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**OR 7709**

**Auditory and visual P300 event-related potentials to detect minimal hepatic encephalopathy**

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**ABSTRACT**

**Introduction**

Diagnosis of Minimal hepatic encephalopathy (MHE) requires psychometric tests, although new methods are needed since sensitivity, specificity, and accuracy are low. The P300 event-related potential (ERP) is obtained by auditory and visual stimuli, although only the auditory P300 has been used to detect MHE. We aimed to compare the diagnostic features of auditory and visual P300 to detect MHE.

**Materials and methods**

Sixty patients with liver cirrhosis and thirty-five healthy controls completed the Psychometric Hepatic Encephalopathy Score (PHES), the critical flicker frequency (CFF), auditory, and visual P300. MHE was diagnosed if PHES and CFF scores were abnormal.

## Results

Fifty-three cirrhotic patients (age  $54.5 \pm 8.6$  years) completed all tests. Abnormal scores were: PHES (49.1 %), CFF (67.9 %). The proportion of MHE was 21.4 %. The area under the receiver operating ROC curves (AUROC) for auditory P300 was better than visual P300 for distinguishing MHE from controls (AUROC 0.792 vs 0.725;  $p < 0.005$  for both; accuracy 73.8 % vs 70.2 %; sensitivity 72.2 % both; specificity 74.2 vs 69.7, respectively. Among cirrhotic patients, only auditory P300 was useful to detect MHE, AUROC 0.723  $p < 0.05$ ; 77.4 % accuracy; 61.1 % sensitivity; and 81.8 % specificity.

## Conclusions

The auditory P300 sensitivity, specificity, and accuracy were similar to those of CFF. Our results showed that only auditory P300 is useful to differentiate patients with MHE. Although both modalities, auditory and visual, differentiated patients with cirrhosis from controls, we consider the visual P300 is not suitable for detecting MHE.

## Abbreviations

AUROC: Area under the receiver operating curve; CFF: Critical flicker frequency; EEG: Electroencephalogram; ERP: Event-related potential; Hz: Hertz; MHE: Minimal hepatic encephalopathy; ms: Millisecond; PHES: Psychometric hepatic encephalopathy score; SD: Standard deviation

## INTRODUCTION

Minimal hepatic encephalopathy (MHE) in patients with liver cirrhosis is characterized by a series of subtle cognitive alterations that reflect deficits in different areas. MHE has a prevalence of up to 80 % in patients with cirrhosis(1). The cognitive changes in MHE are psychomotor speed, attention, visual-spatial abilities, working memory, and inhibition, among others(2,3,4,5). The test to diagnose MHE, and considered the gold standard, is the Psychometric Hepatic Encephalopathy Score (PHES), which consists of five tests which accepted criterion to diagnose MHE is a combined addition of lower or equal to minus four standard deviations ( $\leq 4$  SD). The PHES sensitivity (SE) is 73 %, and

specificity (SP) 94 % (6). The use of a psychometric test is sometimes the only available means, but given the low sensitivity and specificity of this method, we use it in conjunction with the critical flicker frequency (CFF) (7)

The CFF cutoff point to detect MHE is 39 Hz (8) in cirrhotic patients, 22 % SE and 100 %SP (9). The PHES and the CFF have higher sensitivity when combined than when performed separately. Torlot and colleagues assessed the accuracy of both tests in 2013 and reported 61 % pooled sensitivity and 79 % pooled specificity (10).

Despite the widespread use of PHES and CFF, these tests are not always available. Thus, it is necessary to consider complementary tests with competitive SE, SP, and reliability (11). For instance, the event-related potentials (ERP), mainly the P300 ERP, is a neurophysiologic marker already used in MHE. Amplitude and latency are two essential parameters to evaluate the P300 (12,13). Sharma et al. (2008) (14) compared the characteristics of P300, CFF, and psychometric tests in patients with MHE, finding abnormal latency ( $> 2SD$ ) in 83 % of patients also with alterations in psychometric tests and 80 % of those with  $CFF < 39$  Hz.

The latency represents the time required for processing the stimuli and is sensitive to cognitive slowing ((15, 16). The cognitive processes associated with the P300 are context updating, working memory, and sustained attention. The auditory P300 latency was more prolonged in patients with MHE diagnosed with PHES (13,17,18).

The P300 can be obtained with different stimuli (auditory, visual, or somatosensory), but only auditory stimuli have been used to diagnose MHE. Amplitude and latency are different depending on the sensory modality. Latency is delayed when comparing auditory versus visual P300 in the same subjects (19, 20). These relationships between auditory and visual stimuli have not yet been explored in patients with MHE.

Visual P300 has not been studied in patients with MHE diagnosed with PHES and in conjunction with CFF; therefore, its usefulness has not been demonstrated. In the present investigation, we evaluated the auditory and visual P300 latency to detect MHE in cirrhotic patients and the errors committed in the performance of the oddball task.

## **MATERIAL AND METHODS**

### **Subjects**

Sixty patients with liver cirrhosis and thirty-five healthy controls participated in the study. Cirrhosis was diagnosed according to clinical history, laboratory tests, and liver histology (if available). The sample size was calculated for proportions considering 61 % sensibility, 80 % specificity, 95 % interval confidence, and 10 % precision yielded a total of 30 patients for each group, control, MHE, and without MHE. Controls were recruited from the general population without a neurologic or psychiatric history that affects psychometric or EEG tests.

Patients were recruited from the gastroenterology service of the General Hospital of Mexico. All participants underwent psychometric PHES and the CFF tests. According to these tests, cirrhotic patients were divided into two groups, with and without MHE. The stimuli, auditory or visual, were delivered separately and simultaneously with EEG registration to obtain the P300. All of the tests were administered by the same researcher. The Ethics in Research Committee of the General Hospital reviewed and approved the protocol. All participants signed informed consent according to the declaration of Helsinki.

### **Psychometric test**

All patients and controls were literate and completed the five tests of the PHES paper-pencil battery. The time required to perform each test and the number of errors were recorded and adjusted for age and schooling according to the validation of Duarte-Rojo et al. (2011)(21) for the Mexican population. The standard deviations of all PHES tests were calculated and considered abnormal if the sum was  $\leq -4$  SD.

### **Estimation of CFF**

We use the portable Hepatonorm Analyzer (Accelab GmbH D-72127 Kusterdingen, Germany). The CFF is a visual discrimination test to determine the frequency at which a flickering light is perceived. The initial frequency is 60 to 25 Hz. The threshold is the

frequency at which a person perceives the light as flickering and presses a button that stops the test. Each participant performed ten repetitions, and the average was calculated. The test was considered abnormal if the detection threshold of the CFF was  $\leq 39$  Hz.

### **Recording of auditory and visual event-related potentials P300**

Auditory and visual stimuli were delivered using STIM2 interfaced with Grael 4K EEG System (Compumedics, Charlotte, USA). Electrodes were placed at the Fz, Cz, and Pz positions, and the earlobes were used for reference. SCAN version 4.5 (Compumedics Neuroscan, Charlotte, USA) was used to acquire the EEG and process the P300. EEG acquisition parameters were a sampling rate of 200 Hz, bandpass filters 0.1-30 Hz, and 60 Hz notch filter. For auditory stimuli, pure tones (150 ms duration 5 ms rise/fall) were delivered in a semi-random sequence comprising 300 tones 1000 Hz target and 500 Hz standard tones in a proportion 1:5 (target: standard). The visual stimuli were white circles in black background delivered in the same proportion and number as the auditory paradigm. Target and standard stimuli had diameters of 10 cm and 7 cm, respectively. Subjects were seated in a comfortable chair 1 meter from the computer screen. The task for eliciting P300 responses was pressing a computer button each time the target was detected (reaction time). Movement and ocular artifact-free epochs (-100 to 1000 ms) were independently averaged for target and standard stimulus. P300 was identified and measured as the most positive peak in an analysis window between 200-500 ms from stimuli onset.

### **Detection of MHE**

MHE was defined in cirrhotic patients by abnormal psychometric battery PHES ( $\leq -4SD$ ), and abnormal CFF mean  $\leq 39$  Hz. The same researcher assessed MHE and CFF.

### **STATISTICAL ANALYSIS**

Statistical analyses were performed with the package IBM SPSS Statistics for Windows version 19 (Armonk NY: IBM Corp.) Results are expressed as mean  $\pm$  standard deviation for continuous data whereas for discrete values median or percentages.

Receiver operating characteristic (ROC) curves were used to determine the cutoff values of P300 latency. Then, SE, SP, accuracy (ACC), positive predictive value (PPV), and negative predictive value (NPV) were calculated for auditory and visual P300. Comparisons of auditory and visual P300 latency were assessed with the Student's t-test for independent samples (control and cirrhotic) or analysis of variance (ANOVA) with patients as a between-group factor (control, MHE, and without MHE). Statistical significance was set at  $p < 0.05$ .

## RESULTS

Four controls and seven cirrhotic subjects were discharged from the analysis due to excessive ocular and movement artifacts in EEG recordings. The study groups were: cirrhotic patients (female 49 %; age  $54.5 \pm 8.6$  years old; education  $8.2 \pm 3.7$  years; Child-Pug A, 54.7 %, B, 39.6 %, and C 5.7 %; controls (female 33 %; age  $39.8 \pm 9.2$  years old; education  $14.4 \pm 2.8$  years).

### Psychometric and CFF tests

Of 53 cirrhotic patients, 26 patients (49.1 %) had abnormal PHES ( $\leq -4$  SD), and, given a cutoff of  $\leq 39$  Hz, 36 patients had abnormal CFF (67.9 %). MHE was detected in 18 patients (21.4 %) by abnormal psychometric and CFF tests.

### Accuracy of auditory and visual P300

The areas under the receiver operating curve (AUROC) for the auditory and visual P300 were allowed differentiation of patients with MHE from controls. The AUROC allowed us to identify MHE among cirrhotic patients in the auditory condition but could not discriminate patients with MHE with visual P300. Sensitivity, specificity, and accuracy for the auditory P300 in detecting MHE was determined by measuring cutoff values of P300 latency by ROC curves (Figure 1). For the visual P300, the detection of MHE was not possible due to the low classification rate. Table 1 shows the detection of MHE between control and cirrhotic patients and within cirrhotic patients. The cutoff value for all P300 conditions was shorter for control subjects and even for patients without MHE.

### **Latency of auditory and visual P300**

The overall latency of P300 in the control group was shorter than cirrhotic patients in both auditory and visual conditions. P300 latency of MHE patients was more prolonged than without MHE. There was a significant difference in auditory latency of P300 between control and cirrhotic groups ( $360.1 \pm 33.7$  vs  $410.4 \pm 56.9$  ms, respectively;  $p < 0.0001$ ) and in visual P300 ( $386.9 \pm 34.4$  vs  $471.3 \pm 56.7$  ms, respectively;  $p < 0.0001$ ). There was also a significant difference among cirrhotic patients of the auditory P300 (MHE  $437.5 \pm 62.7$  ms vs without MHE  $396.4 \pm 48.8$  ms;  $p = 0.008$ ) and between control and MHE groups ( $p = 0.008$ ), and for the visual P300 between control and MHE patients ( $p = 0.011$ ), but not among cirrhotic patients (MHE  $472.4 \pm 52$  ms vs without MHE  $470$  ms) (see Figure 2).

### **Reaction times of auditory and visual P300**

The reaction times (RT) of the auditory, there were statistically significant differences between the RTs from the control vs cirrhosis group in the auditory P300 ( $422.01 \pm 60.72$  vs  $472.58 \pm 96.98$  ms, respectively;  $p = 0.011$ ), whereas, in the visual P300, no difference was found ( $452.6 \pm 73.15$  vs  $473.01 \pm 94.35$  ms, respectively;  $p = 0.304$ ). In the ANOVA analysis, between control, MHE, and without MHE, there was statistical significance between patients with MHE vs without MHE in the auditory P300 ( $517.34 \pm 99.44$  vs  $449.55 \pm 88.45$  ms, respectively;  $p = 0.015$ ), control vs MHE ( $p = 0.01$ ), and no significance between control vs without MHE ( $p = 0.368$ ). In contrast, there were no statistical differences in the visual P300 (MHE,  $506.75 \pm 105.88$  vs without MHE  $455.15 \pm 88.87$  ms;  $p = 0.102$ ), control vs MHE ( $p = 0.88$ ), and control vs without MHE ( $p = 0.992$ ).

### **DISCUSSION**

We obtained both auditory and visual P300 to compare their ability to detect MHE in patients diagnosed with hepatic cirrhosis. In our study population, 21.4 % met the criteria of altered scores of PHES and CFF. 26 cirrhotic patients had abnormal PHES from which 18 also met CFF, that is a difference of 6 patients (11 %) of overdiagnosed MHE. This could lead to a misestimation of the P300's cutoff points and in inconsistencies in detecting MHE. In our study, the cirrhotic group, abnormally

prolonged latency of the auditory P300 was present in 39.6 % and 52.8 % in the visual P300. Sharma et al. (2010) found abnormal P300 latency in 48 % of cirrhosis patients (22). Other studies with cirrhotic patients reported 13 %, 71 %, 80 %, and 67 % of altered auditory P300 (14,23,24). ). Abnormality criteria in MHE studies are usually scores above 2-2.5 SD of the P300 latency from the control group (20,24). Due to the limited references of P300 and the variability in this condition, instead of using the standard deviations of control subjects, we employed the ROC curves' cutoff values. This method has been used to assess the CFF's accuracy in diagnosing MHE in patients with post-hepatitis C liver cirrhosis (25).

In our study, the cutoff point for the latency of P300 was 399 ms, and we obtained 70.2 % ACC for distinguishing MHE among cirrhotic patients, with 72.2 % SE, 69.7 % SP, 39.4 % PPV, and 90.2 % NPV. Accuracy for visual P300 was not calculated due to low AUROC for identifying MHE among cirrhotic patients. For differentiating controls from MHE patients, we found 73.8 % ACC, 72.2 % SE, 74.2 % SP, 43.3 % PPV, and 90.7 % NPV. For the visual P300, the cutoff point was 445 ms. We obtained 77.4 % ACC, 61.1 % SE, 81.8 % SP, 47.8 % PPV, and 88.5 % NPV. Our results are similar to those reported by Sharma and colleagues, where they addressed the treatment effect with lactulose and follow-up in patients with MHE. Considering abnormal scores in psychometric and auditory P300 as diagnosis criteria (80 % ACC, 65 % SE, 91 % SP, 85 % PPV, 77 % NPV) (26). Although experimental methods were different, the latency for auditory P300 between controls and MHE patients were similar (latency of P300  $392.7 \pm 25.7$  ms, and a cutoff point of 413 ms). We also found similarities with other reported values of sensitivity and specificity for CFF and PHES combined (10) (61 % SE [95 % CI: 55-67 %], 79 % SP [95 % CI: 75-83 %]).

We evaluate the characteristics of the visual P300 to detect MHE, but our results were not as favorable as we expected. Compared to CFF, the accuracy for auditory P300 was lower than reported by Sharma and colleagues (2010)(27). The combined use of the P300 with psychometric tests has variable results, and differences could be attributed to the stimuli employed to obtain the P300, the psychometric tests, and the abnormality criteria. Adjustment for the effects of age and educational level must be considered in psychometric tests. One limitation of using ERPs, such as P300 is the

artifacts caused by ocular movements, which requires patients' collaboration to acquire adequate EEG data and avoid losing patients or prolonging the recording time. On the contrary, P300 and CFF are independent of many of these factors, but they require standard procedures to ensure reproducibility. In this regard, our results of P300 are in agreement with CFF findings in cirrhotic patients to identify MHE. Our results showed that visual P300 is more variable than auditory P300 in cirrhotic patients. Differentiation of controls was achieved for both conditions, but only auditory P300 was useful in cirrhotic patients.

The auditory task's reaction times were shorter than for the visual task and were more delayed in patients with MHE. Statistical significance was only for the auditory task. Thus, the RTs from the visual task were not useful for distinguishing patients with MHE from those without this condition. We expected the visual P300, and consequently, the RTs from the visual task allowed detecting MHE as in the case of auditory P300 and their respective RTs. Instead, we found the visual P300 and the behavioral performance apparently require less cognitive demand than the auditory P300, which remained a useful tool to detect MHE but was not the case for the visual P300.

## **CONCLUSIONS**

We tested the accuracy of the P300 for detecting MHE, as diagnosed by standard PHES and CFF tests, in cirrhotic patients. Auditory P300 performed better than visual P300. For the auditory P300, the sensitivity, specificity, and accuracy were similar to those of CFF. Our results showed that only auditory P300 and their reaction times were useful for differentiating patients with MHE. Although both modalities, auditory and visual, differentiated patients with cirrhosis from controls, we consider the visual P300 is not suitable for detecting MHE.

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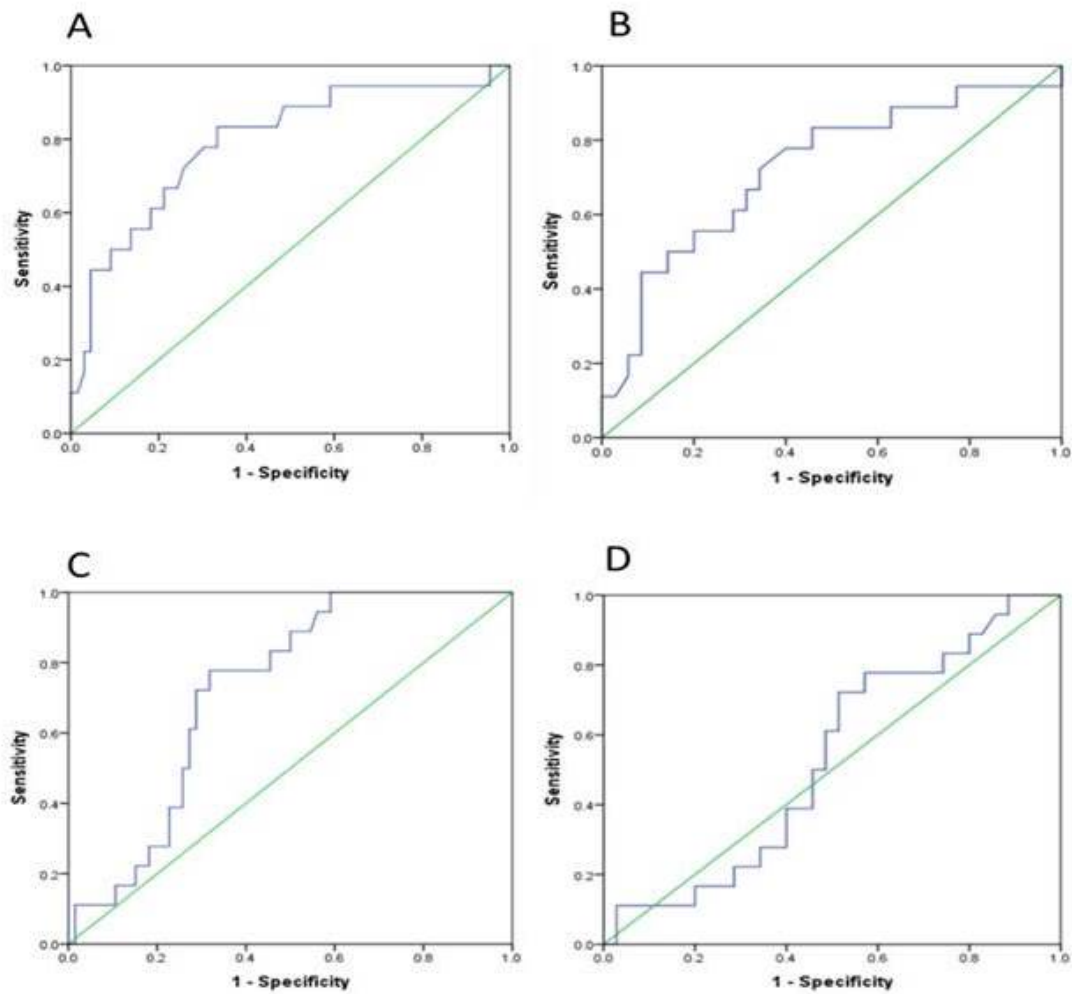
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**Table 1. Diagnosis of MHE by P300**

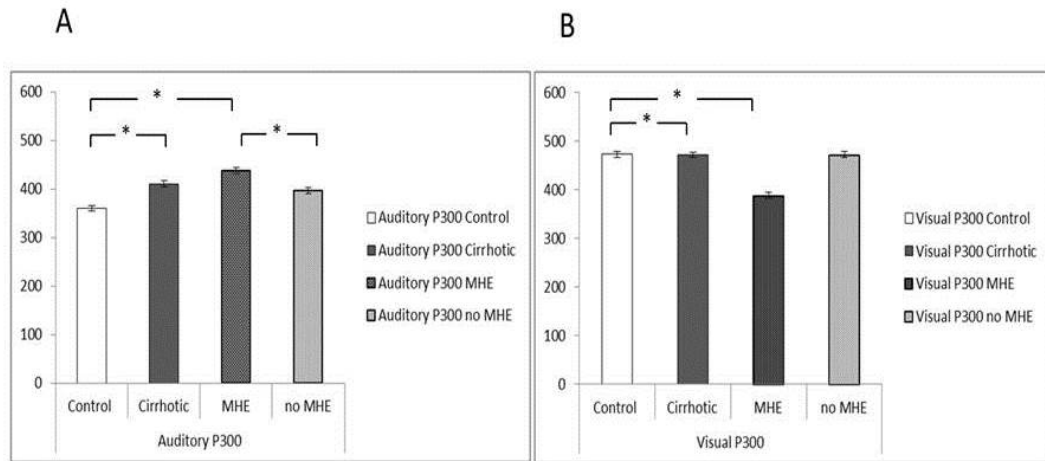
P300	Classification	P300		Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio	Accuracy (%)
		Cut-off point (ms)	AUC (95% IC)							
Auditory	MHE compared with Controls	399	0.792 (0.668 - 0.917); p=0.0001	72.2 (46.5 - 90.3)	74.2 (62.0 - 84.2)	43.3 (25.5 - 62.6)	90.7 (79.7 - 96.9)	2.8 (1.7 - 4.6)	0.37 (0.175 - 0.798)	73.8 (63.1 - 82.8)
	MHE among Cirrhotics	413	0.725 (0.574 - 0.875); p=0.008	61.1 (35.7 - 82.7)	81.8 (70.4 - 90.2)	47.8 (26.8 - 69.4)	88.5 (77.8 - 95.3)	3.4 (1.8 - 6.3)	0.47 (0.263 - 0.857)	77.4 (66.9 - 85.8)
	Visual MHE	445	0.723 (0.613 - 0.833); p=0.001	72.2 (46.5 - 90.3)	69.7 (57.1 - 82.3)	39.4 (22.9 - 55.9)	90.2 (78.6 - 96.9)	2.4 (1.5 - 4.0)	0.39 (0.186 - 0.812)	70.2 (59.3 - 81.1)

compared		0.834); p=0.004	90.3)	80.4)	57.9)	96.8)	3.8)	0.853)	79.7)
with									
Controls									
MHE among		0.531 (0.372 -							
Cirrhotics	453	0.690); p=0.714	NC*	NC*	NC*	NC*	NC*	NC*	NC*

\*NC; Not calculated



**Figure 1. A. Receiver operating characteristic (ROC) curve of auditory P300 Latency for differentiating minimal hepatic encephalopathy (MHE) patients from controls. B. ROC curve of auditory P300 latency for identifying MHE among cirrhotic patients. C. ROC curve of visual P300 latency for identifying MHE from controls. D: ROC curve of visual P300 latency for identifying MHE among cirrhotic patients.**



**Figure 2. A. Comparison of mean latencies of auditory and visual P300 between control and cirrhotic patients. B. Comparison of mean latencies of auditory and visual P300 among cirrhotic patients with and without minimal encephalopathy.**

**\*p<0.05**