Hepatic Encephalopathy Is Reversible in the Long Term After Liver Transplantation

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Cognitive dysfunction caused by hepatic encephalopathy (HE) improves within the first year after liver transplantation (LT). However, cognitive restitution seems to be incomplete in a subset of patients and after LT a new-onset cognitive decline was described. Data about the longterm development of cognitive function after liver transplantation (LT) are sparse. This prospective study analyzed whether a history of hepatic encephalopathy (HE) before LT had an impact on the longterm outcome of cognitive function after LT and if patients who underwent LT 5 years earlier showed worse cognitive function than healthy controls. The cognitive function of 34 patients was assessed before LT and at 1 year and 5 years after LT by psychometric tests, including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the portosystemic encephalopathy syndrome test, which provides the psychometric hepatic encephalopathy score (PHES). Furthermore, patients completed surveys to assess health-related quality of life (HRQOL). An 22 additional patients were included after LT. Patients were subdivided by having a history of HE before LT. The control group consisted of 55 healthy patients adjusted for age and education. Before LT, patients performed significantly worse than controls in the psychometric tests: RBANS Total Scale (TS), mean ± standard deviation (SD), 92.6 ± 13.3 versus 99.9 ± 12.0, P = 0.01; and PHES, median (interquartile range [IQR]), 0 (−3 to 1) versus 1 (0−2), P < 0.001. At 1 year after LT, patients with a history of HE still showed cognitive impairment compared with controls: RBANS TS, mean ± SD, 89.8 ± 15.1 versus 99.9 ± 12.0, P < 0.01; and PHES, median (IQR), 0 (−2 to 1.25) versus 1 (0−2), P = 0.03. At 5 years after LT, patients with and without a history of HE showed normal cognitive function and improved HRQOL. In conclusion, HE-associated cognitive impairment seems to be reversible within 5 years after LT.

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Up to 50% of the patients undergoing liver transplantation (LT) for chronic liver disease (CLD) suffer from hepatic encephalopathy (HE) at transplantation and between 35% and 45% of the patients have a history of HE episodes.(1) Cognitive function and health-related quality of life (HRQOL) were shown to improve within the first year after LT.(2,3) However, recovery seemed to be incomplete in some patients, particularly in those with a history of HE.(1,4–7) Furthermore, a new-onset cognitive decline within the first year after LT was detected in patients without a history of HE.(8) In addition, cognitive impairment and alterations of brain structure have been observed in patients 7–10 years after LT.(9–11) Possible underlying mechanisms might be residual HE-associated structural brain alterations,(7) alterations of brain structure and metabolism accompanying the surgical procedure, or posttransplant medication.(11)

This prospective, single-center, observational study assessed the longterm development of cognitive

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; CFF, critical flicker frequency; CKD, chronic kidney disease; CLD, chronic liver disease; CNI, calcineurin inhibitor; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRQOL, health-related quality of life; ICT, inhibitory control test; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MHE, minimal hepatic encephalopathy; NHE, no hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; PSC, primary sclerosing cholangitis; PSE, portosystemic encephalopathy; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard
function and HRQOL in patients after LT to analyze whether HE-associated cognitive dysfunction is reversible in the long term after LT and if the new-onset cognitive impairment observed 1 year after LT remains or progresses in the long term after LT.

Patients and Methods

All patients received a neurological examination by an experienced neurologist to assess the presence of neurological symptoms or neurological diseases. The variables of age at LT, sex, years of education, underlying liver disease, immunosuppressive therapy, chronic kidney disease (CKD) grade defined by glomerular filtration rate, diabetes mellitus, laboratory Model for End-Stage Liver Disease (MELD) score, and/or match MELD score (considers severe comorbidities and consequently results in higher MELD scores) were collected from anamnesis and case records. Overt hepatic encephalopathy (OHE), according to the West Haven criteria, was assessed from case records or by third-party interviews in those patients who were included after LT (Table 1). Diagnosis of minimal hepatic encephalopathy (MHE) was made as further described below. All patients gave written informed consent. The study was approved by the institutional review board and conducted according to the ethical guidelines described in the Declaration of Helsinki of 1975 (revised in 2008). No organs from executed prisoners were used.

PSYCHOMETRIC TEST BATTERY

The psychometric test battery applied before and/or after LT comprised the portosystemic encephalopathy (PSE) syndrome test, which provides the psychometric hepatic encephalopathy score (PHES), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the inhibitory control test (ICT; represented as correct target responses), and the critical flicker frequency (CFF) to assess cognitive function and evaluate the presence of MHE. The PSE syndrome test is a paper-pencil–based test comprising the number connection tests A and B, digit symbol test, serial dotting test, and line tracing test. It evaluates attention, concentration, and psychomotor ability. The PHES predicts the development of OHE and improves with HE treatment. The RBANS is a paper-pencil test that includes 12 subtests to assess attention, language, visuospatial/constructional ability, immediate memory, and delayed memory. It was designed for the detection of dementia but is also employed to diagnose cognitive impairment in various diseases. The ICT is a computer-based test assessing attention and deficits in response inhibition. The subject has to respond to the alternating letters X and Y (targets) and to inhibit a response to the nonalternating presentation of the letters X and Y (lures). The CFF is measured by using the Hepatonorm Analyzer (R&R Medi-Business Freiburg, Freiburg, Germany). It presents a red light to the subject. The frequency of the light reduces slowly, and the subject has to press a button when the light flickers. These psychometric tests each take approximately 30 minutes to be performed and assessed. They are made to be easily applied in the clinic and, thus, are recommended to screen for and diagnose MHE before LT as well as cognitive impairment after LT.

Parallel versions of the PSE syndrome test and RBANS were applied to prevent learning effects. The patients were diagnosed with MHE before LT if at least 1 of the test results exceeded the cutoff value by each test: PHES <=4, RBANS Total Scale [TS] <80, ICT <87.5% correct targets, and CFF < mean – 2 standard deviations (SDs) of age-adjusted norm.
Furthermore, the results of the patients were compared with the healthy control group. Not all tests were completed by every patient at each visit for several reasons. No psychometric data were available before transplantation (T1) for those 22 patients who were included after LT. One patient refused to participate in the RBANS after LT. The CFF was not completed by 3 patients after LT because of technical problems (n = 1) or because they did not achieve stable test results in the test run (n = 2). ICT results are missing in 4 patients after LT because 2 patients did not understand the task and 2 patients refused to complete the test. In the subgroup of patients who were included before LT (n = 34), the CFF (n = 4), the ICT (n = 8), and the RBANS (n = 5) were not completed before LT for similar reasons.
SELF-REPORTING QUESTIONNAIRES

All patients were asked to complete the following self-reporting questionnaires: Hospital Anxiety and Depression Scale–Anxiety (HADS-A) and Hospital Anxiety and Depression Scale–Depression (HADS-D), Beck Depression Inventory, Fatigue Impact Scale, and Short Form 36 (SF-36) to assess HRQOL. The results from before to after LT were compared. Data are missing in some cases because patients were included after LT, test evaluation was impossible, or the patient refused to complete the questionnaires.

STATISTICAL METHODS

The normal distribution of data was analyzed with Kolmogorov-Smirnov test. Continuous variables are expressed as median (interquartile range [IQR]) for abnormally distributed variables or means with SDs for normally distributed variables. Group differences were assessed by Kruskal-Wallis test (abnormally distributed data) or analysis of variance (normally distributed data). If the overall comparison of the groups was significant, Mann-Whitney rank sum test or post hoc analysis with Bonferroni correction was performed. Paired follow-up data within the patient group were evaluated by paired sample t test or Wilcoxon matched pairs test. Linear mixed modeling was performed using the unstructured repeated covariance type to test for an overall difference at the 3 assessment times. The assessment time (T1 to 5 years after transplantation [T3]) was specified as repeated measures. The model comprised the respective psychometric test results as dependent variables, the assessment time (T1-T3) as fixed effect, and used the maximum likelihood estimation. Categorical variables were tested with a chi-square test and are displayed as numbers with percentage. Binary logistic regression and multiple linear regression analyses were applied to identify predictive factors for cognitive function. P values <0.05 were considered significant. Statistical analysis was performed using SPSS, version 24 (IBM, Armonk, NY).

Results

PATIENTS

The participants considered for this analysis took part in a prospective longterm follow-up study of post-LT patients at Hannover Medical School, Hannover, Germany, between September 2008 and November 2017. Patients were recruited following the procedure as previously described. To summarize, patients on the LT waiting list aged ≥18 years were asked to participate in the study at the occasion of a follow-up visit in the liver transplant outpatient clinic. Patients who had not been met before LT were asked to participate within 7 days after LT. Exclusion criteria were neurological or psychiatric diseases other than HE, a regular intake of drugs affecting brain function, CKD, grade >4 defined by glomerular filtration rate (in mL/minute), liver retransplantation more than 3 months after first LT, additional transplantation of another organ, non-German native language, and patient refusal.

In total, 217 patients were recruited while wait-listed for LT at our outpatient transplantation clinic between September 2008 and October 2013. Additionally, 69 patients were included directly after LT; 11 of those patients underwent LT for acute liver failure (ALF). Up to December 2013, 98 (45%) of the recruited patients on the waiting list for LT had received LT. Thus, data of 167 patients were available for follow-up on principle, but 41 (24%) patients died before the 5-year follow-up visit. Cause of death was multiorgan failure in 10 cases, infection/sepsis in 13 cases, heart failure in 4 cases, internal bleeding in 4 cases, malignancy in 3 cases, and unknown in 7 cases. Furthermore, 59 (35%) patients were lost to follow-up or excluded from further analysis due to exclusion criteria. The 11 patients with ALF were analyzed separately (Supporting Table 1).

Finally, 56 patients (age, 49.1 ± 11.2 years, 64% male) were included in the present analysis (Fig. 1). Of these, 34 (61%; age 49.6 ± 10.7 years, 65% male) had been recruited before LT. Until receiving LT, the waitlisted patients were examined every 6 months, and the data obtained at the last visit at T1 were considered for the present analysis (n = 34; 3.4 ± 3.1 months before LT). Follow-up examinations after LT were completed at 8.8 ± 3.6 months (9 months after transplantation [T2]; n = 56) and 61.3 ± 12.1 months (T3, n = 56). At T3, the immunosuppressive therapy regimen consisted of tacrolimus combined with mycophenolate mofetil and/or prednisolone (n = 38); cyclosporin combined with mycophenolate mofetil and/or prednisolone (n = 16); or everolimus combined with mycophenolate mofetil and prednisolone (n = 2). The patients were subdivided according to a history of HE before LT (n = 26 with HE and n = 30 with no hepatic encephalopathy [NHE]). A total of 55 healthy patients adjusted for age, sex, and education served as a control group at T1 and T2, and 46 patients from this control group served as age-readjusted controls at T3 (Table 1).
CHARACTERISTICS

Patients and healthy controls did not differ concerning age or years of education (Table 1). The age-adjusted healthy control group for T3 contained significantly more women ($P = 0.02$). Patients with and without a history of HE (age, $48.5 \pm 10.1$ versus $49.7 \pm 12.2$ years; male/female, $17/9$ versus $19/11$; education, median [IQR] $10$ [3] versus $10$ [3] years) did not differ. None of the patients showed signs of a neurological disorder other than HE, and $26$ (46%) of the included $56$ patients had a history of HE before LT. Of the $34$ patients tested before LT, $13$ were diagnosed with HE (MHE as diagnosed at T1, $n = 9$; reported OHE episodes until T1, $n = 4$). The laboratory MELD score before LT was significantly higher in patients with HE than in the NHE patient group ($21.9 \pm 7.4$ versus $13.7 \pm 7.4$; $P < 0.001$; $n = 56$). Compared with patients with CLD, the patient group with ALF contained significantly more women ($9$ of $11$ [82%] versus $20$ of $56$ [36%]), whereas age and years of education did not differ.

FOLLOW-UP OF PSYCHOMETRIC TEST RESULTS FROM T1 TO T3

Before LT, the patients ($n = 34$) performed worse in the PSE syndrome test ($P < 0.001$), the CFF ($P = 0.001$), and the ICT targets ($P = 0.01$) compared with healthy controls. Furthermore, the patients achieved lower
attention ($P < 0.01$) and lower immediate memory scores ($P = 0.02$) than the healthy controls, leading to a reduced RBANS TS ($P = 0.01$). At 5 years after LT, no significant differences in the test results of patients and controls were present (Fig. 2).

Linear mixed modeling, including the 34 patients, showed a significant effect of the assessment time (T1-T3) on PHES ($P < 0.01$), RBANS TS ($P < 0.001$), RBANS sum score ($P < 0.001$), RBANS attention score ($P = 0.01$), RBANS delayed memory ($P < 0.001$), RBANS visuospatial/constructional ability ($P < 0.04$), and RBANS immediate memory ($P < 0.03$). The assessment time showed no overall significant effect for the RBANS language score ($P = 0.23$), CFF ($P = 0.05$), and ICT targets ($P = 0.15$). Paired analysis of the data showed an overall improvement in the psychometric test results especially in the long term except for the visuospatial/constructional and language subdomains of the RBANS, which both had also not differed from controls before LT (Fig. 2). Notably, however, the RBANS visuospatial/constructional score increased from 87 before LT to 96 at 5 years after LT, although the language score decreased from 104 to 99. The level of significance was probably missed due to a significant variability of the respective test results.

Lower performance in the psychometric tests applied indicates reduced attention, concentration, and impaired memory as well as impaired visual-motor skill. From a clinical point of view, for example, impairment in these cognitive domains may appear as reduced ability to take part and follow a conversation or to complete tasks involving fine motor skills.

**FOLLOW-UP OF PSYCHOMETRIC TEST RESULTS FROM T1 TO T3 SUBDIVIDED BY HE HISTORY**

After the patients were subdivided according to their HE history ($n = 34$), a paired analysis investigated the general longterm improvement for both patient groups,

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**FIG. 2.** Psychometric test results of the 34 patients followed up from T1 to T3 compared with the results of adjusted groups of healthy controls before LT and in the long term after LT. This figure illustrates the results of the PSE syndrome test, RBANS, ICT, and CFF of the patients at T1, T2, and T3 compared with age-adjusted healthy controls. Furthermore, paired analysis was performed to compare the results of the patient group at T1 with T3. $P$ value $\leq 0.05$ was considered significant. *$P < 0.05$.
particularly regarding the RBANS results. The analysis also demonstrated a notable decrease in the RBANS language domain score at T2 in both patient groups (Table 2). An additional decrease in the visuospatial/constructional domain and TS was only seen in the patient group without former HE (Fig. 3). The median of the groups is still within the normal range, and thus, a clinical impact was not detected in the majority of patients. However, 7 patients (n = 2 with HE history) had a pathological score in visuospatial/constructional ability, and 4 patients (all with HE history) had a pathological score in the RBANS subdomain language 1 year after transplantation. In these patients, the decrease of speech fluency and performance in visual-motor tasks became clinically apparent.

Before LT, HE patients showed significantly worse results than healthy controls (P < 0.001) and NHE patients (P < 0.05) in all tests applied (PHES, RBANS TS and sum score, CFF, and ICT targets). At T3, no group differences were detectable, neither between the patient groups nor between patients and controls (Supporting Table 2).

Additionally, 5 (15%) patients with an abnormal PHES at T1 were compared with patients with normal PHES at T1 (n = 29) and to healthy controls in the follow-up examinations at T2 and T3. Patients with an abnormal PHES before LT showed a significantly lower RBANS TS than healthy controls after transplantation at T2 (83.8 ± 20.2 versus 99.9 ± 12.0; P = 0.03). All other test results at T2 and all tests performed at T3 showed no significant group differences. In comparison to patients who had HE before LT, the patients with an abnormal PHES at T1 showed better results at T2.

### Table 2. Paired Analysis of Results for T1, T2, and T3 Subdivided by Patients’ HE History

| Test            | T1               | T2               | T3               | PValue |
|-----------------|------------------|------------------|------------------|--------|
| **HE**          |                  |                  |                  |        |
| PHES (n = 13)   | -3 (-7 to -1.5)  | 0 (-1.5 to 2)    | 0 (-1.5 to 2.5)  | T1 versus T3: 0.01 |
| TS (n = 11)     | 85.7 ± 12.6      | 91.8 ± 17.8      | 97.8 ± 10.9      | T1 versus T3: 0.01 |
| Sum score (n = 11) | 445.7 ± 49.1  | 479.2 ± 54.1     | 494.1 ± 41.6     | T1 versus T2: 0.03  
| Attention (n = 11) | 85 (64-94)    | 85 (82-106)      | 91 (88-106)      | T1 versus T3: 0.04  |
| Delayed memory (n = 11) | 88 (83-99)  | 99 (94-108)      | 105 (94-108)     | 0.07* |
| Visuospatial/constructional (n = 11) | 84 (75-92)  | 87 (81-102)      | 87 (81-116)      | 0.11* |
| Immediate memory (n = 11) | 94 (83-109)  | 97 (83-109)      | 97 (90-114)      | 0.12* |
| Language (n = 11) | 104 (84-112) | 94 (79-105)      | 99 (88-110)      | 0.60* |
| CFF (n = 11)    | 40 (37.4-41.7)  | 41.2 (40.8-43)   | 42.9 (39.3-43.5) | 0.06* |
| ICT targets, % (n = 12) | 94 (90.5-95.8) | 97 (96-98)       | 98 (95-100)      | T1 versus T3: <0.001 |
| **NHE**         |                  |                  |                  |        |
| PHES (n = 21)   | 0 (-0.5 to 1)    | 1 (0-2.5)        | 2 (0.5-2.5)      | 0.07* |
| TS (n = 18)     | 97.2 ± 11.9      | 95.4 ± 11.8      | 102.5 ± 13.5     | T1 versus T3: <0.01 |
| Sum score (n = 18) | 491.4 ± 42.7 | 485.3 ± 42.2     | 510 ± 49.0       | T1 versus T3: <0.01 |
| Attention (n = 18) | 98.5 (88-109)  | 101.5 (85-115)   | 104.5 (90.3-119.8) | 0.43* |
| Delayed memory (n = 18) | 97.5 (94-100.3) | 98.5 (96.5-103.8) | 101.5 (98-111.3) | T1 versus T3: 0.02 |
| Visuospatial/constructional (n = 18) | 90.5 (84-106) | 87 (81-102)      | 103.5 (84-113)   | 0.22* |
| Immediate memory (n = 18) | 100 (86-105) | 100 (82.5-113.3) | 109 (93-114)     | 0.13* |
| Language (n = 18) | 105 (98.5-109.5) | 97.5 (93.5-108) | 100.5 (95.5-114.8) | 0.52* |
| CFF (n = 19)    | 42.5 (41.5-43.9) | 42.4 (41.3-46.2) | 45.2 (42.4-46.7) | 0.34* |
| ICT targets, % (n = 14) | 98 (97-99)    | 99 (96-100)      | 99 (97-100)      | 0.34* |

**NOTE:** Data are given as median (IQR) or mean ± SD.

*Overall between groups. P value ≤0.05 was considered significant.
FOLLOW-UP FROM T2 TO T3

Paired analysis of all patient results (n = 56) from T2 to T3 (now also including patients who had not been examined before LT) showed a significant improvement in the PHES and RBANS (data not shown). Both patients with and without a history of HE before LT showed a significant improvement in the RBANS from T2 to T3 (Figs. 4).

Regarding group comparison, patients without former HE had reached the score levels of healthy controls approximately 1 year after LT. The HE group performed worse than the healthy controls in most tests at T2 but finally achieved similar results at T3 (Table 3).

REGRESSION ANALYSIS

A binary logistic regression analysis using the RBANS percentile below 25 as the dependent variable and a multiple linear regression analysis using the RBANS TS at T3 as the dependent variable were performed. The independent variables history of HE, age, diabetes mellitus, CKD, and steroid medication at T3 were not predictors for the outcome of cognitive function at 5 years after LT.

SELF-REPORTING QUESTIONNAIRES

Patients showed a significant improvement of mood and HRQOL from T1 until T3 as represented by HADS-A (P = 0.05), HADS-D (P = 0.01), and SF-36 physical and mental sum scores (P < 0.01; Supporting Table 3).

Discussion

Patients with both MHE and OHE have lower HRQOL and show cognitive deficits especially regarding attention, visuospatial construction, psychomotor speed, and motor accuracy.\(^{(22,23)}\) Using cerebral magnetic resonance imaging and spectroscopy, alterations of brain structure, such as increased ventricle volume,\(^{(10)}\) subtle brain edema, and T2/Flair-hyperintense white
matter lesions as well as alterations of cerebral metabolism, were detected in patients with liver cirrhosis and HE.\textsuperscript{(24-26)} After LT, these changes seem to recover as studies showed a significant improvement in cognitive function and HRQOL, a decrease in the volume of T2-weighted white matter lesions, and a normalization of brain metabolites in magnetic resonance spectroscopy studies.\textsuperscript{(27-30)} Concerning the longterm outcomes of cognitive function after LT, data are sparse. The studies available showed either cognitive impairment especially concerning visuospatial and constructional function or a good overall outcome even with remaining structural brain alterations, such as brain atrophy and white matter lesions, in patients after LT.

Campagna et al. described a cognitive improvement within the first year after LT particularly for patients with a history of HE. However, the patients’ cognitive function remained slightly worse compared with patients without a history of HE until 12 months after LT.\textsuperscript{(1)} In a previous study, we showed that patients with a history of HE had remaining impairments of cognitive function 1 year after LT although they had improved compared with their performance before LT. Furthermore, patients without a history of HE before LT showed a significant decline in cognitive function in the first year after LT.\textsuperscript{(8)} This new-onset cognitive decline had different features from HE, indicating that other factors besides HE might as well cause cognitive impairment in patients after LT. We therefore applied 3 psychometric tests to assess different domains of cognitive function.

Before LT and in the first follow-up examination approximately 9 months after LT, our patients showed significantly worse results in the psychometric assessments compared with healthy controls. Approximately 5 years after LT, the patients showed a notable improvement in cognitive function, even those with a former history of HE, and did not significantly differ from healthy controls. The HRQOL of the patients had also significantly increased in the long term after LT.

Surprisingly, patients who were included before LT and had no previous HE history showed a slight decrease in the language score and the visuospatial/constructional score of the RBANS in the first follow-up examination after LT, but probably due to patient numbers, the level of significance was missed. Nevertheless, it might be an indicator of the previously described new-onset cognitive dysfunction after LT.\textsuperscript{(8)}

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**FIG. 4.** Development of the RBANS results after LT in patients with and without a history of HE. This figure illustrates the change of the different RBANS subdomains from T2 to T3 in (A) 25 patients with a history of HE and (B) 30 patients without a history of HE. For visual comparison, results of the 46 age-readjusted healthy controls at T3 were added. Statistical analysis was done with the Wilcoxon matched pairs test to compare the RBANS subdomains attention, delayed and immediate memory, visuospatial/constructional ability, and language. For the RBANS TS, a paired sample t test was used. *P value <0.05 was considered significant.
TABLE 3. Psychometric Test Results of All Patients Subdivided by HE History Compared With Adjusted Healthy Controls at T2 and T3

|                  | HE (n = 26) | NHE (n = 30) | Healthy Controls (n = 55) | P Value |
|------------------|------------|--------------|--------------------------|---------|
| T2               |            |              |                          |         |
| PHES             | 0 (−2 to 1.25) | 0.5 (−1 to 2) | 1 (0.2) | HE versus controls: 0.03 |
| RBANS            |            |              |                          |         |
| TS               | 89.8 ± 15.1 | 94.4 ± 12.5  | 99.9 ± 12.0              | HE versus controls: <0.01 |
| Sum score        | 460.0 ± 52.9 | 480.8 ± 45.9 | 500.0 ± 39.9            | HE versus controls: <0.01 |
| Attention        | 91 (79-103) | 98.5 (86-106.8) | 103 (94-112)       | HE versus controls: <0.01 |
| Delayed memory   | 95.5 (91-103.5) | 97.5 (94.8-102) | 99 (94-106) | 0.45* |
| Visuospatial/constructive | 85.5 (81-102) | 85.5 (77.3-102) | 89 (81-105) | 0.66* |
| Immediate memory | 92 (82.5-101.5) | 95.5 (86-109.8) | 106 (94-112) | HE versus controls: 0.001 |
| Language         | 98 (84.75-111) | 99 (93.5-110.5) | 101 (96-106) | 0.44* |
| CFF              | 41.3 (38.7-43.8) (n = 24) | 42.4 (41.3-46.2) (n = 29) | 44.4 (41.8-46.9) | HE versus controls: <0.01 |
| ICT targets, %   | 97 (96-98) (n = 24) | 97 (96-99) (n = 28) | 98.6 (96.7-99.5) | 0.06* |
| T3‡              |            |              |                          |         |
| PHES‡            | 1 (−0.25 to 2.25) | 1 (0-2.5) | 2 (0-3) | 0.45* |
| RBANS‡           |            |              |                          |         |
| TS               | 98.6 ± 11.9 | 101.1 ± 15.6 | 100.5 ± 12.5            | 0.78* |
| Sum score        | 496.6 ± 43.1 | 504.1 ± 57.2 | 502.4 ± 41.2            | 0.83* |
| Attention        | 97 (88-110.5) | 103 (88-115) | 103 (94-112)           | 0.48* |
| Delayed memory   | 102 (95-107.5) | 100.5 (96.5-110.5) | 100.5 (94.5-100.5) | 0.61* |
| Visuospatial/constructive | 92 (81-107) | 100 (84-112) | 89 (81-109) | 0.28* |
| Immediate memory | 100 (99-112) | 106 (90-114) | 106 (94-112)           | 0.73* |
| Language         | 100 (93-110.5) | 98 (85-114) | 101.5 (95.5-108) | 0.74* |
| CFF‡             | 42.5 (46.5-49.0) | 43.9 (40.9-45.5) (n = 29) | 44 (41.7-45.5) | 0.41* |
| ICT targets, %   | 97.5 (94-100) | 99 (97.8-100) (n = 28) | 98 (96.7-99.1) | 0.08* |

NOTE: Data are given as median (IQR) or mean ± SD.
*Overall between groups. P value ≤0.05 was considered significant.
‡For healthy controls: n = 46.
†For HE group: n = 25.

considering as well that a decrease in language function was also observed in the HE group at T2. However, alterations of language are uncharacteristic for HE. However, the decline of the median in both subtests was only mild and can be expected to become clinically apparent only in those few patients with a pathological score.

In contrast to the present study, former studies showed cognitive impairment and structural brain alterations in patients 6-12 years after LT.\cite{9,10,31} This might suggest that cognitive development after LT follows an inverse “U” course in the long term, with an initial improvement and secondary decrease which exceeds the effect of normal aging, and it remains unclear by which factors this development is driven. One factor might be calcineurin inhibitor (CNI) therapy. Neurotoxic adverse effects of CNIs have already been shown for the first weeks after LT.\cite{32,33} and CNI therapy might be involved in the onset of longterm cognitive dysfunction by impairment of the cerebral immune system leading to neurodegeneration,\cite{34} enhancing cerebrovascular risk factors\cite{35} and/or by impairment of the cerebral mitochondrial energy metabolism.\cite{36,37} In a previous study, we showed that CNI therapy was associated with cognitive impairment and structural brain alterations 10 years after LT.\cite{11} The results indicated that, in particular, patients who showed CNI-induced nephrotoxicity early after transplantation had cognitive impairment in the long term, which led to the conclusion that these patients might be vulnerable toward CNI-induced toxicity. Considering these results, we hypothesized that the patients of our present study would show worse psychometric test results than the healthy controls 5 years.
after LT. Interestingly, this hypothesis could not be proven.

The differing results of our 2 studies may be explained by patient selection, which limits the comparability. In the previous study, patients were selected according to their immunosuppressive therapy regimen and applied CNI dose, whereas in this study, the immunosuppressive therapy regimen was not considered as an inclusion criterion. Consequently, in the present study, 96% (n = 54) of the patients were treated with CNI. Of these, 71% (n = 40) received a standard-dose CNI therapy (stable tacrolimus trough levels above 5 μg/L or stable cyclosporin trough levels above 50 μg/L), 25% (n = 14) received a low-dose CNI therapy (stable tacrolimus trough levels below 5 μg/L or stable cyclosporin trough levels below 50 μg/L), and 4% (n = 2) received a CNI-free immunosuppressive therapy regimen at the 5-year follow-up examination. The previously mentioned CNI-related cognitive impairment was described for patients who received a reduced CNI therapy after CNI-related decrease of kidney function and therefore might be particularly susceptible toward CNI-related toxicity. In the present study, the patients receiving a reduced CNI therapy showed lower results in the RBANS T5 compared with controls at T3 (96.1 ± 11.9 versus 100.5 ± 12.5; P = 0.81). However, the difference was not significant probably due to patient numbers. A further reason for the different results might be the difference of the time intervals between LT and follow-up examination. Although the patients in the present study were examined at approximately 9 months and 5 years after LT, the patients in our previous study were examined about 10 years after LT; thus, the longterm neurotoxic effects of CNIs played a more important role than in the present study. In summary, we neither found evidence for an effect of former HE on cognitive function nor an indication of a new-onset cognitive impairment 5 years after LT. However, patients with a reduced CNI therapy regimen who might be especially susceptible toward CNI-induced toxicity were underrepresented in this study.

Interestingly, only patients without a former HE history showed deterioration on the visuospatial/constructional RBANS subdomain after LT. A masking effect, caused by an overall restitution of cognitive function characteristic for HE in the HE group after LT, could have covered the appearance of new cognitive alterations due to adverse effects of surgery or medication. This hypothesis is supported by the observation that both patient groups, both those with and those without HE before LT, showed a decrease in language function approximately 9 months after LT.

A total of 11 patients with ALF were included after LT. They were analyzed separately because CLD and ALF patients might have a different neurological longterm outcome after transplantation due to differing pathomechanisms underlying HE in these 2 conditions. Our data, though based on small numbers, did not show a significant difference between ALF and CLD regarding the recovery from HE after LT (Supporting Table 1). However, the patients transplanted for ALF performed worse than CLD patients regarding visuospatial/constructional function and attention after LT. This observation should be reassessed in a larger group of patients with ALF.

Some limitations apply to our study. First, this is a single-center study, which might limit the transferability to other centers. Second, there were only 34 of the 217 initially included patients from the transplant waiting list available for the 5-year follow-up. Furthermore, 22 (39%) of the considered 56 patients were included after LT, and thus, no psychometric data from before LT were available. In these patients, the distribution into the HE or NHE patient group relied on case records. Subsequently, some of these patients classified as NHE might be wrongly allocated due to missing documentation of HE or MHE before LT. Interestingly, the patients included before LT (n = 34) had a low mean laboratory MELD score at LT, indicating that these patients might have been healthier than the rest of the patient group. Another aspect is the differing combination of immunosuppressive drugs in our patients, which might affect cognitive function on its own. Furthermore, a selection bias might have influenced the results because severely disadvantaged or very healthy patients might have been lost for follow-up 5 years after LT. Lastly, the included patients had different underlying liver diseases.

In conclusion, we state that a history of HE before LT has no impact on the longterm cognitive outcome after transplantation and support the hypothesis that HE-associated cognitive impairment at T1 is reversible in the long term after LT. Furthermore, we found no indication for the persistence of a new-onset cognitive dysfunction 5 years after LT.

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