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Validation of the simplified Animal Naming Test as primary screening tool for the diagnosis of covert hepatic encephalopathy

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ABSTRACT

Background: Diagnosis of covert hepatic encephalopathy (CHE) is time consuming in clinical practice. Recently, a new diagnostic tool - the simplified Animal Naming Test (S-ANT1) - was presented with promising results in an Italian cohort. The aim of the present study was to validate S-ANT1 in a cohort of cirrhotic patients from a German tertiary referral centre.

Methods: 143 cirrhotic patients and 37 healthy controls were enrolled. Hepatic encephalopathy (HE) grade 1 (HE1) was clinically diagnosed according to the West-Haven Criteria. Critical flicker frequency and Psychometric Hepatic Encephalopathy Score were used to detect minimal HE (MHE). All participants were additionally examined by S-ANT1.

Results: 58 (40.6%) patients presented with CHE (40 MHE, 18 HE1). S-ANT1 was lowest in patients with HE1, followed by patients with MHE, patients without CHE, and healthy controls, respectively (each $p < 0.05$). Naming < 20 animals discriminated best between patients with and without CHE in ROC analysis (with Youden's index). With a cut-off value of ≥23 mentioned animal names further testing for CHE could be avoided in 38.5% of patients with a negative predictive value of 84%.

Conclusions: S-ANT1 may become an important first screening tool for the assessment of CHE in clinical practice.

1. Introduction

Hepatic encephalopathy (HE) is a frequent and devastating complication of end-stage liver disease. Minimal HE (MHE) and HE grade 1 (HE1) are compromised as covert HE (CHE) in the current joint guideline from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [1]. Notably, MHE itself affects up to 80% of cirrhotic patients in the course of their disease [2,3]. MHE is defined as evidence of neurocognitive impairment identified only by neuropsychiatric tests in patients with no obvious clinical sings of HE. In contrast, HE1 is defined by the presence of mild clinical alterations like euphoria, anxiety or a shortened attention span. Although the clinical consequences of CHE like impaired quality of life, increased rates of falls or car accidents or even higher mortality are of utmost importance, CHE is often overlooked or neglected in clinical practice due to only very mild symptoms (HE1) or not performed diagnostics (MHE) [4–7].

The diagnostic gold standard for the detection of MHE is the Psychometric Hepatic Encephalopathy Score (PHES) consisting of the number connection test-A (NCT-A), the number connection test-B (NCT-B), the digit symbol test (DST), the serial dotting test (SDT), and the line tracing test (LTT) [1,8]. Another established tool is the assessment of the Critical Flicker Frequency (CFF) with a specialized device (HEPAtonorm-Analyzer© 2.0) [9]. In recent years, more modern testing strategies like the Stroop EncephalApp or the Inhibitory Control Test (ICT) were evaluated and established [10,11]. Despite the availability of all these different tools, screening for CHE is often neglected in clinical practice. Main reasons may be the time-consuming and/or expensive testing process or the unavailability of required devices, underlining the importance of and the need for a fast, inexpensive and easy to perform primary screening tool for the detection or the exclusion of CHE.

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Recently, Campagna et al. demonstrated that the simplified Animal Naming Test (S-ANT1) may be a fast tool to detect CHE in patients with cirrhosis in clinical practice [12]. The ANT1 itself is a semantic fluency test especially used in psychology [13,14]. Patients are asked to name as many animals as possible in one minute, and using an age and education adjusting procedure, the S-ANT1 was obtained. However, up to now, S-ANT1 is not externally validated. Therefore, the aim of the present study was to validate S-ANT1 in a large cohort of cirrhotic patients from a German tertiary referral centre.

2. Patients and methods

2.1. Patients and participants

203 consecutive cirrhotic patients were screened for this prospective study between March 2017 and January 2018 at the Cirrhosis Centre Mainz (CCM) which takes part of the Department of Internal Medicine I of the University Medical Centre of the Johannes Gutenberg-University in Mainz, Germany. The leading aetiology of underlying liver disease was determined according to clinical, serological and histological findings. Diagnosis of liver cirrhosis was made by histology, typical appearance in ultrasound or radiological imaging, endoscopic features of portal hypertension, and medical history. Blood biochemistry (bilirubin, albumin, INR, sodium, potassium, creatinine, c-reactive protein, white blood cell count, haemoglobin) was performed in all cirrhotic patients. Model of end-stage liver disease (MELD) and Child-Pugh (CP) score were calculated to determine the severity of liver disease. Cirrhotic patients were excluded if they fulfilled one or more of the following criteria: previous episode of overt HE (OHE) during the last six weeks, chronic alcohol consumption during the last three months, any intake of psychotropic drugs or opioids, daltonism, the presence of pre-terminal comorbidities (heart disease NYHA III-IV, chronic obstructive pulmonary disease Gold C and D, renal failure with creatinine > 1,5 mg/dl), the presence of hepatocellular carcinoma (HCC) or other active malignancies, a history of transjugular intrahepatic portosystemic shunt (TIPSS), active infection, neurological comorbidities (i.e. dementia or history of stroke), anamnestic hints of recent trauma, and electrolyte disorders (serum potassium < 3,5 mg/dl or > 5 mg/dl, serum sodium < 130 mg/dl or > 150 mg/dl). Additionally, 37 healthy volunteers were recruited as control group.

2.2. Diagnosis of HE

At first, every patient was examined by an experienced hepatologist to rule out OHE. The presence of HE1 was diagnosed after detailed neurological examination according to the West-Haven criteria [1]. The diagnosis was based on findings like euphoria, anxiety, lack of awareness, impaired performance of addition and/or shortened attention span as recommended in the current joint AASLD/EASL guideline [1]. If patients showed no clinical signs of HE1, portosystemic encephalopathy (PSE) syndrome test that produces the PHES and/or measurement of CFF were performed in all cirrhotic patients. Interpretation of PHES was done as previously described with German norms [8]. All tests were conducted by trained medical staff and performed in a quiet, lighted room between 09.00 a.m. and 04.00 p.m. A score < 4 was considered as pathologically [8]. CFF was measured using the validated HEPAtonorm-Analyzer© 2.0 (nevoLAB GmbH, Maierhöfen, Germany). CFF was conducted by trained medical staff in a quiet, semi darkened room between 09.00 a.m. and 04.00 p.m. Results < 39 Hz were considered as pathologically [9]. After instruction, the patient had a training phase with at least 4 measurements to adapt to the procedure. Finally, 8 measurements were conducted and a mean was calculated.

In addition, every patient was tested with the S-ANT1. Animal Naming Test 1 (ANT1) is a semantic fluency test [12]. Patients are asked to name as many animals as possible in one minute. Repeats and errors were excluded from the calculation. The number of named animals after one minute was the definitive score. To compensate for the influence of age and education on the results in ANT1, we calculated the S-ANT1 which has been described recently [12]. In patients with an educational level < 8 years 3 animals were added and in patients with low education (< 8 years) and high age (> 80 years) 6 animals were added. All procedures were carried out on the same day with the respective patient. S-ANT1 was additionally performed in 37 healthy volunteers (control group).

2.3. Ethics

The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study protocol was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (Nr. 837.232.17 [11066]). Written informed consent was obtained from every participant.

2.4. Statistical analysis

Quantitative data are expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR) when appropriate. Comparisons for quantitative variables were performed using the unpaired *t*-test or the Mann-Whitney *U* test. Categorical variables were given as frequencies and percentages, respectively, and for comparison of two or more patient-groups the chi-square test was applied. All tests were two-tailed and a p-value < 0.05 was considered statistically relevant.

To investigate how S-ANT1 discriminates between patients with CHE and patients without HE, we calculated the area under the curve (AUC) of receiver operating characteristic (ROC) and its respective 95% confidence interval (CI).

Thresholds for S-ANT1 were determined based on two different optimality criteria: First, we determined the cut-off value maximizing the Youden Index (corresponding to an equal weighting of sensitivity and specificity). In order to use S-ANT1 as a primary screening test, we second calculated the best cut-off with double weighting on sensitivity compared to specificity.

Both for the established (Italian study) and our new cut-off values, the discriminative performance is reported in terms of sensitivity, specificity, negative and positive predictive values (NPV and PPV) along with their 95% CI.

Our complete data analysis is exploratory. Hence no adjustments for multiple testing were performed. For all tests we used a 0.05 level to define statistically relevant deviations from the respective null hypotheses. However, due to the large number of tests, p-values should be interpreted with caution and in connection with effect estimates.

Data were analysed using IBM SPSS Statistic Version 23.0 (Armonk, NY: IBM Corp.) and Microsoft Excel 2016 Version 15.11 (Redmond, Washington, USA: Microsoft Corp.).

Datasets generated and analysed during the present study are available from the corresponding author on reasonable request.

3. Results

3.1. Baseline characteristics of the study population

60 out of 203 cirrhotic patients were excluded because they fulfilled one or more of the exclusion criteria (mainly TIPSS, malignancy [HCC] or OHE). Finally, a total of 143 in- and outpatients were prospectively included into the study between March 2017 and January 2018 (baseline characteristics are displayed in Table 1). Almost 60% of the study patients were males with a median age of 60 years (interquartile range [IQR] 53; 67). The most common aetiology of underlying liver disease leading to cirrhosis was chronic alcohol consumption (34.6%), followed by viral hepatitis (21.0%), autoimmune/cholestatic liver diseases (13.3%) and non-alcoholic steatohepatitis (NASH) (12.6%). The

Table 1
Baseline characteristics of 143 cirrhotic patients and 37 healthy controls included into the final analysis.

Variable	Cirrhotic patients	Healthy controls	p-value
Age in years (IQR)	60 (53; 67)	56 (50; 63)	0.063
Male gender	85 (59.4%)	18 (48.6%)	0.237
School education in years (IQR)	10 (9; 12)	10 (10; 12.5)	0.096
Outpatients	95 (66.4%)		
aeTiology of underlying liver disease			
• Chronic alcohol consumption	49 (34.6%)		
• Viral hepatitis	30 (21.0%)		
• Autoimmune/cholestatic liver diseases	19 (13.3%)		
• NAFLD/NASH	18 (12.6%)		
• Unknown	27 (18.9%)		
Child-Pugh-Score (IQR)	6 (5; 7)		
MELD (IQR)	10 (7; 14)		
Ascites at study inclusion	33 (23.1%)		
History of Ascites	73 (51.0%)		
History of OHE	27 (18.9%)		
Abnormal PHES	49 (34.3%)		
Abnormal CFF	28 (19.6%)		
PHES and CFF abnormal	19 (13.3%)		
Mean S-ANT1	20.7 ± 5.5	26.4 ± 5.4	
Patients with CHE	58 (40.6%)		
Patients with MHE	40 (28.0%)		
Patients with HE1	18 (12.6%)		

Data are expressed as means ± standard deviations or as medians with interquartile ranges; MELD, model for end-stage liver disease; CHE, covert hepatic encephalopathy; HE1, hepatic encephalopathy grade 1; MHE, minimal hepatic encephalopathy; PHES, portosystemic hepatic encephalopathy score; CFF, critical flicker frequency.

median school education time was 10 years (IQR 9; 12). Median Child-Pugh (CP) score was 6 points (IQR 5; 7), and median Model of end-stage liver disease (MELD) score was 10 (IQR 7; 14), respectively. More than half of the study population had a history of hepatic decompensation (history of ascites 51.0%, history of OHE 18.9%). At the day of study inclusion, 33 (23.1%) patients presented with ascites. 18 patients were diagnosed with HE1 based on the West Haven criteria and 40 patients were classified as having MHE based on abnormal results in either PHES and/or CFF. Of 58 patients with CHE, 49 (84.5%) showed abnormal results in PHES, 28 (48.3%) in CFF, and 19 (23.8%) in both tests. 85 cirrhotic patients presented without CHE.

3.2. Comparison of S-ANT1 in cirrhotic patients with and without CHE and healthy controls

S-ANT1 differentiated well between cirrhotic patients with and without CHE and healthy controls. Lowest values were measured in patients with HE1, followed by patients with MHE, patients without CHE, and healthy controls, respectively ($p < 0.05$ in each pairwise comparison, Table 2).

Table 2
Comparison of S-ANT1 in cirrhotic patients with HE1, MHE, without CHE and healthy controls.

Variable	HE1	MHE	Without CHE	Healthy controls
S-ANT1	15.2 ± 5.0	18.5 ± 5.0	22.8 ± 4.6	26.4 ± 5.4

Data are expressed as means ± standard deviations; MHE, minimal hepatic encephalopathy; HE1, hepatic encephalopathy grade 1.
MHE vs. without CHE, $p < 0.001$; HE1 vs. without CHE, $p < 0.001$; HE1 vs. MHE, $p = 0.025$; without CHE vs. healthy controls, $p < 0.001$.

Table 3
Diagnostic quality of S-ANT1 for the detection of CHE considering established cut-off values (< 15 and < 10 animals).

Cut-off value	< 15 named animals	< 10 named animals
Sensitivity	31% (20–45)	7% (2–18)
Specificity	98% (91–100)	100% (95–100)
Positive predictive value	90% (67–98)	100% (40–100)
Negative predictive value	68% (58–76)	61% (53–69)
+LR	15.5	–
−LR	0.70	0.93

+LR, positive likelihood ratio; −LR, negative likelihood ratio; in brackets 95% confidence interval.

3.3. Comparison with established cut-offs for S-ANT1

Campagna et al. recommended cut-offs of < 15 and < 10 animals for the detection of mild or severe cognitive impairment [12]. Applying a cut-off value of < 15 named animals in our cohort, sensitivity was 31%, specificity 98%, PPV 90%, and NPV 68%, respectively. Applying a cut-off of < 10 named animals in our cohort, sensitivity was 7%, specificity 100%, positive predictive value (PPV) 100%, and negative predictive value (NPV) 61%, respectively (Table 3).

3.4. Modified S-ANT1 cut-offs for the present cohort

Next, we analysed the diagnostic performance of the S-ANT1 in our patients with CHE. The area under the receiver operating characteristic (ROC) curve was 0.781 (standard error 0.040, 95% confidence interval [CI] 0.703–0.859, $p < 0.001$) (Fig. 1). The ideal cut-off to discriminate CHE from no HE patients was < 20 animals, if sensitivity and specificity are equally weighted. Applying this cut-off, sensitivity was 64%, specificity 78%, PPV 66% and NPV 76%, respectively. The positive and negative likelihood ratio (+L and −L) were 2.91 and 0.46, respectively.

Additional, we identified a cut-off value with focus on sensitivity to use S-ANT1 as a primary screening tool to rule out patients without CHE and avoid further testing for the presence of CHE with specialized tools. Therefore, we calculated the ideal cut-off value with a weighting of 2:1 for sensitivity/specificity. A cut-off value of < 23 named animals

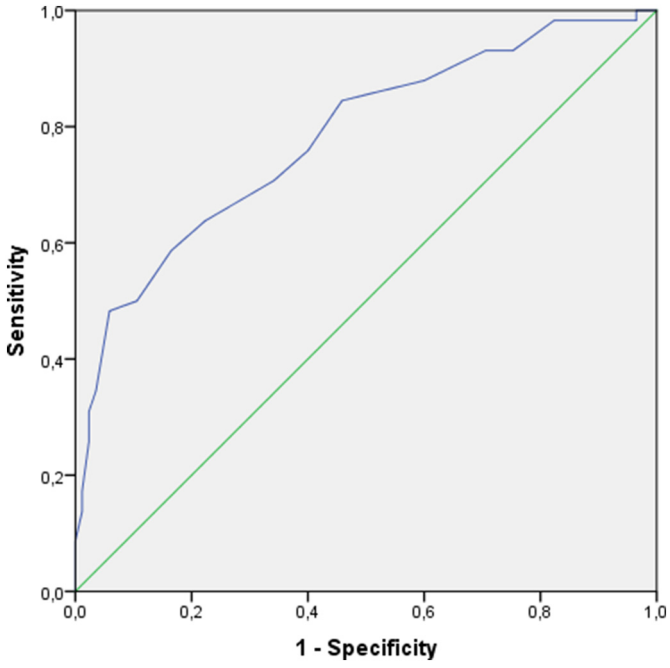

Fig. 1. ROC curve for S-ANT1 in cirrhotic patients with and without CHE.

Table 4
Diagnostic quality of S-ANT1 for the detection of CHE considering cut-off values of < 20 and < 23 animals.

Cut-off value	< 20 named animals	< 23 named animals
Sensitivity	64% (50–76)	85% (72–92)
Specificity	78% (67–86)	54% (43–65)
Positive predictive value	66% (52–78)	56% (45–66)
Negative predictive value	76% (65–84)	84% (71–92)
+LR	2.91	1.85
-LR	0.46	0.28

+LR, positive likelihood ratio; −LR, negative likelihood ratio; in brackets 95% confidence interval.

fulfilled these conditions with a sensitivity of 85%. Specificity, PPV and NPV were 54%, 56% and 84%, respectively (Table 4). Only 16.4% (n = 9) of all patients with results of ≥23 named animals suffered from CHE.

4. Discussion

A fast, inexpensive and easy to perform primary screening tool for the assessment of CHE is urgently needed in clinical practice. In accordance to the current EASL/AASL guideline the gold standard for diagnosis of MHE (as part of CHE) is the PHES [1]. Additionally, other testing methods like the assessment of CFF, the Stroop EncephalApp or the ICT were introduced in the last two decades [9–11]. However, all tests are not often used outside of hospitals or centres with a special interest the field of HE and liver cirrhosis. Main reasons may be the time-consuming and/or expensive testing process or the unavailability of required devices leading to the neglect of this relevant complication of end-stage liver disease in routine clinical practice. Recently, Campagna et al. demonstrated that the S-ANT1 may be a fast and reliable tool to detect CHE in patients with liver cirrhosis in clinical practice [12]. In our present study, we could externally validate these results. S-ANT1 was able to discriminate well between patients with HE1, patients with MHE, patients without CHE, and healthy controls, respectively ($p < 0.05$ in each pairwise comparison).

For the detection of HE, Campagna et al. suggested a three-staged cut-off system for the identification of no (0 = ≥ 15 named animals), mild (1 ≤ 15 and ≥ 10 named animals) and severe (2 ≤ 10 named animals) cognitive impairment. In our study, these cut-offs had only a low diagnostic power for the detection of CHE. Particularly, sensitivity was unacceptable low for the proposed cut-off values of 15 and 10 named animals (sensitivity: 31% and 7%, respectively). Our results are in contrast to the former results which demonstrated a sensitivity of 78%, a specificity of 63%, a PPV of 61%, and a NPV of 79% for a cut-off < 15 animals, and a sensitivity of 26%, a specificity of 92%, a PPV of 70%, and a NPV of 30% for a cut-off < 10 animals. These distinct differences may be partially attributed to the throughout higher results in S-ANT1 in every group analysed in our study when compared with the respective counterparts in Campagna's study. One possible explanation for this finding may be a higher educational degree of the investigated patients in our analysis. For instance, 34% of the Italian cirrhotic patients had only an educational level of elementary school. In contrast, in our cohort only 2 patients have received < 8 years of school education. Another explanation for the diverse results may be the different testing strategies used for the detection of MHE. Campagna et al. used only the PHES, while we defined the presence of MHE according to pathological results in PHES and/or CFF. It is a well-known fact that MHE is a continuum of symptoms and not every symptom may be present in every patient at any given time. Therefore, different testing strategies may partially detect different patients. In recent years, multiple studies have shown that the agreement between the different testing strategies like PHES, EEG, or CFF may be very low [15,16]. Taken together, the low diagnostic power of the recently proposed cut-off values in our cohort emphasizes that cut-offs for S-ANT1 may not be generalized in different populations, even not in Western Europe. For that reason, we aimed to establish new cut-off values for our study population. In our cohort a cut-off value of < 20 named animals (based on a 1:1 weighting ratio between sensitivity and specificity) differentiated well between patients with and without CHE (Table 4). However, the S-ANT1 investigates only one aspect of HE; and will therefore never be a specific diagnostic tool for CHE itself. In recent years, the search for fast, inexpensive and easy to perform primary screening tests for the stratification of cirrhotic patients at risk for complications, i.e. oesophageal varices, accelerates [17,18]. Therefore, we developed a cut-off value with focus on higher sensitivity (2:1 sensitivity:specificity) to exclude a preferably high number of unimpaired patients and by that to reduce the number of patients with need for specialized testing (e.g. with PHES or CFF). When using the appropriate cut-off value of < 23 named animals, 38.5% (55 of 143) of patients could be excluded from further testing with a total rate of only 16.4% (9 of 55) false negative tested patients.

However, there are some weaknesses in our study. Since we excluded patients with HCC, electrolyte disorders, TIPSS or pre-terminal comorbidities, our results may not be generalized for all patients with liver cirrhosis. However, advanced comorbidities can lead to cognitive deficits and consequently influence results of tests like PHES [19], justifying our stringent exclusion criteria. Although patients with an established neurological diagnosis were excluded from the study and a basic neurological examination was performed in every patient, we cannot completely rule out factors contributing to poorer performance in S-ANT1 like early dementia or mild traumatic brain injuries. Another point that has to be mentioned is that Campagna et al. demonstrated that their cut-offs had a prognostic value regarding the 1-year mortality and the risk for developing OHE. Notably, this has not been evaluated in our study and therefore the prognostic significance of our presented cut-offs cannot be judged by this data. In addition, we did not have normative data for the ANT1 in a healthy German population. Therefore, we are not able to judge the reliability of the S-ANT1 in our cohort. However, there are plenty of data regarding this topic in comparable populations [12,13]. Another point that has to be discussed is that an improvement or deterioration in S-ANT1 caused by medical treatment cannot be judged with the presented data. This should be investigated in further study. Lastly, it should be clearly stated that S-ANT1, as every test used in this clinical setting, may not be specific for the detection of CHE and will never be a specific test for establishing the diagnosis of CHE itself [20].

5. Conclusion

In summary, the present study demonstrates that S-ANT1 may become an important screening tool for the assessment of CHE in cirrhotic patients with the aim to detect either patients at high risk for CHE who should undergo further testing or to avoid further testing in patients with a very low risk for CHE.

Disclosure statement

The authors disclose no potential financial or non-financial conflict of interests.

Author contributions

C.L., L.B., and M.A.W. conceived and designed the study. C.L., L.B., Y.H., M.N., M.N.-T., J.U.M., M.S., T.Z., J.M.S., and M.A.W. performed experiments. C.L., L.B., and M.A.W. analysed final data. C.L., M.A.W., and P.R.G. contributed reagents/materials/analysis tools. G.T. and C.L. performed the statistical analysis. C.L. and M.A.W. wrote the manuscript. All authors revised critically and acknowledged the final version of the manuscript.

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