

Diagnostic value of fine motor deficits in patients with low-grade hepatic encephalopathy

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Abstract

AIM: The role of motor dysfunction in early diagnosis of low-grade hepatic encephalopathy remains uncertain. We performed a pilot study to comparatively investigate the kinematic characteristics of small and large rapid alternating movements in patients with liver cirrhosis and low-grade hepatic encephalopathy.

METHODS: A kinematic analysis of alternating handwriting (7.5 mm) and large drawing movements (DM, 175 mm) was performed in 30 patients with liver cirrhosis (no hepatic encephalopathy: $n = 10$; minimal hepatic encephalopathy: $n = 9$; grade I hepatic encephalopathy: $n = 11$; healthy controls: $n = 12$). The correlation between kinematic parameters, clinical neuro-psychiatric symptoms of cerebral dysfunction and the grade of encephalopathy was investigated.

RESULTS: Both movement types, handwriting and drawing, were significantly slower in cirrhotic patients. In contrast to large DM, the deterioration of handwriting movements significantly correlated with the increase of symptoms of motor dysfunction and differentiated significantly within the group of cirrhosis patients corresponding to the degree of hepatic encephalopathy.

CONCLUSION: The deterioration of fine motor control is an important symptom of low-grade hepatic encephalopathy. The kinematic analysis of handwriting allows the quantitative analysis of alterations of motor function and is a possible tool for diagnostics and monitoring of motor dysfunction in patients with low-grade hepatic encephalopathy.

INTRODUCTION

The majority of patients with liver cirrhosis suffer from mild cerebral dysfunction which is characterized by a variety of clinical symptoms and psychometric deficits^[1]. This dysfunction is partly related to the current ammonia level^[2,3] and, as recently suggested, could to a certain degree be caused by neurodegenerative processes triggered by recurrent hyperammonemia frequently associated with liver cirrhosis^[4].

Mild forms of cerebral dysfunction in liver cirrhosis include minimal hepatic encephalopathy (MHE) and grade I hepatic encephalopathy (grade I HE). Patients with grade I HE manifest with minor signs of motor dysfunction, such as asterixis and tremor, as well as with attention and concentration deficits^[5-7]. Minimal hepatic encephalopathy is diagnosed in patients that demonstrate deficits in attention and visuo-motor co-ordination but otherwise show no evident or only transient symptoms of cerebral dysfunction^[1,6,8]. The exact differentiation between these forms of low-grade hepatic encephalopathy still remains difficult.

Symptoms of motor dysfunction are an important finding in patients with liver cirrhosis and can be detected in different movement types^[9]. Although alterations of handwriting have been earlier observed in patients with liver cirrhosis^[10,11] a quantitative analysis of handwriting in these patients has not yet been performed. Meanwhile, handwriting has been applied for a quantitative and qualitative analysis of movement deficits in a variety of movement disorders^[12-14].

The purpose of this study was to comparatively investigate the alteration of two types of rapid alternating movements large drawing and small handwriting movements in patients with liver cirrhosis and to assess the feasibility of kinematic analysis of handwriting for diagnosis of motor dysfunction in low-grade hepatic encephalopathy.

MATERIALS AND METHODS

Subjects

Thirty patients (w/m: 10/20, mean age 55.53 years, range:

27-72 years) with liver cirrhosis at the out-patient Clinic of the Department of Gastroenterology and Hepatology of Innsbruck Medical University participated in this study, which was approved by the Ethics Committee of Innsbruck University. Prior to inclusion, patients underwent a detailed hepatologic workup and gave informed consent. At the time of testing patients did not show any clinical or laboratory signs of infection, gastrointestinal bleeding, anemia, electrolyte abnormalities or renal insufficiency. The following exclusion criteria were applied in this study: (1) hepatic encephalopathy, clinical grade II-IV^[15], as revealed by clinical neurological investigation; (2) abuse of psychotropic substances; (3) known major neuropsychiatric disorder, as defined by ICD-10; (4) less than 6 mo of complete alcohol abstinence. The patients were diagnosed as follows: cirrhosis associated with hepatitis C ($n = 12$); alcoholic steatohepatitis ($n = 10$); non-alcoholic steatohepatitis ($n = 2$); primary biliary cirrhosis ($n = 1$); primary sclerosing cholangitis ($n = 1$); autoimmune hepatitis ($n = 1$); cirrhosis associated with hepatitis B ($n = 2$); polycystic liver disease ($n = 1$). The severity of cirrhosis was assessed as follows: Child A ($n = 4$); Child B ($n = 25$); Child C ($n = 1$). A group of 12 healthy subjects (w/m: 7/5, mean age 56.08 years, range: 49-66 years) served as controls.

Movement analysis

A commercially available system CS (CS, Munich, Germany) for the analysis of planar movements was applied in this study. The system consists of a digitizing graphic tablet (WACOM IV, UltraPad A4 serial tablet, model DU-1212, WACOM Europe GmbH, Krefeld, Germany) with a sampling rate of 200 Hz and a spatial resolution of 0.05 mm and software for signal processing and data analysis. Processing and kinematic analysis were performed using a CSWin 1.0 software, which allows processing of raw digital data using an established filtering algorithm for kinematic analysis based on kernel functions^[16]. The following basic kinematic parameters were analyzed: mean frequency of movements (number of strokes per second)-the measure of ability to perform a sequence of alternating movements (FREQ), the mean duration of the movement cycle (CYCD; ms/cycle) and the number of velocity inversions per movement (NIV). Patients performed two types of rapid alternating movements: a block of handwriting movements (HW), performed as a series of connected letters "λλλ" (7.5 mm high) and a block of drawing movements (DM), performed as a repeated drawing of a connection line between two points (about 175 mm distance). In both tests subjects were instructed to perform movement as fast as possible. In order to make the subjects familiar with the digital board and the experimental set-up a series of standardized training attempts were performed by all subjects prior to the main tests.

Clinical neuro-psychiatric rating and psychometric tests

The clinical investigation focused on the symptoms which are frequently found in patients with liver cirrhosis and low-grade hepatic encephalopathy^[7,17] and was performed by an experienced neuropsychiatrist prior to the motor tests. Neurological examination included the assessment of asterixis, postural tremor, rigidity, adiadochokinesia (pronation-supination of both forearms), slowing of upper extremities,

impaired concentration and attention deficits. The intensity of symptoms was defined as a combination of their frequency of appearance and their severity. The symptoms were assessed as follows: absent, slight, moderate and severe and were assigned with 0, 1, 2, and 3 scores, respectively. The cumulative clinical score was calculated as a sum of scores of the seven symptoms listed above. The psychometric test battery included trail-making tests A and B (TMT A and TMT B)^[18,19] as well as the digit symbol test (DST). A cumulative psychometric index was calculated as the sum of age-adjusted percentile scores for TMT A, TMT B and DST^[18,19] while one score point was assigned for every 10 percentiles. Patients without obvious symptoms of hepatic encephalopathy and normal psychometric performance (cumulative visuo-motor index >9.0) were assigned with absent HE ($n = 10$). Patients without clinical symptoms but with reduced psychometric performance (cumulative index below 9.0) were diagnosed with minimal hepatic encephalopathy ($n = 9$). Patients with apparent clinical symptoms of cerebral dysfunction but without somnolence and disorientation were diagnosed with grade I hepatic encephalopathy ($n = 11$).

Statistical analysis

The analysis of the difference between patients and controls was performed using *t*-test statistics. ANOVA was applied for the analysis of the association between the degree of cerebral dysfunction and movement parameters. The analysis of the association between kinematic parameters and clinical symptoms was performed using Spearman's correlation analysis. For data processing and statistical analysis the SPSS 11.5 software package was applied.

RESULTS

The kinematic parameters of both investigated movement types were substantially altered in patients with liver cirrhosis as compared to controls (Figure 1A). In particular, the frequency of handwriting movements (FREQ-HW) was significantly lower in cirrhotic patients (mean FREQ-HW = 2.03) than in controls (mean FREQ-HW = 3.76, *t*-test: $P < 0.001$). Similarly, the frequency of DM was significantly reduced in patients (mean FREQ-DM = 0.84) as compared to controls (mean FREQ-DM = 1.85; *t*-test: $P < 0.001$). Cycle duration (CYCD) was significantly increased in cirrhotic patients with respect to both movement types (*t*-test: $P < 0.001$ for HW and DM).

The kinematic parameters of handwriting movements significantly differed within the group of patients depending on the degree of hepatic encephalopathy. The results of the one-way ANOVA analysis presented in Table 1 show that, in contrast to DM, for all parameters of handwriting the difference between the subgroups of patients (no encephalopathy, MHE, and grade I) was highly significant. The Spearman's correlation analysis showed that FREQ-HW and CYCD-HW correlates significantly with the visuo-motor index (Table 1) and the cumulative clinical score (Table 1 and Figure 1B). In contrast, the corresponding parameters of DM (FREQ-DM and CYCD-DM) did not show any association with the decrease of visuo-motor index nor with the increase of the cumulative clinical score (Table 1).

Table 1 Correlation between kinematic parameters and symptoms of low-grade hepatic encephalopathy and analysis of the association between the degree of hepatic encephalopathy and kinematic parameters within the group of patients with liver cirrhosis (ANOVA)

Kinematic parameters	One-way ANOVA	Spearman correlation analysis: <i>P</i> -value and (<i>P</i>)	
	grade 0 HE, MHE and grade I HE	Visuo-motor index	Cumulative clinical score
FREQ-HW	0.003 ^b	0.594 (0.000) ^b	-0.611 (0.000) ^b
FREQ-DM	0.592	0.136 (0.245)	-0.203 (0.150)
CYCD-HW	0.010 ^a	-0.504 (0.003) ^b	0.537 (0.002) ^b
CYCD-DM	0.699	-0.128 (0.258)	0.220 (0.131)
NIV-HW	0.002 ^b	-0.618 (0.000) ^b	0.672 (0.000) ^b
NIV-DM	0.934	-0.370 (0.053)	0.310 (0.108)

^a*P*<0.05, ^b*P*<0.01 *vs* others HW-handwriting; DM-drawing movements; FREQ-frequency; CYCD-cycle duration; NIV-number of velocity inversions per stroke; HE-hepatic encephalopathy; MHE-minimal hepatic encephalopathy.

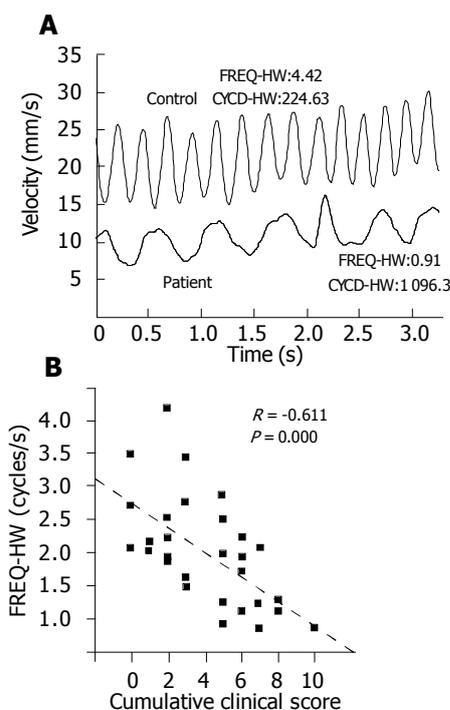


Figure 1 A: Examples of velocity curves of handwriting movements; a patient (man, 66 years) with liver cirrhosis (Child B, hepatitis C) with minimal hepatic encephalopathy (curve below) and a control subject (man, 65 years; curve above); **B:** Correlation between frequency of handwriting movements (FREQ-HW) and cumulative clinical score.

The analysis of impairment of movement automatization was performed using the NIV which indicates the degree of decomposition of velocity profile. Values of NIV were significantly increased in patients with liver cirrhosis as compared to controls for both movement types. Again, the degree of decomposition of handwriting movements (NIV-HW) increased significantly within the group of patients depending on the degree of hepatic encephalopathy (Table 1). In contrast, Spearman’s correlation analysis showed no association between the deficits in DM (NIV-DM) and the degree of hepatic encephalopathy (Table 1).

DISCUSSION

The main finding of this pilot study is that the impairment of handwriting correlated significantly with the grade of hepatic encephalopathy, clinical neuro-psychiatric symptoms

and visuo-motor psychometric tests. These findings are consistent with the previous studies, which have shown motor deficits in hepatic encephalopathy^[9] and suggest that deficits in fine motor control are common in cirrhotic patients with low-grade encephalopathy. Furthermore, the comparison between handwriting and DM show that the former are strongly associated with the degree of hepatic encephalopathy, whereas the latter showed no correlation within the group of patients.

Low-grade hepatic encephalopathy and in particular motor deficits in patients with liver cirrhosis are associated with alterations in basal ganglia, different cortical regions and dysfunction of cortico-cerebellar pathways^[20-23]. Similarly, several motor control subsystems, such as frontal and parietal cortical regions, cortico-cerebellar pathways as well as basal ganglia are involved in handwriting^[24]. The dysfunction of one or several of these subsystems in patients with liver cirrhosis may result in motor deficits during the course of disease. Early detection of motor deficits would provide the possibility to reveal cirrhosis-associated cerebral dysfunctions in an early stage. Our study shows that the analysis of fine motor control is more sensitive in diagnostics of low-grade hepatic encephalopathy than the analysis of large-scaled movements. We suggest that the impairment of handwriting can be reliably detected and monitored because of the high level of automatization of handwriting movements. On the other hand, the availability of established tools for the kinematic analysis of handwriting allows a quantitative assessment of movement parameters^[16,25]. Our study suggests the use of handwriting analysis for the early detection and assessment of minor motor deficits in diagnostics and monitoring of low-grade hepatic encephalopathy in patients with liver cirrhosis. This would lead to substantial improvement of the clinical management of these patients.

Additionally, our findings point towards another important practical aspect of motor impairment in patients with liver cirrhosis. Patients with low-grade hepatic encephalopathy and even those without apparent signs of cerebral dysfunction may suffer from impairment of basic fine motor skills which are important for every day functioning and could be easily overseen in a standard clinical investigation.

We conclude that further studies of low-grade hepatic encephalopathy in patients with liver cirrhosis should address the detailed evaluation of motor function and that the analysis of handwriting may provide the basis for studies in this context.

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