical practice.

Methods: The system was used prepare basic values according to age in 542 healthy subjects, and the results were compared with 292 liver cirrhosis patients. The software is composed of eight tests: NCT-A, NCT-B, Figure Design Test, Digit Symbol Test, Block Design Test, and the Reaction Time-A, Reaction Time-B, and Reaction Time-C.

Results: Performance time is approximately 15 to 20 min. There is no need to select a specific test location and it is convenient to use even without a professional examiner. When the top and bottom 10%, which correspond to the outlier values statistically in the healthy subjects, were used as the cutoff values abnormal results were observed in approximately 25% of the liver cirrhosis patients. Moreover, 58% of the patients had abnormal values according to the results of at least one of the tests.

Conclusion: It is expected that this test will be used to further assess the diagnosis and pathology of SHE and that it will be utilized as a routine method of diagnosis.

Key words: liver cirrhosis, quantitative neuropsychological function test, sub-clinical hepatic encephalopathy

INTRODUCTION

HEPATIC ENCEPHALOPATHY IS a neuropsychiatric disease that develops as a result of serious liver disease, such as in fulminant hepatitis or cirrhosis, or a portosystemic shunt. Hepatic coma is used almost as a synonym, and there is a broad spectrum ranging from mild to deep coma. There is also a sub-clinical form of hepatic encephalopathy with unclear neuropsychiatric manifestations that it is only detected by quantitative neuropsychological function tests. This article reviews sub-clinical hepatic encephalopathy (SHE), including its diagnosis, the pathophysiology of the consciousness disorder and the classification of hepatic encephalopathy.

Correspondence: Dr Akinobu Kato, Morioka Municipal Hospital, 15-1 Koyashiki Motomiya, Morioka 020-0866, Japan. Email: nobukato@morioka-city-hosp.jp

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CONCEPT AND CLASSIFICATION OF HEPATIC ENCEPHALOPATHY

Overt encephalopathy

BASED ON ITS clinical course and the pattern of onset of the encephalopathy, hepatic encephalopathy is classified into an acute type, a chronic type, and a special type. The acute type is represented by fulminant hepatitis and the chronic type by liver cirrhosis in which portosystemic shunt has developed. The chronic type is subdivided into a type in which the portosystemic shunt factor is more prominent, and a type in which the hepatocellular damage factor is more prominent. Citrullinemia is a frequent cause of the special type in congenital urea-cycle enzyme abnormalities.

Problems such as cases in which hepatic encephalopathy develops as a result of a portosystemic shunt alone in the absence of liver cirrhosis, and cases of the acute type in which it is difficult to distinguish between whether the patient has hepatic encephalopathy secondary to acute liver failure or an acute onset of encephalopathy in liver cirrhosis, have been pointed out, and

Hepatology Research 2008; 38 (Suppl. 1): S122–S127

new classifications of hepatic encephalopathy have been devised, mainly in Western countries.[1]

Sub-clinical hepatic encephalopathy

Abnormalities of neuropsychological function have sometimes been detected by conducting sensitive quantitative neuropsychological tests in liver cirrhosis patients who have no clear neuropsychiatric manifestations or evidence of hepatic encephalopathy clinically, and such cases are referred to as SHE. This concept lies in the part of the classification of the severity of encephalopathy that would correspond to grade 0. Decreases in motor ability and attentiveness have been pointed out clinically in SHE, and assuming that approximately half of the liver cirrhosis patients in Japan exhibit SHE, the estimated number of patients would be about 150 000.

It has not yet been determined whether SHE should be perceived as a precursor of overt hepatic encephalopathy, but 23% (5/22) of the patients in the author's study[2] manifested grade II or more encephalopathy within 6 months of being diagnosed with SHE for the first time, and in some of the cases diagnosed as SHE it can be viewed as a precursor of overt hepatic encephalopathy.

Although there have been criticisms that the significance of a diagnosis of SHE is not very important clinically,[3] based on studies showing a clear decrease in quality of life (QOL) of patients with SHE,[4] their difficulty in performing complex actions, such as driving maneuvers, etc.,[5] and a negative impact on the outcome of liver cirrhosis,[6–8] Sub-clinical hepatic encephalopathy is of diagnostic significance clinically, and in Western countries the term minimal hepatic encephalopathy has been proposed.[1]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

Diagnosis and differential diagnosis of overt hepatic encephalopathy

THE DIAGNOSIS OF coma is evaluated on the basis of the Inuyama classification, however, judging grade I coma is often problematic. Amodio *et al.*[9] have proposed a diagnostic evaluation method from grade I to grade IV based on tests described below that include quantitative neuropsychological function tests (Table 1).

When there is no clear preceding liver disease and when the patient has liver cirrhosis but the diagnosis of hepatic encephalopathy based on the results of clinical tests is not definitive, additional tests must be performed to differentiate it from other diseases that give rise to consciousness disorders. Brain computed tomography (CT) scans, cerebrospinal fluid findings, etc., are useful in making the differential diagnosis from central nervous system diseases, and blood glucose, urinary ketone body, blood gas, and serum electrolyte values are useful in making the differential diagnosis from diabetic ketoacidosis. Since alcohol-dependent patients who have chronic liver disease sometimes have subdural hematomas as a result of head injuries or have alcohol withdrawal syndrome, it is especially important to make the differential diagnosis from hepatic encephalopathy.

Table 1 Modification of West Haven Criteria for the grading of mental state in patients with cirrhosis

Grade	Proposed operative definition
0	
I	• Not able to complete Trail-Making test A in 120 sec, or naming <7 animals in 120 sec • Oriented in time and space
II	• Disoriented in time: (>3 items incorrect) Day of the week, day of the month, the month, the year • Orientated in place
III	• Disoriented in place: (>2 items incorrect) state/country, region/county, city, place, floor/ward • Disorientated in time and reduction of Glasgow score (8–14)
IV	• Unresponsive to pain stimuli Glasgow score (<8)

Diagnosis of sub-clinical hepatic encephalopathy

In order to make the diagnosis of SHE strictly, (i) it seems necessary to ask questions related to QOL, including changes in behavior patterns of daily living, such as appetite, sleep, activity level, etc., and (ii) questions related to changes in mental status, such as in memory, concentration, ability to concentrate, cognitive ability, etc. (iii) It also appears important to modify the conventional classification of coma severity in overt hepatic encephalopathy and make the diagnosis by adding relatively convenient quantitative neuropsychological function tests. In addition, (iv) it is important to conduct comprehensive neuropsychological function tests, and tests for both linguistic cognitive function disorders, such as dysarthria, and for motor cognitive function disorders, such as of reaction time, spatial perception, etc.[9]

Hepatology Research 2008; 38 (Suppl. 1): S122–S127

Table 2 Diagnosis of sub-clinical hepatic encephalopathy

- Quantitative neuropsychological function test
  - Trail making test A and B
  - Reaction time to light and sound
  - Wechsler Adult Intelligence Scale (WAIS-R)
    - Block design test
    - Digit Symbol test
- Electrophysiological examination
  - Electroencephalogram
  - Auditory and visual evoked potentials
  - P300 evoked potentials
- Radiological examination
  - Magnetic resonance spectroscopy
  - Positron emission tomography

Nevertheless, it is difficult to perform all of the above in ordinary clinical practice, and usually an attempt is made to make the diagnosis on the basis of a combination of quantitative neuropsychological function tests (trail making test, reaction time to light and sound), the Wechsler Adult Intelligence Scale (WAIS), etc., and the EEG and cerebral evoked potentials (auditory, visual), which are electrophysiological tests[10] (Table 2).

Quantitative neuropsychological function tests

The WAIS and other quantitative neuropsychological function tests are used as convenient so-called "paper and pencil" diagnostic tests to make the diagnosis of SHE. Intelligence tests assume that intelligence is a set of several abilities, and they determine the degree to which the cognitive functions of the brain have been impaired based on the level of successful completion of the tests. When intelligence test items encompass a diversity of diverse tests, such as tests of spatial perception, psychomotor ability (psychomotor function, eye-hand coordination), memory, attentiveness, etc, they are difficult to conduct in ordinary clinical practice.

Since SHE is characterized by a marked decrease in motor cognitive ability, whereas linguistic cognitive ability in the form of knowledge, counting, and words is relatively preserved, three tests are conducted, the Block Design Test of the WAIS value, the Digit Symbol Test, and the Number Connection Test Part A or Part B (NCT-A, NCT-B). Sub-clinical hepatic encephalopathy is often diagnosed when the results of any one of the tests are abnormal.

The frequency of SHE when the WAIS and Symbol Connection Test were used in combination was 25–80%, and thus there was a wide range in the frequency of abnormal results, and the fact that the frequency of pathology termed "sub-clinical" varied with the test that was conducted was a problem. With the aim of resolving these problems, Weissenborn *et al.*[11] recommended five tests, including the NCT-A, NCT-B, and Digit Symbol Test, but since two of the tests in the combination, the Line Drawing Test and the Serial Dotting Test, are not very well known in Japan, it would not necessarily be easy to include them.

With paper-and-pencil type neuropsychological function tests, it is considered necessary to have a trained examiner conduct them under standardized environmental conditions in order to achieve reproducibility, and while they can be conveniently conducted in ordinary clinical practice, caution is required when evaluating them.

Moreover, when making comparisons between countries, differences in education level and cultural background must basically be taken into consideration and assessed when evaluating neuropsychological functions.[12,13]

Electroencephalography mapping (topography; isopotential maps)

Changes in responses to electrophysiological tests occur in liver cirrhosis as a result of the effect of toxic substances, including ammonia, and of electrolyte imbalances and energy metabolism abnormalities, and electroencephalography (EEG) and evoked potential alterations are often observed even in SHE in which clinical, overt encephalopathy is not observed.[14]

Numerous EEG analyses of overt hepatic encephalopathy have been carried out in the past, but most of them have been based on visual evaluations (Parson-Smith classification),[15] and a subjective element entered into them. When the EEG in SHE is analyzed in the usual manner, a decrease in α waves (12–8 c/s) and increase in θ waves (7–4 c/s) is observed in both cerebral hemispheres, and so-called slow-wave activity is occasionally seen, but the frequency of the abnormality is 9% to 33% and not very high.[16]

By contrast, EEG mapping by frequency analysis has made it possible to analyze the EEG objectively, and there is a report of a high rate of brain wave slowing of 83%.[17] Our own results[18]) showed a decrease in the frequency of α waves (%α) in the occipital area in 86% and an increase in θ-wave frequency (%θ) and δ-wave frequency (%δ) in 40% to 70%.

Amodio *et al.*[16] claimed that it is possible to diagnose SHE based on EEG abnormalities, and they have even reported that there is a rough correlation between

Table 3 Composition of neurophychological test (NP-test)

1 Number connection test A	(NCT-A)
2 Number connection test B	(NCT-B)
3 Figure position test	(FPT)
4 Digit symbol test	(DST)
5 Block design test	(BDT)
6 Reaction time test A	(RTT-A)
7 Reaction time test B	(RTT-B)
8 Reaction time test C	(RTT-C)

ammonia concentrations and SHE becoming overt, but their theory has not always been accepted.[19]

Cerebral evoked potentials

Diagnosis of SHE on the basis of evoked potentials has also been reported, and prolongations of the latency of auditory evoked potentials, etc., has been reported. More specifically, visual, auditory, and somatosensory evoked potentials and p300 event-related potentials have been used, but investigators' views differ as to which potential is the most useful for diagnosing SHE.[20–22]

Moreover, because of the fact that the abnormalities are not specific for SHE, that similar changes are also seen in alcohol-dependency[23] and diabetics,[24,25] and that there is no clear association with the degree of liver damage or outcome, they do not necessarily appear to be useful.

Quantitative neuropsychological function testing by computer

Based on multicenter cooperative research the authors have developed new software for the conventional WAIS revised version (WAIS-R) with a personal computer.[26] The software is composed of 8 tests, the NCT-A, NCT-B, Figure Design Test, Digit Symbol Test, Block Design Test, and the Reaction Time-A, Reaction Time-B, and Reaction Time-C tests (Table 3). Performance time is approximately 15 to 20 min. There is no need to select a specific test location, and it is convenient to use even without a professional examiner. The system was used to prepare basic values according to age in 542 healthy subjects, and the results were compared with 292 liver cirrhosis patients (Table 4). When the top and bottom 10%, which correspond to the "outlier values" statistically in the healthy subjects, were used as the cutoff values abnormal results were observed in approximately 25% of the liver cirrhosis patients. Moreover, 58% of the patients had abnormal values according to the results of at least one of the tests. Whether to make abnormal results on just one of the tests or on more than one of the tests the criterion for the diagnosis of SHE will require further study, but it is expected that this test will be used to further assess the diagnosis and pathology of SHE and that it will be utilized as a routine method of diagnosis.

CONCLUSIONS

SCHOMERUS *ET AL.*[27] conducted the neuropsychological function testing described above in 40 liver cirrhosis patients without overt hepatic encephalopathy and then assessed them in regard to fitness to drive. The results showed that 60% of the patients were unfit to drive a motor vehicle. The results also showed that 25%

Table 4 Clinical and laboratory characteristics of patients and healthy subjects

	Cirrhotic patients ($n = 292$)	Healthy subjects ($n = 542$)	P-value
Male/female ratio	65 : 32	51 : 49	$P < 0.0001$*
Age (year), mean ± SD	59.0 ± 7.3	52.6 ± 7.9	$P < 0.0001$**
Age (year) ratio, (n)			
40–44	5 (14)	18 (98)	
45–49	9 (27)	21 (112)	
50–54	11 (33)	20 (112)	
55–59	19 (54)	18 (99)	
60–64	28 (82)	15 (79)	
65–69	28 (82)	8 (45)	
Total bilirubin (mg/dL)	1.6 ± 1.9		
ALT (IU)	70.1 ± 50.0		
Child (A/B/C) ratio	45/46/9		
Virus/alcohol/others ratio	81/13/6		

*Chi-square test, **students-t test.

of the patients were capable of limited driving only. The investigators also found significantly more persons unfit to drive in an alcoholic liver cirrhosis group than in a non-alcoholic liver cirrhosis group. By contrast, Srivastava *et al.*[28] compared 15 patients with non-alcoholic liver cirrhosis with abnormal results on neuropsychological function tests and healthy subjects with the same age composition in regard to actual driving ability on the road and claimed to have found no significant differences between the results in the two groups. It is impossible to make simple comparisons between the two groups, but such results have a great impact on society, and further study appears necessary.

Groeneweg *et al.*[4] and Marchesini *et al.*[29] evaluated the QOL of SHE patients by the Sickness Impact Profile questionnaire and the SF-36, respectively, but they both found a reduction in QOL. Schomerus *et al.*[30] reported that ability to perform manual labor and learning ability were reduced in SHE, but they were not prospective studies, and investigating changes in response to treatment also appears to be a future task.

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肝・胆・膵疾患

Question 15 C型慢性肝炎では鉄毒性が肝炎を悪化させると聞きますが，どのようなメカニズムで起こるのですか？ また，それに対する栄養療法と薬物療法の注意点を教えてください．

Answer

■ C型慢性肝炎患者は肝臓の中に鉄が過剰になっており，それが原因で肝臓が障害されていることが明らかとなってきている．鉄の過剰な沈着は酸化ストレス状態を惹起し，炎症の増悪，線維化の促進をもたらす． ····· Lecture 1

■ C型慢性肝炎患者の肝臓における鉄過剰状態を改善する方法（除鉄療法）の基本として，たまった鉄を体外に出す（瀉血療法）方法がある． ····· Lecture 2

■ 栄養療法では「鉄制限食療法」を行い，肝機能の改善が試みられている． ····· Lecture 3

■ 具体的には管理栄養士の指導により鉄を多く含む食品を理解してもらうことが大切である． ····· Lecture 4

Lecture 1 C型慢性肝炎と鉄過剰

C型慢性肝炎では貯蔵鉄を反映する血清フェリチン値が高値を示し，肝組織の鉄量も増加していることが知られている．C型肝炎ウイルス感染チンパンジーに過剰な鉄を摂取させると肝病変が悪化することが報告されており，鉄が直接的な肝細胞毒性をもつものと考えられている．なぜC型慢性肝炎で鉄が過剰に沈着するかについては十分に解明されていない．鉄過剰状態にあるC型慢性肝炎では，肝細胞内の鉄が過剰状態となり，遊離鉄（2価と3価の鉄の総和）が増加する．この遊離鉄は酸素を活性酸素に変換させる反応を触媒する．H_2O_2とFe^{2+}の作用にてOH^-+・OH+Fe^{3+}が産生され，最も毒性の強い活性酸素であるヒドロキシラジカル（・OH）が大量に産生される[1]．この結果として酸化ストレスの増加を励起して脂質過酸化の亢進，DNAの損傷，アポトーシスの誘導などが起こり，肝炎の進展をきたしていると考えられている[2,3]．

Lecture 2 慢性肝炎に対する瀉血療法とは

C型慢性肝炎患者での肝臓における鉄過剰状態を改善する方法（除鉄療法）の基本は，食事により余分な鉄を体内に入れない（鉄制限食）とたまった鉄を体外に出す（瀉血療法）の2つであり，経静脈的に鉄のキレート剤を投与するといった方法は行われていない．

瀉血療法[3]についてはすでに保険適応があり，瀉血をすることで約半数の症例の血清トランスアミナーゼが正常化することが報告されている．瀉血により鉄欠乏性貧血を作り出し肝臓における過剰な鉄を赤血球造血に動員して，結果として肝臓での鉄含有量を減少させることを目的としている．インターフェロン抵抗性あるいは副作用のためにインターフェロンを中止した症例などに用いられている．

食事からの鉄摂取をコントロールしないと瀉血の効果が少なくなることから，通常，瀉血療法と後述する鉄制限食療法を併用することが多い．瀉血量としては，初期瀉血期間として200 g/週を12週間をめどに，ヘモグロビン11 g/dL以下またはフェリチン10 ng/mL以下となるまで瀉血を行う．続いて維持瀉血期間として，ヘモグロビン値またはフェリチン値を上記程度に維持するよう1～3ヵ月間隔で200 gの瀉血を行う．

瀉血療法を行った前後で症例の肝臓生検組織の鉄を検討すると，著明に減少しているのが観察され，簡便かつ有用な治療法として期待される．

Lecture 3 鉄制限食療法の基本

瀉血療法による除鉄療法に，鉄制限食を併用すると，瀉血維持療法時期の追加瀉血回数の減少や肝機能の安定に有用であることが報告されている．鉄制限食の目標は「鉄量6 mg/日以下」であるが，C型慢性肝炎の食事療法の基本はバランスの取れた食事であることから，鉄量だけでなく，エネルギー30～35 kcal/kg/日，蛋白質1.2 g/kg/日，脂質エネルギー比は20～25％程度の食事内容を摂ることも目標におく．

具体的に鉄制限食療法を行うためには，鉄製の調理器具（鉄鍋など）や器を控える．次に食材としては後述するように，赤い肉類，緑の濃い野菜に鉄分を多く含むことからできるだけ摂取する回数を減らす．

Lecture 4 食品の鉄含有量

・魚と肉類には赤身質・内臓・血合い部分に鉄分が多く含まれ，赤身の程度が強くなるほど鉄分は多くなる[4]．小魚・貝類は内臓を一緒に摂取するので鉄量は多い．鶏や豚のレバー，

煮干し，かつおの角煮や煮干し，シジミ，アサリなどに鉄は多く含まれる．

・豆類（豆・納豆・きな粉）も鉄量が多い．卵は卵黄に多く，卵白には少ない．

・野菜類はほうれん草や小松菜などの青菜類に多く，大根やたまねぎなどの淡色・黄色野菜には少ない．

・穀類ではパンやうどんなどの小麦粉製品より米飯のほうが鉄量は少ない．調味料ではみそ，しょう油は大豆から作られるので鉄の含有量は多い．カレーは香辛料のなかに鉄を多く含むウコン（ターメリック）を含むので注意が必要である．

・菓子類では豆菓子，チョコレート菓子に注意する．ココア，チョコレートには鉄が多い．

・調理する場合，鉄製の調理器具（中華鍋・フライパン・すきやき鍋）の使用を避ける．

・鶏肉，豚肉，ハム，ソーセージ，白身魚，エビ，カニ，イカ，タコや乳製品などは鉄分の少ない食材であり，このような食材を用いた献立を考える．

鉄の吸収効率を考慮すると肉・魚に多く含まれるヘム鉄は吸収がよく，野菜に含まれる非ヘム鉄は吸収率は低い．肉・魚の鉄吸収効率は10～40％程度，野菜の鉄吸収効率は0.3～5％程度とされている．

（解説：加藤章信／鈴木一幸）

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肝・胆・膵疾患

Question 16 従来，脂肪肝は肝硬変に進展しないと聞きますが，本当ですか？また，その鑑別はどのようにするのですか？

Answer

■ 脂肪肝が肝硬変に進展するか否かは，脂肪肝の成因によって異なる．従来，進展する例の多くはアルコール性の脂肪肝であり，過栄養や肥満などによる脂肪肝においては脂肪肝から肝硬変への進展はないものと考えられてきた．しかしながら，最近，非アルコール性の脂肪肝の一部の症例で肝硬変から肝癌にいたる例が報告されるようになり注目されている． ····· **Lecture 1**

■ 最近，非アルコール性の脂肪肝は非アルコール性脂肪性肝疾患（non-alcoholic fatty liver disease：NAFLD）という疾患概念に統一され，これはさらに単純性脂肪肝（simple fatty liver）と非アルコール性脂肪肝炎（non-alcoholic steatohepatitis：NASH）に分類される．
したがって，脂肪肝から肝硬変さらに肝癌へ進展する可能性のある症例はNASHである．
····· **Lecture 2**

■ 脂肪肝の診断は各種画像検査（腹部CT，超音波検査）により比較的容易であるが，単純性脂肪肝とNASHの鑑別は血液生化学検査および画像検査を用いても難しく，最終的に確定診断をするためには肝組織検査が必要となる． ····· **Lecture 3**

Lecture 1 非アルコール性脂肪肝炎(NASH)とは

1980年米国のメイヨクリニックのLudwig[1]はアルコール飲酒がないにもかかわらず，肝臓の組織所見がアルコール性肝炎に類似したものをNASHと呼ぶことを提案した．この時に示された症例の肝臓の組織は，中程度から高度の大滴性脂肪沈着を認め，好中球を含めた種々の炎症性細胞浸潤と小壊死巣を伴う脂肪肝炎を示すものであった．さらにNASHは組織学的に類洞周辺部の肝の線維化を特徴として，肝硬変を認めることもある．従来から脂肪肝の大部分はアルコール多飲によるもので，肥満に伴う脂肪肝はあったとしても，肝硬変などへの進展はないと考えられていたために，Ludwigの報告は広く認められなかった．

その後1986年にSchaffner[2]は飲酒が1日20 g以下であるのにもかかわらず，アルコール性肝障害に類似した組織像を示す種々の成因による疾患をまとめてNAFLD（non-alcoholic fatty liver disease）と報告した．NASHという概念がわが国に定着したのはここ数年のことであるが，その発症原因の多くは過栄養による肥満であり，メタボリックシンドロームの肝臓におけ

る表現型の一部とも考えられる．

NASHの成立機序としてDay[3]らは2段階説（two hit theory）を提唱している．すなわち第1段階で単純脂肪肝が成立し，それに第2段階として種々の要因が加わり，炎症性細胞浸潤，肝細胞の変性・壊死が生じNASHが生じるとした．脂肪沈着にはインスリン抵抗性が重視され，種々の要因には炎症性サイトカイン，酸化ストレス，エンドトキシンなどが考えられている．

Lecture 2 NASHが進行すると肝硬変になる例がある

欧米での報告で，NASHを約10年間経過を追うと，その半数で病期の進展があり，2割の症例は肝硬変に移行したとされている．一方，2年程度の観察では明らかな肝硬変に進展した症例はなく，NASHの病期の進展は比較的穏やかであると推定されている．

わが国ではいまだ，同様の長期にわたる検討はなく，わが国におけるNASHの予後は確立されてはいないが，罹患期間が長くなるほど病期は進行すると考えられている．NASH症例がすべて肝硬変に進展するものではないが，糖尿病や肥満は線維化進展に寄与する因子であると考えられている．

NASHでは病期が進行し肝臓への線維化が進展すると，肝臓の脂肪沈着は徐々に失われる．このため肝硬変への移行期にさしかかるとNASHに特徴的な所見は失われる（burn-out）ため，病因の特定が困難となり，肝硬変に進展したNASH症例は従来原因不明の肝硬変と分類されており，原因不明の肝硬変の中に進展したNASHが含まれている可能性がある．

Lecture 3 NASHの鑑別診断

前述のようにLudwigは，飲酒歴がないにもかかわらず肝臓の組織で脂肪肝炎を示した症例をNASHという新しい疾患概念として報告しており，NASHは病理診断より生まれた概念である．したがって，肝生検による病理診断がゴールデンスタンダードであり，これに替わる診断法は現在ない．

しかしながら，脂肪肝症例全例に肝生検を行うことは困難であり，現実的には血液検査（**表1**）など非侵襲的検査からして，どのような症例に肝生検を行うべきか考慮することが重要と考えられる．

NASHの血液検査にはいくつかの特徴があげられており[4]，肝機能ではALT優位のトランスアミナーゼの上昇が特徴的であり，最も一般的に観察される．アルコール性肝疾患の場合にはASTが優位なことが多く，鑑別に役立つ．NASH症例におけるトランスアミナーゼの上昇は軽度であり，100 IU/L以下の症例が多い．また，AST/ALT比はNASHの進行度を予測するうえ

で参考となるとされている．通常その比は1以下のことが多いが，肝線維化の進展に従って上昇する．しかしNASHの場合AST/ALT比が2以上になることはなく，2以上の場合はアルコール性肝障害を疑う．γ-GTPやALPなどの胆道系酵素の上昇はアルコール性肝疾患では高値を示すことが多いが，NASH患者では正常から軽度の上昇にとどまることが多い．進行したNASH症例では線維化マーカーであるヒアルロン酸やⅣ型コラーゲンなどが高値を認めることがあり，診断の参考になる．さらにフェリチン値も単純脂肪肝よりNASH例で高値である．

▽ 表1 NASHを疑うべき血液検査所見

一般生化学検査
トランスアミナーゼの上昇
AST/ALT比が1以上
血小板の減少
プロトロンビン時間の延長
アルブミン値が低下
フェリチン値の上昇
線維化マーカーの上昇
その他の検査
インスリン抵抗性の存在（HOMA-IRの上昇）
酸化ストレスマーカーの高値
TNF-α高値
レプチン高値
アディポネクチン低値　など

（鎌田佳宏，田村信司：IV 病態　1 血液検査所見．NASH診療ハンドブック，p23-33，中外医学社，2007より改変）

肝線維化が進行してくると血小板，プロトロンビン時間，アルブミン値が低下し，肝硬変に類似する血液検査値を示す．

NASHの発症にはインスリン抵抗性や酸化ストレス，アディポサイトカインの関与が指摘されている．インスリン抵抗性を評価する，HOMA-IRや酸化ストレスマーカーのthioredoxin，malondialdehydeなどがNASHで有意に上昇しているとの報告や，アディポサイトカインのTNF-αやレプチンなどがNASH例で上昇しているとの報告もある．また，実験的に肝線維化を改善する効果を持つとされているアディポネクチンが線維化の進行とともに減少していくことも報告されている．

その他，脂肪肝に高血圧，糖尿病，高脂血症などのメタボリックシンドロームのリスクファクターを合併する症例でもNASHの存在が疑われる．

（解説：加藤章信／鈴木一幸）

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肝・胆・膵疾患

Question 17 脂肪肝を防ぐ観点から栄養療法を行うコツはありますか？

Answer

■ すべての肝疾患症例に対して食事療法は必要であるが，ことに非アルコール性脂肪肝炎（non-alcoholic steatohepatitis：NASH）を含む脂肪肝では重要となる．肝臓は栄養代謝の中心であり，栄養療法は治療の基本となる．…… Lecture 1

■ 脂肪肝に対する栄養療法を行う場合にはその病態についての理解も重要となる．…… Lecture 2

■ 脂肪肝を防ぐ食事の基本は過食・過栄養に注意し，間食や過度の飲酒も控えた食事をすることである．飽食の時代と言われて久しい現代では，普通の食事がすでに高蛋白・高カロリーになっており，むしろ高蛋白・高カロリーを意識することなく，控えめな食事が大事である．…… Lecture 3

Lecture 1 食事療法の基本について

健診で肝機能異常が指摘される場合に，頻度の高い疾患は，NASHを含む脂肪性肝疾患，慢性肝炎，一部に肝硬変などがある．すべての肝疾患症例に対して食事療法は必要であるが，ことにNASHを含む脂肪性肝疾患では重要となる．肝臓は栄養代謝の中心であり，栄養療法は治療の基本となる．食事療法の基本はバランスの取れた食事，すなわち，炭水化物，脂肪，蛋白質だけでなく，ビタミンやミネラルにも配慮した，さまざまな食材を用いた食事が理想である．しかし，食事は毎日のことであり，患者を取り巻く環境により必ずしも理想通りにはいかないこともある．実際に家庭で食事療法を行う場合は，長続きできるよう月単位，季節単位でさまざまな食材を取り入れるのがコツである．また，管理栄養士による食事指導が可能な場合は積極的に活用し，短時間で頻回の指導を行うことが有用である．

Lecture 2 脂肪肝・NASHの病態栄養

脂肪肝は生活習慣の欧米化により近年増加している．最近の統計では脂肪肝は健診受診者の約3割にのぼるとされている．男性では30歳代より，女性では閉経後よりその割合が増加する．

脂肪肝は動脈硬化の危険因子だけでなく，糖尿病，肥満，高脂血症や高血圧とも関連し，それぞれの病態を増悪させる．また，最近ではC型慢性肝炎の肝臓での線維化を促進させるという報告もあり栄養療法は重要となる．成因としては肥満・過栄養，アルコール，薬剤など多岐にわたる．

脂肪肝の発生要因として肝臓での脂肪酸合成の亢進，肝臓での脂肪酸化の低下，肝臓から末梢への脂肪輸送の障害などがあげられる．脂肪肝では肥満，高脂血症，高血圧などの生活習慣病の合併が高頻度であることから，これらの病態の理解も重要である．

NASHでは7割の症例に肥満を伴っており[1]，高頻度で内臓脂肪沈着（内臓肥満）と耐糖能異常も伴っていることが病態の特徴である[2]．さらにインスリン抵抗性のため，空腹時の高インスリン血症により空腹時血糖値は正常で，糖負荷2時間後に高血糖を示す例が多い．したがって，肥満やインスリン抵抗性が軽減できれば脂肪肝に明らかな改善がなくとも，合併する肝障害の程度を軽減できる．肥満を伴わないNASHでも同様に高頻度の内臓肥満やインスリン抵抗性を示し，インスリン抵抗性はNASHの病態の本質を表していると考えられる．

Lecture 3 脂肪肝・NASHとその食事療法

治療には適度の運動と食事療法が基本である．食事療法について，基本は食事制限となるが，急激な体重の減少や極端な食事制限を行うと，合併症としての胆石の形成や，NASHにみられる線維化の進行を促進させることが知られており注意を要する．

肥満，耐糖能異常，高脂血症，高血圧などの生活習慣病を高頻度に合併することから，これらの病態に見合った食事療法を行うのが基本である．過栄養による肥満や運動不足を認める例では運動療法も併用する．脂肪肝・NASHの食事療法のポイントとしては，糖尿病症例に対するバランスの取れた食事摂取療法に準じている．エネルギー25～35 kcal/kg/日，蛋白質1.0～1.5 g/kg/日，三大栄養素の配分として，蛋白質20～25 %，脂質15～20 %，糖質60 %と脂質を抑制した割合が推奨されている[3]．さらに糖質はショ糖などの単純糖質でなく穀類などの複合糖質を摂取すること，食物繊維やビタミンE・Cなどを多く摂るようにすること，早食い，間食，夜食は控えること，定期的な栄養指導を受け，ダイエットによる急激な体重減少は避けることなどがあげられる（**表1**）[3]．

飲酒は基本的に禁ずる．内容としては脂肪に関しては極端な脂肪制限は脂溶性ビタミンの不足につながることから注意する．逆に飽和脂肪酸の過剰摂取は血中コレステロールを上昇させることから，バター，牛乳，獣肉類は制限する．

さらにNASHと鉄代謝の関係が検討されており，Question 15（p.261）にある鉄制限食がNASHに対しても有用であることが報告されている．

しかしながらNASH症例では食事療法と運動療法のみでは十分な治療効果が得られないため

▼ 表1 脂肪肝・NASHの食事療法のポイント

1. 1日のエネルギー摂取量：25～35 kcal/kg/（標準体重）	5. 食物繊維やビタミンE・Cなどを多く摂るようにする
2. 蛋白質：1.0～1.5 g/kg/（標準体重）	6. 早食い，間食，夜食は控える
3. 三大栄養素の配分：蛋白質20～25％，脂質15～20％，糖質60％	7. 定期的な栄養指導を受ける
4. 糖質はショ糖などの単純糖質でなく穀類などの複合糖質を摂取する	8. ダイエットによる急激な体重減少は避ける

（遠藤龍人，鈴木一幸：V 治療・管理，1 食事療法，NASH診療ハンドブック，p129-142，中外医学社，2007より引用）

に，薬物療法を必要とする例が多い．NASHに対する薬物療法としては，インスリン抵抗性改善薬として糖尿病に用いられているチアゾリジン誘導体やビグアナイド，またNASHでの肝細胞障害の機序とされる酸化ストレスを抑制する薬剤としてのビタミンEやCといった抗酸化薬も用いられている．さらに肝庇護薬，高脂血症用薬，降圧薬などもNASHの治療に用いられている．

（解説：加藤章信／鈴木一幸）

◆文 献

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Original Article

Effect of symptomatic gastroesophageal reflux disease on quality of life of patients with chronic liver disease

Kazutomo Suzuki, Kazuyoshi Suzuki, Kazuhito Koizumi, Hiroshi Takada, Ryoichi Nishiki, Hiroki Ichimura, Shigeki Oka and Hajime Kuwayama

Department of Gastroenetrology and Hepatology, Koshigaya Hospital, Dokkyo Medical University, Saitama, Japan

Aim: Reflux esophagitis is becoming increasingly more prevalent in Japan. It has been noted that symptomatic gastroesophageal reflux disease (GERD) and chronic liver disease may adversely affect patients' quality of life.

Methods: In the present study, 238 chronic liver disease patients (151 patients with chronic hepatitis and 87 patients with liver cirrhosis) were enrolled. The diagnosis of GERD was made based on the Quality-of-Life and Utility Evaluation Survey Technology questionnaire. Health-related quality of life was evaluated using the Short Forum 36 questionnaire.

Results: Symptomatic GERD was present in 31.8% (48/151) of patients with chronic hepatitis and 36.8% (32/87) of patients with liver cirrhosis. Among the chronic hepatitis group, compared to the GERD-negative group, the GERD-positive group had significantly lower scores in six domains, including "role limitation due to physical problem", "bodily pain", "general health perception", "vitality", "role limitation due to emotional problem", and "mental health". Among the cirrhotic group, compared to the GERD-negative group, the GERD-positive group had significantly lower scores in the "role limitation due to emotional problem" domain. Significant improvement in the "physical functioning", "bodily pain", and "general health perception" domain scores was noted in chronic hepatitis patients treated with rabeprazole.

Conclusion: The QOL of chronic liver disease patients with symptomatic GERD was impaired.

Key words: chronic liver disease, gastroesophageal reflux disease, quality of life, Quality-of-Life and Utility Evaluation Survey Technology, Short Forum 36 questionnaire

INTRODUCTION

REFLUX ESOPHAGITIS IS becoming increasingly more prevalent in Japan due to Westernization of the diet, aging of the population, and a decrease in the *Helicobacter pylori* (*H. pylori*) infection rate among younger individuals. It has been reported that in Japan, lifestyle changes reflected by dietary changes, such as increased alcohol consumption and excessive fat intake, as well as a decrease in the rate of *H. pylori* infection in younger individuals, may have led to the decreased frequency of atrophic gastritis. This in turn may have led to excessive gastric acid secretion and therefore an increased frequency of gastroesophageal reflux disease (GERD).[1] Some researchers have noted that GERD is associated with respiratory diseases, including chronic bronchitis, interstitial pneumonia, and bronchial asthma,[2] as well as coronary artery disease.[3] However, patients with chronic liver disease due to hepatitis C virus infection have a higher *H. pylori* infection rate.[4] This has led to speculation that there is only a weak association between GERD and chronic liver diseases. The present clinical study was done to determine the association between chronic liver diseases and symptomatic GERD. In addition, the present study also assesses the therapeutic effects and the effect on the health-related quality of life (HRQOL) of proton pump inhibitor (PPI) treatment in chronic liver disease patients with symptomatic GERD.

Correspondence: Dr Kazutomo Suzuki, Department of Gastroenterology and Hepatology, Koshigaya Hospital, Dokkyo Medical University, 2-1-50 Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan. Email: s-kazu@dokkyomed.ac.jp
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METHODS

Patients

A TOTAL OF 238 patients with chronic liver disease who had received regular outpatient treatment at the Department of Gastroenterology and Hepatology, Koshigaya Hospital, Dokkyo Medical University, Saitama, Japan from 2003 to 2004 were recruited. Patients who had ascites or any self-reported abdominal symptoms were excluded. Patients who were taking drugs that could affect gastric acid secretion, including H_2-receptor antagonists and PPI, those who were taking a gastrointestinal tract motility regulator, and those with upper gastrointestinal disease were also excluded. Chronic liver disease was diagnosed based on biochemical blood tests and abdominal imaging. Hepatitis B virus (HBV) infection was confirmed by a positive reaction to hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) infection was confirmed by a positive reaction to HCV-RNA (reverse transcription polymerase chain reaction). Among the patients who were not HBsAg and HCV-RNA positive, patients without serum immunoglobulin G (IgG) levels ≥2000 mg/dL, and patients who were not antinuclear antigen positive were diagnosed as non-B non-C (NBNC). Of the 151 patients with chronic hepatitis (57 men and 94 women; average age 60 ± 11 years), 30 had HBV infection, 114 had HCV infection, and seven had NBNC. Of the 87 cirrhotic patients (41 men and 46 women; average age 65 ± 7 years), 12 had HBV infection, 55 had HCV infection, and 20 had NBNC. Serum hyaluronic acid levels, a marker of liver fibrosis, were measured using the sandwich binding protein assay.

Diagnosis of symptomatic GERD

In the present study, the diagnosis of GERD was made based on the results of the Quality-of-Life and Utility Evaluation Survey Technology (QUEST) questionnaire developed by Carlsson *et al.*[5] Patients whose QUEST score was four or higher were judged to have symptomatic GERD. Upper gastrointestinal endoscopy was not performed in the present study. The frequency of symptomatic GERD in patients with chronic liver disease was determined. In addition, the severity of cirrhosis was assessed according to Child–Pugh's classification system. The patients were classified into two groups (group A and group B/C). Furthermore, the correlation between the severity of liver fibrosis and the frequency of symptomatic GERD was determined. The patients were stratified into three groups based on their hyaluronic acid (or hyaluronan) levels: <50 ng/mL ($n = 30$), 50–200 ng/mL ($n = 58$), and >200 ng/mL ($n = 47$). The frequency of symptomatic GERD was examined in the three groups.

Evaluation of HRQOL

HRQOL was evaluated using the Medical Outcome Study 36-item Short-Form Health Survey (SF-36) questionnaire, which is currently recognized as a reliable quality of life (QOL) assessment instrument worldwide.[6] We reviewed eight categories of physical functioning (PF), role limitation due to physical problem (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitation due to emotional problem (RE), and mental health (MH) using the SF-36 questionnaire (version 1.20). The SF-36 questionnaire for the QOL assessment and the QUEST questionnaire were administered to patients on the same day. Normative data for the Japanese general population reported by Fukuhara *et al.*[7] were used for the comparison. The effect of symptomatic GERD on HRQOL was evaluated in patients with chronic liver disease, which may in itself be a risk factor for the deterioration of patients' HRQOL. In order to elucidate the effect of symptomatic GERD on HRQOL in chronic liver disease patients, the patients were first classified by type of chronic liver disease (chronic hepatitis group and liver cirrhosis group) and then further subdivided into four subgroups based on the presence/absence of symptomatic GERD (GERD positive/GERD negative). The HRQOL scores of the patients with and without symptomatic GERD in each chronic liver disease group were then compared.

Diagnosis of *H. pylori* infection

The presence of *H. pylori* infection was confirmed using a serological method. Serum anti-*H. pylori* IgG antigen levels were measured by enzyme immunoassay. *H. pylori* infection was diagnosed based on a *H. pylori*–IgG titer >1.7 EV.

Effects of rabeprazole treatment

In the patients with symptomatic GERD who consented to treatment, rabeprazole (10 mg/day) was given for 6 months. At the end of the 6-month treatment period, the QUEST and SF-36 (version 1.20) questionnaires were administered to these patients to assess the therapeutic effect of rabeprazole, as well as the effect on HRQOL.