Relationship between clock and star drawing and the degree of hepatic encephalopathy

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ABSTRACT

Purpose of the study Current hepatic encephalopathy grading tools are limited because of complexity or subjectivity. The degree of constructional apraxia could serve as a simple, objective and reproducible tool to grade encephalopathy.

Study design In this cross-sectional study of patients with chronic liver disease, the degree of constructional apraxia was judged by their ability to copy a star and clock face and compared with conventional encephalopathy grading by the West Haven Criteria (WHC) and the Porto Systemic Encephalopathy Index (PSEI). Three blinded observers independently graded the figures. Sensitivity, specificity and positive predictive value (PPV) of clock and star scores (score 0 implying no encephalopathy and >0 hepatic encephalopathy) were assessed against conventional scoring systems (WHC grade >0 or PSEI ≥0.33 indicating encephalopathy). Mosaic and box plots were generated to assess if the degree of constructional apraxia correlated with the severity of encephalopathy.

Results 71 patients were studied between October 2008 and July 2009; 11 (15.4%) had WHC grade 0, 32 (45%) grade 1, and 28 (39.4%) grades 2 and 3 encephalopathy. The sensitivity, specificity and PPV of the clock drawing for the diagnosis of encephalopathy was 85%, 80%, and 96%, respectively, and 77%, 70%, and 94%, respectively, for the star drawing. Box plots and intervals on mean PSEI showed an increasing relationship between clock/star scores and PSEI. There was substantial agreement between WHC and clock (weighted κ 0.61) and star scores (weighted κ 0.71). Inter-observer reliability was at least 0.70 for star and at least 0.79 for the clock score.

Conclusion Clock and star drawing may serve as reproducible, inexpensive bedside tools for diagnosing and grading the severity of hepatic encephalopathy.

INTRODUCTION

Hepatic encephalopathy, a neuropsychiatric manifestation of liver disease,[1] is a poor prognostic sign in chronic liver disease.[2] Grading the severity of hepatic encephalopathy enables documentation of response to therapy and helps define the impact of experimental therapeutic strategies. It also helps in prognostication.[3] Existing clinical scales for grading hepatic encephalopathy are limited either by the complexity of the tool or by subjectivity of assessment. The West Haven Criteria (WHC),[4] which is based upon the subjective assessment of changes in consciousness, intellectual function and behaviour is relatively insensitive in distinguishing milder forms of encephalopathy.[5] The Glasgow Coma Scale (GCS), initially developed for brain injury patients,[6] has not been rigorously evaluated in hepatic encephalopathy.[7] The Porto Systemic Encephalopathy Index (PSEI) encompasses neuropsychiatric parameters (number connection test), neurophysiologic (electroencephalogram, EEG) and biochemical (ammonia) tests and clinical assessment of mental status and degree of asterixis (table 1). However, EEG, number connection skills and mental status are not independent of each other; the number connection test component may be influenced by age, and education and scoring of ammonia levels is arbitrary.[10] The Clinical Hepatic Encephalopathy Staging Scale (CHESS) distinguishes minimal from overt encephalopathy but cannot be used in severe encephalopathy.[11] The Hepatic Encephalopathy Severity algorithm, that uses clinical and neuropsychological indicators to provide objective assessment of cognitive areas outlined in the WHC, has been validated in patients with WHC grades 3 and 4 encephalopathy but not in milder degrees of cognitive impairment.[5] Thus, there are, at present, no clinically valid, sensitive, objective, simple, bedside tools for grading hepatic encephalopathy.[3]

Constructional apraxia is a well recognised manifestation of hepatic encephalopathy.[12] Constructional ability involves the combination of visuospatial perception with motor activity and includes tests of drawing as well as tests of copying. Tests of drawing are considered to be better standardised and more reliable than tests of copying.[13] Although the star drawing test has been classically described in textbooks as a test for encephalopathy, it is said to be relatively insensitive for diagnosing hepatic encephalopathy when compared with the number connection test.[14] Clock drawing, on the other hand, requires cognitive executive functions in addition to visuospatial ability. There is paucity of literature on the correlation of the star and clock drawing with conventional grading of hepatic encephalopathy. This study was thus undertaken to evaluate if the degree of constructional apraxia, as measured by the patient's ability to copy a clock face and a five pointed star from a template, was related to the degree of hepatic encephalopathy as measured by the WHC and the PSEI.

PATIENTS AND METHODS

Study design and setting

The study design was cross-sectional, and was conducted in the hepatology and medical wards of a tertiary care university hospital.

Patients

All adult patients admitted with hepatic encephalopathy secondary to cirrhosis, during the period

Table 1 Porto systemic encephalopathy score[3 8 9]

Score	Mental state	Trail making (sec)	Asterixis	Venous ammonia (μg/dl)	EEG abnormality
0	No abnormality detected	<30	Nil	≤80	Normal α waves 8.5–12 cycles/s
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired addition or subtraction	31–50	Rare flapping motion	81–105	7–8 cycles/s
2	Lethargy Disorientation to time Obvious personality change Inappropriate behaviour	51–80	Occasional irregular flaps	106–135	5–7 cycles/s
3	Somnolence to semi stupor Responsive to stimuli Confused Gross disorientation Bizarre behaviour	81–120	Frequent flaps	136–160	3–5 cycles/s
4	Coma	>120	Continuous flapping	>160	≤3 cycles/s

EEG, electroencephalogram.

October 2008 until July 2009, were considered for inclusion. The presence of sonologic evidence of a shrunken liver, splenomegaly with collaterals and/or endoscopically proven oesophageal varices constituted evidence of cirrhosis. Histological confirmation was not mandatory for inclusion in the study. Patients with acute liver cell failure, those comatose or having an alternate non-hepatic cause for low sensorium such as hyponatraemia, sedative overdose, alcohol consumption, uraemia and hypoglycaemia were excluded. The study was approved by the Institutional Review Board and Ethics Committee. Consent was obtained either from the patient or from the next of kin.

Methods

Demographic data such as age, gender, education status and cause of cirrhosis were recorded on data abstraction forms. As part of the routine aetiologic evaluation, serology for hepatitis B surface antigen and hepatitis C virus antibodies were undertaken in all individuals. In the presence of a history of significant alcohol consumption, a presumptive diagnosis of alcohol related chronic liver disease was made. Non-alcoholic fatty liver was diagnosed based upon histopathologic evidence of steatohepatitis in the absence of alcohol consumption or serologically proven viral infection. Serum cerruloplasmin and serum ferritin concentrations were assayed in order to screen for Wilson's disease and haemochromatosis, respectively. Individuals in whom no clear cause of cirrhosis was determined despite investigation were categorised as having cryptogenic cirrhosis. Patients with intrahepatic portal hypertension and a negative aetiologic workup for chronic liver disease were diagnosed as having cryptogenic cirrhosis, given that idiopathic non-cirrhotic intrahepatic portal hypertension contributes to 48% of cryptogenic cirrhosis at our centre.[15]

The patients' mental status at the time of evaluation was documented as per the WHC. Venous ammonia samples were drawn, transported to the laboratory in ice and assayed within 12 h of collection. Serum bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum electrolytes, creatinine as well as prothrombin time were tested for all patients.

The PSEI was calculated for all patients. For the number connection component, the patient was asked to connect a series of 25 arbitrarily arranged numbered dots in sequence within 2 min. EEG, which is not routinely done for the evaluation of hepatic encephalopathy, was not performed due to resource constraints as well as the fact that removal of the EEG score does not alter the validity of the PSEI test.[8] The porto systemic encephalopathy (PSE) sum was thus calculated using the formula: (3× mental state score + trail making score + asterixis score + ammonia score) while the PSEI was calculated as PSE sum/highest possible PSE sum—that is, PSE sum/21. As comatose individuals were excluded, the highest possible mental status score was 9. Thus, the PSE sum ranged from 0–21 and the PSEI from 0–1. The PSE sum and PSEI increase with increasing severity of encephalopathy.

In the absence of a gold standard for the diagnosis of hepatic encephalopathy, a diagnosis of hepatic encephalopathy was made if the WHC grade was >0 **or** the PSEI was ≥0.33,[16] in the setting of underlying cirrhosis and other causes of altered conscious state (stated above) were excluded. Otherwise hepatic encephalopathy was considered to be absent.

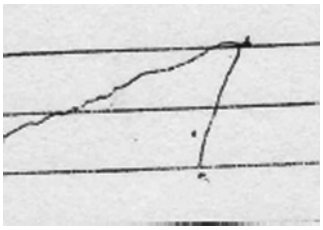
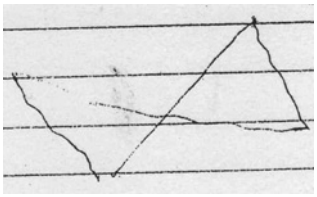
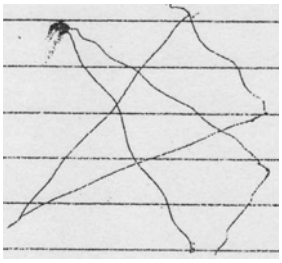
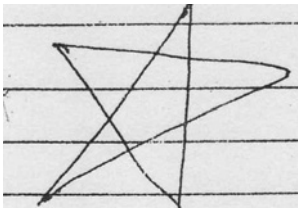
The drawings of the clock face and the star were scored by three observers: two independent blinded observers with no prior training or experience in grading encephalopathy, and a third trained observer. The third trained observer also re-scored the drawings a year after data collection to evaluate intra-observer variation. The scoring systems were designed such that a lower score indicated a more accurate figure. While the scoring system for clock face drawing had been previously validated, the scoring system used for star drawing was novel and devised for the study (tables 2 and 3). Clock scores had a possible range of integer values between 0 and 3. Similarly, the range for star scores was integers between 0 and 4. The clock and star scores were inverted (for analysis) so that increasing clock and star scores had the same interpretation as increasing PSEI or WHC.

Statistical methods

The sensitivity, specificity, positive and negative predictive values of clock and star score for the diagnosis of hepatic encephalopathy were computed. The weighted κ statistic[18] and mosaic plots were used to determine the level of agreement between the clock and star scores and the degree of encephalopathy graded by WHC. To compute weighted κ for the star score and WHC, two grades of the star score (0 and 1) had to be collapsed. The relationship between PSEI and clock or star scores was presented using box plots and assessed using analysis of variance (ANOVA). If the ANOVA was significant then Tukey all-pairwise multiple comparisons were undertaken to determine which pairs of scores were significantly different. None of the ANOVA models violated any of the usual linear modelling assumptions.

Mosaic plots were used to determine visually the level of agreement between WHC grades and the clock and star scores.

Table 2 Scoring system for star drawing

Score	Criteria for star drawing	Sample figure*
0	Unable to draw	
1	Scribble	
2	Able to draw lines but unable to connect sensibly to form the desired figure	
3	Able to draw but imperfect	
4	Perfect star	

*Sample figures depicted in the table have been drawn by patients in the study.

Mosaic plots present the proportion of observations within each category for each index. Perfect agreement for the lowest level of both indices, for example, would be represented by the left hand column being entirely the darkest colour (implying 100% of observations were coded by both as 0). No agreement would be indicated by representation of all colours (categories) in all rows/columns.

Inter-observer reliability was also assessed using the weighted κ statistic.

Data analysis

Data analysis was undertaken using various packages within the R statistical software.[19]

RESULTS

Patient profile

Of 193 inpatients screened during the study period, 71 fulfilled criteria for inclusion. Exclusion criteria in the 122 patients were hyponatraemia or uraemia (n=73), coma at presentation (n=39), use of alcohol or sedative drugs (n=4), refusal to participate (n=4), and inability to draw due to cellulitis and thrombophlebitis of the hand (n=2). The mean (±SD) age of the study cohort was 47±12 years (range 25–80 years) with a male preponderance (n=63, 89%). The most common cause of chronic liver disease was alcohol (n=29, 40.8%). Hepatitis B and C virus together accounted for 22% (n=16) of the patients. Non-alcoholic fatty liver was implicated as the cause in three (4.2%) patients. Cryptogenic cirrhosis was diagnosed in 31 patients (43.6%).

Forty-five patients (63.4%) had Child's class C cirrhosis, 24 (34%) had class B cirrhosis, and 2 (3%) had class A cirrhosis. The MELD score for patients in the study ranged between 8–39 (median score 16). Thirty-two patients (45%) had WHC grade 1 encephalopathy and 39.4% (n=28) were in grades 2 and 3. Eleven patients (15.4%) had grade 0 encephalopathy.

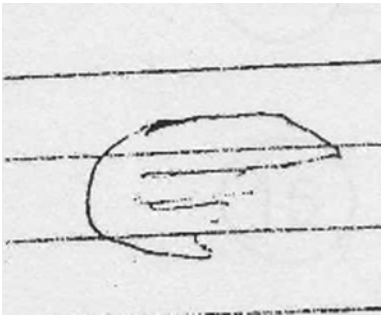
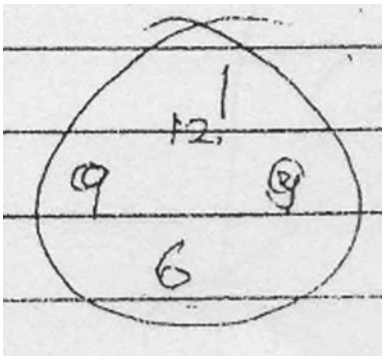
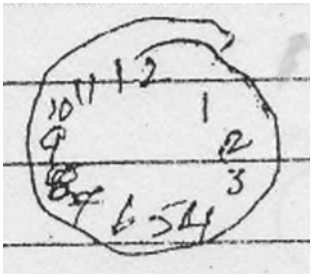
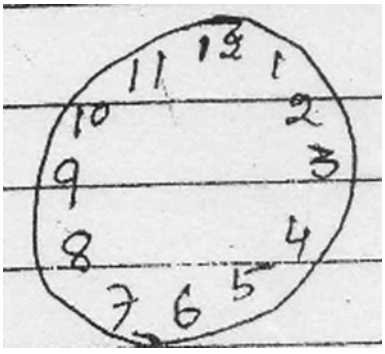
Relationship between hepatic encephalopathy and tests of constructional apraxia

Based upon our definition of hepatic encephalopathy above, we classified 10 individuals as having no overt encephalopathy. Using the reversed clock and star scores, we classified individuals with a score of 0 as having no impairment in constructional ability and thus no encephalopathy. Individuals who scored higher than 0 were deemed to have an impediment in drawing ability possibly owing to hepatic encephalopathy. Sensitivity and specificity were calculated for each of the tests of drawing ability (table 4). The clock test had a sensitivity of 85% and a specificity of 80% for the diagnosis of hepatic encephalopathy, while the star test was found to be slightly less sensitive and specific (sensitivity of 77% and specificity of 70%). Use of both star and clock tests together (star and clock grade of 0 indicated no impairment, star or clock >0 indicates impairment) had the highest sensitivity for the diagnosis of encephalopathy (89%). Positive predictive values were high (>0.93%) and negative predictive values were between 33–47%. The use of different categorisations for the definition of impaired drawing ability (eg, an inverted score of 0 or 1 being considered normal; results not presented) led to a decrease in the sensitivity with higher specificity. The positive predictive value remained the same but the negative predictive value decreased as different dichotomising points were employed.

Mosaic plots were used to assess visually the level of agreement between WHC grades and the clock and star scores (figures 1 and 2). The mosaic plot depicted in figure 1 for clock drawing indicates that patients with the highest WHC grades tended also to have the poorest scores on clock drawing. Conversely patients with only mild encephalopathy tended to perform best on clock drawing. A similar relationship has been depicted for star scores in figure 2. Weighted κ suggested substantial agreement between the clock score and WHC (0.61) and the star score and WHC with star categories 0 and 1 collapsed (0.71).

The box plot for PSEI versus clock and star clearly show an increasing relationship between clock ratings and increasing PSEI scores (figures 3 and 4). PSEI scores for the lowest clock score (0) appear substantially different from those at the highest scores (the boxes on the box plot do not overlap at all). Analysis of variance for clock or star scores versus PSEI were highly significant ($p<0.001$) Tukey all-pairwise multiple comparisons indicated that the mean PSEI for a clock score of 0 was significantly smaller than the mean PSEI for scores of 2 and 3, and that mean PSEI for a clock score of 1 was significantly smaller than the mean PSEI for a clock score of 3. Ninety-five per cent confidence intervals show the increasing mean PSEI with increasing clock rating (figure 3). Figure 4 demonstrates that PSEI scores for the lowest star scores (0 and 1) were substantially different to those at the highest scores. Tukey all-pairwise multiple comparisons indicated that mean PSEI for star scores of 0 and 1 were significantly smaller than mean PSEI for star scores of 3 and 4. Similarly mean PSEI for a star score of 2 was significantly smaller than that for a score of 4.

Table 3 Scoring system for clock face drawing[17]

Score	Grade for clock drawing	Criteria for grade of clock drawing	Sample figure*
0	Poor	Non-recognisable drawing or gross distortion of the basic gestalt	
1	Fair	Clock should contain an approximately circular face or the numbers 1 through 12	
2	Good	Clock should contain 2 of the following Circular face Numbers 1 through 12 Symmetric number placement	
3	Excellent	Near perfect representation of the items with all appropriate components placement and perspective	

*Sample figures depicted in the table have been drawn by patients in the study.

Ten patients had serial assessments of clock and star drawing. In these patients, who were assessed at each of three visits, the clock score was in agreement with the conventional tests of encephalopathy on all 10 patients during the first two assessments. At the third visit, one patient was coded as hepatic encephalopathy by the clock score but was determined not to have encephalopathy by conventional tests. The star drawing and conventional scores agreed on the coding of eight patients at the first and second visits and all 10 patients in the third visit.

Inter-observer reliability

The inter-observer reliability between each trained and the untrained observer was, respectively, 0.70 and 0.83 for the star score and 0.79 and 0.85 for the clock score. The inter-observer reliability between the pair of untrained observers was 0.79 for the star score and 0.81 for the clock score. This indicates substantial inter-observer reliability irrespective of training.

DISCUSSION

Tests of constructional apraxia used in the study fulfil the qualities of a good test—that is, reliability, validity, standardisation, and generalisability.[20] The components of reliability include measures such as internal consistency and inter-rater reliability. The inter-rater reliability of the clock and star scores was good. We set out to establish the validity of the assessment of constructional apraxia for the grading of hepatic

Table 4 Sensitivity, specificity, positive and negative predictive values of clock and star drawing tests for the diagnosis of hepatic encephalopathy

	Clock*	Star*	Clock and star
Sensitivity	0.85	0.77	0.89
Specificity	0.80	0.70	0.60
Positive predictive value	0.96	0.94	0.93
Negative predictive value	0.47	0.33	0.46

*For the clock and star scores, a score of 0 corresponded to 'no encephalopathy'. Individuals with scores >0 were classified as having encephalopathy. The gold standard used was a combination of West Haven Criteria (WHC) and Porto Systemic Encephalopathy Index (PSEI). Patients were categorised to have no encephalopathy if the WHC grade was 0 **and** the PSEI was <0.33. Those with a WHC grade >0 **or** a PSEI ≥0.33 were classified as having encephalopathy.

encephalopathy by first estimating the sensitivity and specificity of the tests of drawing ability for the diagnosis of encephalopathy. Having determined that the tests of constructional ability were sufficiently sensitive and specific tools in the diagnosis of hepatic encephalopathy, we set out to determine whether worsening encephalopathy was related to worse impediment in drawing ability. We demonstrated visually and statistically that patients who performed better in tests of drawing tended to have less severe encephalopathy. We thus established the construct validity of drawing tests.

Standardisation of the test does not only refer to the ability to administer the tests under uniform conditions and assess them objectively, but also refers to the establishment of a normative score. The clock and star drawing tests may be administered under standard conditions and lend themselves to objective assessment. The tests were administered in a random sample of inpatients with cirrhosis of liver of many different aetiologies in the gastroenterology/hepatology ward and the general medical wards. The tests were administered in both men and women of varying ages and educational backgrounds. The severity of liver disease also varied in the population studied. This indicates that the tests are generalisable to patients with cirrhotic liver disease irrespective of their age, gender, education, aetiology of cirrhosis, and severity of underlying liver disease.

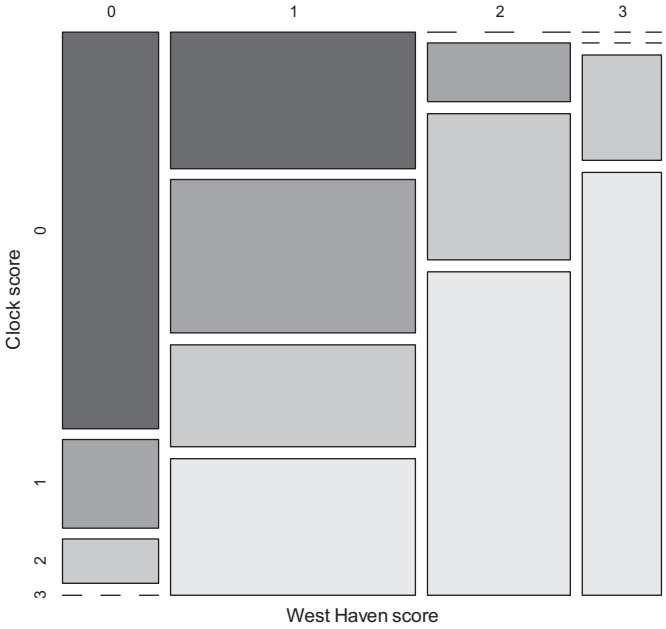


Figure 1 Mosaic plot comparing West Haven Criteria grade with clock score for the grading of hepatic encephalopathy.

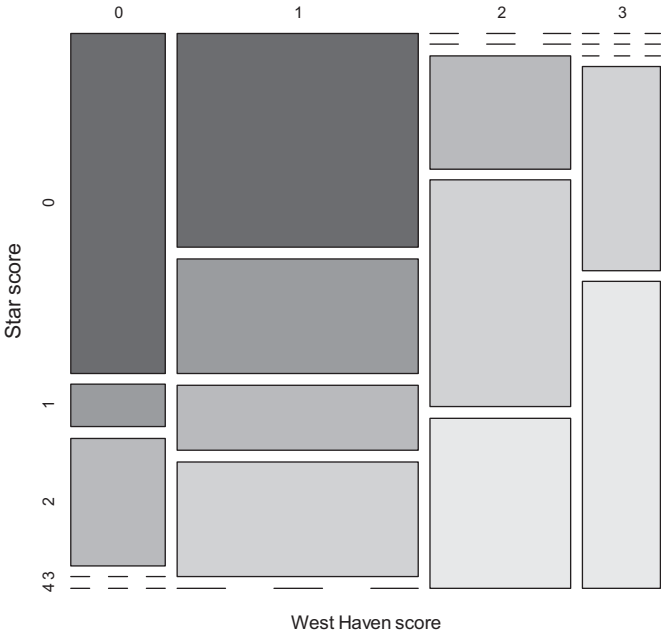
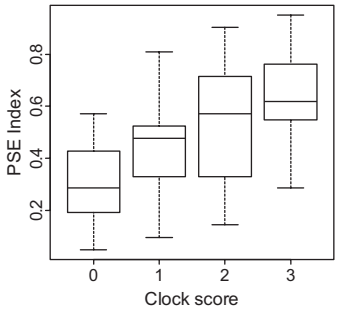


Figure 2 Mosaic plot comparing West Haven Criteria grade with star score for the grading of hepatic encephalopathy.

Use of drawing tests lends objectivity to an otherwise subjective bedside assessment of hepatic encephalopathy. Drawings serve as documentary evidence of the presence of encephalopathy which may be assessed at a later time by another observer. The clock and star drawing tests may thus play a role in repeated assessment of patients with hepatic encephalopathy.

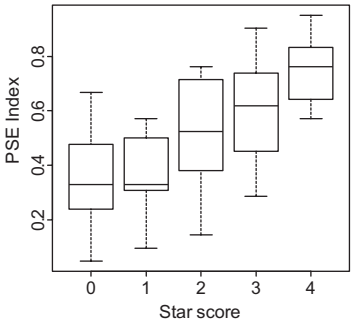
The tests of constructional apraxia require only a pen and paper for their administration. These tests may be undertaken irrespective of the patient's education status. Scoring systems for the tests are simple. A high degree of correlation between scores awarded by trained and untrained individuals was observed. This lends force to the argument that tests of constructional apraxia may be administered by any member of the healthcare team irrespective of training or skill. Tests of constructional ability may be more speedily administered and are less expensive to undertake when compared with neuropsychiatric tests. They are therefore of special significance in resource limited settings.

The study must be interpreted in the light of the following limitation. In the absence of a gold standard for the diagnosis of encephalopathy, we used a composite of the WHC and the PSEI



Clock rating	Mean	Median	95 % CI
0	0.31	0.29	0.22 to 0.40
1	0.46	0.48	0.36 to 0.57
2	0.54	0.57	0.45 to 0.64
3	0.65	0.62	0.58 to 0.72

Figure 3 Box plot comparing clock drawing with the porto systemic encephalopathy (PSE) index for the grading of hepatic encephalopathy. The horizontal bars show the median score. Boxes show the middle 50% of all values.



Star rating	Mean	Median	95% CI
0	0.35	0.33	0.28 to 0.43
1	0.37	0.33	0.25 to 0.49
2	0.52	0.52	0.41 to 0.62
3	0.60	0.62	0.53 to 0.68
4	0.76	0.76	0.66 to 0.86

Figure 4 Box plot comparing star drawing with the porto systemic encephalopathy (PSE) index for the grading of hepatic encephalopathy. The horizontal bars show the median score. Boxes show the middle 50% of all values.

for the diagnosis of encephalopathy. Estimates of sensitivity and specificity of the measures of drawing ability are therefore limited by the lack of a gold standard.

Despite the limitation, these simple bedside tests can be used as screening tests to diagnose encephalopathy as well as for grading the severity of encephalopathy. The good inter-observer reliability and objectivity of the star and clock drawing lends credence for its routine use in the assessment of hepatic encephalopathy. Preliminary observations in the current study support the study of serial assessments of clock and star drawing in the same patient to track changes in the level of hepatic encephalopathy. Further investigation into the utility of tests of constructional ability in the diagnosis of minimal encephalopathy is also warranted.

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Main messages

- The degree of constructional apraxia may be graded by assessing the ability of patients to copy a five pointed star and a clock face.
- Tests of constructional apraxia are sensitive and specific tools in the diagnosis of hepatic encephalopathy.
- The degree of impairment in clock and star drawing appears to increase as the degree of hepatic encephalopathy increases.
- Star and clock face drawing may serve as rapid, reproducible, simple, and objective means of grading the degree of hepatic encephalopathy among patients with chronic liver disease.

Current research questions

- Use of tests of constructional apraxia in the diagnosis of minimal hepatic encephalopathy should be explored.
- To evaluate if tests of constructional apraxia could be used to track the course of patients with hepatic encephalopathy.

CONCLUSIONS

Clock and star drawing are reliable, valid and readily generalisable tests of constructional apraxia. In the presence of a demonstrable relationship between the degree of hepatic encephalopathy and the degree of apraxia, the clock and star scores may be utilised as clinically applicable, inexpensive, objective, and reproducible means of assessment of the grade of hepatic encephalopathy.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee and Institutional Review Board - Christian Medical College Vellore.

Contributors NE: data collection, data entry, manuscript preparation; JVP: conceptualisation, manuscript preparation; GJ: data interpretation and analysis, manuscript preparation; CEE: conceptualisation, data collection; PLG, statistical analysis.

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