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Evaluation of Quality of Life and Risk Factors in Patients With Covert Hepatic Encephalopathy Including Those With Hepatocellular Carcinoma

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Abstract

Background/Aim: Covert hepatic encephalopathy (CHE) is associated with a decline in quality of life (QOL), requiring early detection and intervention. We aimed to determine CHE prevalence, QOL correlations, and risk factors in hospitalized patients with cirrhosis. This study evaluated neuropsychological test (NPT) results and QOL in these patients.

Patients and Methods: This retrospective study included 56 patients with liver cirrhosis who were hospitalized at our institution from January to November 2024 and underwent simultaneous short form health survey (SF-36) testing and NPT. The NPT included the number connection (NCT)-A and Stroop tests. QOL was assessed using the SF-36, and risk factors evaluated using hematological data at admission.

Results: The mean patient age was 67.5 years, with 39 men and 17 women. Hepatocellular carcinoma was observed in 35 patients (63%). Underlying liver diseases were: hepatitis C virus in seven patients, hepatitis B virus in four, alcohol damage in 16, metabolic dysfunction-associated steatohepatitis in 10, autoimmune hepatitis in four, and others in 15. CHE was detected in 24 patients (43%): three (13%) with abnormal NCT-A findings, 14 (58%) with abnormal Stroop findings, and seven (29%) with both abnormalities. On SF-36 assessment, patients with CHE had significantly lower role-physical (RP) scores than those without CHE [30.80 (2.55-55.72) *vs.* 49.07 (12.52-55.72), p=0.022]. Furthermore, role-emotion and vitality tended to be lower in patients with CHE. Patients with CHE also had significantly lower Zn levels than those without [67 (42-110) *vs.* 81 (44-190); p=0.016].

Conclusion: Patients with CHE experienced reduced QOL RP and low Zn levels, suggesting that early Zn supplementation may improve CHE and enhance QOL.

Keywords: Covert hepatic encephalopathy, quality of life, short form 36, zinc level.

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Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome caused by chronic liver conditions such as cirrhosis, acute liver failure, and portal-systemic shunt (1). The International Society for Hepatic Encephalopathy and Neuropathy classification system is commonly used to categorize HE progression into overt hepatic encephalopathy (OHE) and subclinical covert hepatic encephalopathy (CHE) (2).

CHE is the mildest form of neurocognitive impairment caused by an impaired hepatic reserve in patients with cirrhosis (3-5). Although asymptomatic, CHE affects approximately 20%-40% of patients with cirrhosis and progresses to OHE in 10% of cases annually, making early diagnosis critically important. CHE also affects quality of life (QOL), increases the incidence of falls and motor vehicle accidents, and contributes to mortality (6-8). Early detection and appropriate management are vital for improving the prognosis in patients with cirrhosis (2, 9).

Various quantitative CHE diagnostic methods have been reported. The Neuropsychological Test (NPT) is widely accepted, particularly in Japan, utilizing subtests such as the Number Connection (NCT) and Stroop tests (10, 11). However, few studies have provided guidelines for early CHE detection in clinical practice, including QOL assessment. We aimed to examine the status of CHE diagnosis using the NPT, QOL assessment, and diagnostic guidelines.

Patients and Methods

This retrospective study included 56 patients with liver cirrhosis who were hospitalized at our institution between January and November 2024 and underwent NPT and short-form health survey (SF-36) assessments. We used information from the NCT and Stroop tests, which are commonly administered to diagnose CHE, to determine its presence. Additionally, we examined CHE risk factors using SF-36 QOL assessments and blood test data collected during the same period. Risk factors were also examined.

CHE diagnosis. Psychometric tests are the cornerstone of CHE diagnosis. The psychometric HE score is the most popular and easily applied approach to minimal HE (MHE) and includes five psychometric tests: the NCT-A and -B, line tracing, digit symbol, and serial dotting tests (12). The Stroop test was performed to diagnose CHE at each center according to previous reports (13-15). Age-specific cutoff values for CHE diagnosis determined in a previous study of Japanese subjects were applied (16). The Stroop test software (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was distributed by the Japan Society of Hepatology and was installed on an iPad (Apple Computer, Cupertino, CA, USA).

QOL evaluation. QOL was assessed using the SF-36 version 2, which includes four items assessing physical QOL [physical function (PF), role-physical (RP), bodily pain, and general health perception (GH)], and four items assessing mental QOL [vitality (VT), social functioning, role-emotional (RE), and mental health (MH)] (17).

Statistical analysis. Categorical variables are expressed as numbers and percentages, and continuous variables as medians and interquartile ranges. Differences in the percentages between groups were analyzed using the chi-square test. Differences in quantitative values were analyzed using the Mann–Whitney *U*-test. All data analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) (18).

Results

The average patient age was 67.5 years, 39 were male and 17 female. Hepatocellular carcinoma were seen in 35 cases (62.5%). Underlying liver diseases included hepatitis C virus in seven patients, hepatitis B virus in four, alcoholic cirrhosis in 16, metabolic dysfunction-associated steatohepatitis in 10, autoimmune hepatitis in four, and other diseases in 15. CHE was detected

Table I. *Baseline characteristics of patients.*

Categories	n=56
Age (years), mean (range)	67.5 (38-94)
Sex (male/female), n (%)	39 (70%)/17 (30%)
Etiology, n (%) (HCV/HBV/Alcohol/MASH/AIH/Others)	7 (13%)/4 (7%)/16 (28%)/10 (18%)/4 (7%)/15 (27%)
Hepatocellular carcinoma, n (%) (yes/no)	35 (63%)/21 (37%)
Presence or absence of CHE, n (%) (yes/no)	24 (43%)/32 (57%)
Neuropsychological test, n (%) (number connection test positive/Stroop test positive/Both positive)	3 (13%)/14 (58%)/7 (29%)

HCV: Hepatitis C virus; HBV: Hepatitis B virus; MASH: metabolic dysfunction-associated steatohepatitis; AIH: autoimmune hepatitis; CHE: covert hepatic encephalopathy.

Table II. *Analysis of SF36 and blood collection data according to the presence or absence of CHE.*

Factor	CHE negative (n=32)	CHE positive (n=24)	*p*-Value*
PF	50.62 [14.53, 57.84]	45.81 [3.70, 57.84]	0.293
RP	49.07 [12.52, 55.72]	30.80 [2.55, 55.72]	0.022
BP	49.21 [30.90, 61.71]	47.42 [22.42, 61.71]	0.389
GH	40.46 [19.14, 69.76]	44.99 [24.47, 65.50]	0.714
RE	47.75 [18.60, 56.07]	39.42 [6.11, 56.07]	0.146
VT	46.62 [33.78, 65.89]	43.41 [17.72, 65.89]	0.107
MH	53.16 [38.40, 65.24]	48.80 [27.67, 62.56]	0.186
SF	50.58 [5.48, 57.02]	47.35 [11.92, 57.02]	0.684
Alb (g/dl)	3.70 [2.40, 4.30]	3.50 [2.20, 4.60]	0.348
NH_3 (μg/dl)	59.00 [29.00, 149.00]	50.50 [32.00, 152.00]	0.601
Zn (μg/dl)	81.00 [44.00, 190.00]	67.00 [42.00, 110.00]	0.016

Data represent median [interquartile range]. PF: Physical function; RP: role physical; BP: bodily pain; GH: general health; RE: role emotion; VT: vitality; MH: mental health; SF: social functioning; CHE: covert hepatic encephalopathy; Alb: albumin. *Mann–Whitney *U*-test.

in 24 cases (43%), including three (13%) of NCT-A abnormalities, 14 (58%) of Stroop abnormalities, and seven (29%) of both (Table I).

Patients with CHE that had both NCT-A and Stroop abnormalities showed significantly lower RP scores [30.80 (2.55-55.72)] than patients without CHE [49.07 (12.52-55.72)] (p=0.022) (Table II). Similarly, zinc levels were significantly lower in CHE patients [67 (42-110)] than without CHE [81 (44-190)] (p=0.016). In patients with CHE with only NCT-A abnormalities, a significant decrease in QOL was observed for GH (p=0.024) and VT (p=0.031) scores (Table III). Patients with CHE with only Stroop test abnormalities showed a tendency toward reduced overall QOL, but this difference was not significant. No significant differences were observed in albumin or NH_3 levels; however, a significant decrease in Zn (p=0.006) was seen in patients with CHE (Table IV). When comparing NCT-A and Stroop double-positive patients with CHE to those without, significant reductions were observed in MH (p=0.015), PF (p=0.019), RP (p=0.033), and VT (p=0.013) (Table V).

Discussion

CHE is often misdiagnosed in clinical practice and has been reported to occur in approximately 30% of patients with cirrhosis (19). In our hospital cohort, 43% of patients were screened for CHE using NPT. QOL assessments differed depending on the NPT content. When grouped by CHE status, analysis of all 56 patients revealed significant differences in the SF-36 Daily Role Functioning subscale and blood Zn levels. Analysis of patients with CHE with

Table III. *Analysis of SF36 and blood collection data of cirrhotic patients according to the positive or negative in the Number Connection Test-A (NCT-A).*

Factor	NCT-A negative (n=32)	NCT-A positive (n=3)	*p*-Value*
PF	50.62 [14.53, 57.84]	41.60 [28.96, 54.23]	0.542
RP	49.07 [12.52, 55.72]	22.49 [19.17, 42.43]	0.061
BP	49.21 [30.90, 61.71]	45.64 [22.42, 61.71]	0.676
GH	40.46 [19.14, 69.76]	29.80 [25.54, 32.46]	0.024
RE	47.75 [18.60, 56.07]	22.76 [18.60, 56.07]	0.225
VT	46.62 [33.78, 65.89]	36.99 [30.56, 40.20]	0.031
MH	53.16 [38.40, 65.24]	51.82 [41.09, 59.87]	0.941
SF	50.58 [5.48, 57.02]	44.13 [37.69, 44.13]	0.405
Alb (g/dl)	3.70 [2.40, 4.30]	2.90 [2.30, 3.80]	0.147
NH_3 (µg/dl)	59.00 [29.00, 149.00]	63.00 [49.00, 104.00]	0.485
Zn (µg/dl)	81.00 [44.00, 190.00]	71.00 [61.00, 82.00]	0.316

Data represent median [interquartile range]. PF: Physical function; RP: role physical; BP: bodily pain; GH: general health; RE: role emotion; VT: vitality; MH: mental health; SF: social functioning; CHE: covert hepatic encephalopathy; Alb: albumin. *Mann–Whitney *U*-test.

Table IV. *Analysis of SF36 and blood collection data of cirrhotic patients according to the positive or negative in the Stroop test.*

Factor	Stroop negative (n=32)	Stroop positive (n=12)	*p*-Value*
PF	50.62 [14.53, 57.84]	48.82 [3.70, 57.84]	0.824
RP	49.07 [12.52, 55.72]	44.09 [2.55, 55.72]	0.241
BP	49.21 [30.90, 61.71]	49.66 [26.89, 61.71]	0.792
GH	40.46 [19.14, 69.76]	45.78 [24.47, 65.50]	0.416
RE	47.75 [18.60, 56.07]	45.66 [6.11, 56.07]	0.411
VT	46.62 [33.78, 65.89]	47.16 [17.72, 65.89]	0.867
MH	53.16 [38.40, 65.24]	50.48 [35.72, 62.56]	0.746
SF	50.58 [5.48, 57.02]	50.58 [11.92, 57.02]	0.913
Alb (g/dl)	3.70 [2.40, 4.30]	3.60 [2.20, 4.60]	0.811
NH_3 (µg/dl)	59.00 [29.00, 149.00]	52.50 [32.00, 72.00]	0.481
Zn (µg/dl)	81.00 [44.00, 190.00]	66.00 [42.00, 109.00]	0.006

Data represent median [interquartile range]. PF: Physical function; RP: role physical; BP: bodily pain; GH: general health; RE: role emotion; VT: Vitality; MH: mental health; SF: social functioning; CHE: covert hepatic encephalopathy; Alb: albumin. *Mann–Whitney *U*-test.

Table V. *Analysis of SF36 and blood collection data of cirrhotic patients according to both Number Connection Test-A (NCT-A) and the Stroop test positive or both negative.*

Factor	Both negative (n=32)	NCT-A & Stroop both positive (n=7)	*p*-Value*
PF	50.62 [14.53, 57.84]	32.57 [18.13, 57.84]	0.019
RP	49.07 [12.52, 55.72]	29.14 [12.52, 55.72]	0.033
BP	49.21 [30.90, 61.71]	35.37 [26.44, 61.71]	0.215
GH	40.46 [19.14, 69.76]	44.19 [29.80, 46.85]	0.508
RE	47.75 [18.60, 56.07]	39.42 [6.11, 56.07]	0.229
VT	46.62 [33.78, 65.89]	34.85 [27.35, 62.68]	0.013
MH	53.16 [38.40, 65.24]	38.40 [27.67, 59.87]	0.015
SF	50.58 [5.48, 57.02]	50.58 [18.37, 57.02]	0.832
Alb (g/dl)	3.70 [2.40, 4.30]	3.50 [2.70, 4.20]	0.419
NH_3 (µg/dl)	59.00 [29.00, 149.00]	50.00 [40.00, 152.00]	0.585
Zn (µg/dl)	81.00 [44.00, 190.00]	70.00 [44.00, 110.00]	0.585

Data represent median [interquartile range]. PF: Physical function; RP: role physical; BP: bodily pain; GH: general health; RE: role emotion; VT: vitality; MH: mental health; SF: social functioning; CHE: covert hepatic encephalopathy; Alb: albumin. *Mann–Whitney *U*-test.

NCT-A abnormalities revealed significant differences in GH and VT scores. Analysis of patients with CHE with Stroop test abnormalities showed a significant difference in Zn levels; however, unlike the NCT-A group, no significant differences were observed in any SF-36 QOL subscales. Patients with CHE with both NCT-A and Stroop test abnormalities showed significant differences in SF-36 MH, PF, RP, and VT scores.

The NPT is a gold-standard computerized test battery for diagnosing CHE in Japan that shows promise in predicting clinical outcomes; however, its widespread adoption is limited because it requires over 20 min to conduct. The Stroop Test is a point-of-care screening tool that offers promising accuracy in identifying CHE and predicting clinical outcomes (10, 14, 20-21). This study identified the Stroop Test as the most commonly used CHE screening tool in the Japanese population, which may have reflected its shorter administration time and recent efforts to validate its effectiveness in diagnosing CHE and predicting clinical outcomes in this population (22, 23).

Early detection and intervention are crucial for CHE in any screening, because it can impair driving ability, increase fall risk, and negatively impact QOL and prognosis. Additionally, as CHE reportedly progresses to OHE at a consistent rate, prompt treatment is essential. Although not all CHE cases are recommended for treatment according to the clinical practice guidelines of the Japan and American Association for the Study of Liver Diseases or the European Association for the Study of the Liver, additional treatment is proposed for high-risk patients, such as those with worsening underlying liver disease. A high conversion rate from MHE to OHE has been reported in patients with Zn deficiency, elevated ammonia levels, high serum creatinine levels, and low platelet counts (8). Our study confirmed that hypozincemia was a risk factor for CHE. Neuropsychological testing should be actively performed in at-risk patients to assess the presence of CHE in this population, and additional treatments should be considered for positive diagnoses. CHE should be evaluated using NPT to improve QOL, and Zn supplementation should be considered in cases of hypozincemia.

Conclusion

In patients with CHE, QOL was reduced or showed a downward trend in terms of RP, MH, RE, and VT scores. Because CHE negatively affects driving ability, fall risk, QOL, and prognosis, early detection and intervention using NPT are crucial. Patients with CHE also exhibited low Zn levels, warranting future investigations to determine whether early Zn supplementation can improve CHE and enhance QOL.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Conceptualization: Toru Ishikawa; Data Curation: Toru Ishikawa; Formal Analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Riho Ito, Narumi Arita, Yusuke Matsuhashi, and Terasu Honma; Methodology: Toru Ishikawa; Project Administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa; Visualization: Toru Ishikawa; Writing – Original Draft: Toru Ishikawa; Writing – Review & Editing: Toru Ishikawa, Riho Ito, Narumi Arita, Yusuke Matsuhashi, and Terasu Honma.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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