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The Auditory Evoked Potentials in Hepatic Encephalopathy

NADIA EL FFKY, M.D. & MOHAMED I. SHABANA, M.D.

The Internal Medicine. & Audiology Departments,
Faculty of Medicine, Cairo University

Abstract

The present study included 68 subjects, 28 females and 40 males, with an age range from 39 to 60 years (mean 48.4 ± 13.19). They were divided into three groups. Group I is the healthy controls "16 subjects". Group II was further subdivided into Group IIa and Group IIb. The former consisted of 9 patients with liver cirrhosis with no clinical data of hepatic encephalopathy and normal psychometric tests, and the latter consisted of 30 patients with subclinical hepatic encephalopathy (SHE) as they showed abnormal results on psychometric testing. Group III consisted of 13 cirrhotic patients with overt hepatic encephalopathy HE.

All cases were subjected to proper history taking, full clinical examination, routine liver function tests as well as brainstem auditory evoked potential BAEPs and event related potentials p 300 wave latency.

In assessing patients with overt HE, (group III) BAEPs demonstrated a statistically significant delay in interpeak latencies-I-III and III-V, and in the absolute latency of wave V when compared with the controls.

However, no significant differences were found between the cirrhotic nonencephalopathic patients (Group IIa) and patients with SHE (group IIb) when compared to each other and between either of them when compared to the controls.

So BAEPs are an objective tool for studying cases with overt HE, while they lack the sensitivity in detecting cases with SHE.

The latency of P 300 wave was significantly increased (p <0.001) in group II b and group III when compared to the control, the delay in group II a was insignificant. The difference in P 300 wave latency was significant when comparing groups II and IIb (p <0.0001).

P 300 wave latency was found to have diagnostic accuracy of 100% in assessing patients with overt HE, while the test was found to be 58.97% accurate with a predictive value of 100% in detecting cases of SHE.

These results suggest that the event related potential p 300 wave latency can play a role in the detection and follow up of SHE as a simple and objective index of central nervous dysfunction in HE.

Introduction

HEPATIC encephalopathy represent a group of neurologic signs and symptoms accompanying advanced liver disease of all types.

The personality and mental changes of hepatic encephalopathy are frequently divided into stages. This clinical grading scale is relatively insensitive.

Standardized testing has revealed psychomotor abnormalities in a high proportion of patients with cirrhosis in whom conventional neurologic examination is normal.

Such "subclinical encephalopathy" is potentially important as it may be associated with impaired functional capacity and job performance [1].

The picture of hepatic pre-coma and coma is non-specific. The organic psychosis, the flapping tremor, the EEG changes and the raised blood ammonium may be encountered, in whole or in part, in other disturbances such as uraemia or respiratory failure.

There is no sure laboratory method of diagnosis, and recognition depends on clinical suspicion with the association of other features of liver disease such as feter hepaticus, jaundice or ascites.

In recent years, there have been considerable development in the application of event-related potential technology to the diagnosis of hepatic encephalopathy. Tarter et al [2] studied the relationship between hepatic injury status and event -related potentials. Their study revealed the sensitivity of neurophysiologic measurement in detecting hepatic encephalopathy concomitant to only moderate severity of hepatic injury [2].

Davies et al [3] studied the value of the auditory P 300 event-related potential as a tool in this field. They suggested that P 300 marker of grades I and II clinical hepatic encephalopathy.

This work was designed to study the role of auditory evoked potential as an "objective" test in the diagnosis of "subclinical" hepatic encephalopathy in patients with liver cirrhosis.

Material and Methods

This study included 68 subjects, 28 females and 40 males, ranging in age from 39 to 60 years (mean = 48.4 ± 12.19).

They were divided into three groups; (I), and (II) and (III).

Group I: of 16 healthy controls, 8 females and 8 males ranging in age from 39 to 59 years (mean = 47.12 ± 6.05).

They were assessed to exclude any hepatic, neurological or psychological dysfunction.

Group II: of 39 patients with liver cirrhosis as based on clinical, biochemical and sonographic assessment.

Following the criteria proposed by Sherlock [4], non of the patients of this group was considered to have "overt" hepatic encephalopathy.

Psychometric testing was carried out for patients of this group and involved the reaction time to sound (RT), the construction of standard fivepointed star and Reitan number connection test (NCT). Illiterates were excluded from the study to improve the specificity of the tests used.

Table (1) presents the results of the psychometric test (RT) as calculated automatically by the evoked potentials equipment. Only 9 out of 39 patients with liver cirrhosis, without overt encephalopathy, have normal results i.e. RT < 400 ms.

Since patients with abnormal psychometric results are considered to have "subclinical" hepatic encephalopathy [4], group II was further subdivided into group IIa, the non-encephalopathic cirrhotic, and group IIb with" subclinical" hepatic encephalopathy.

Group IIa consisted of 9 patients, 3 females and 6 males, ranging in age from 41 to 60 years (mean = 48.77 ± 6.40). Group IIb consisted of 30 patients, 12 females and 18 males, ranging in age from 39 to 60 years (mean = 49 ± 5.89).

Group III of 13 cirrhotic encephalopathic patients, 5 females and 8 males, ranging in age from 40 to 59 years (mean = 48.76 ± 5.84). According to the criteria proposed by Sherlock [4], patients of this group were considered to have overt hepatic encephalopathy. (N.B.: Patients with grades III and IV hepatic encephalopathy were excluded since some cooperation is needed).

All patients studied were inpatients in Cairo University Hospitals. Proper history taking and clinical assessment were directed to exclude any previous neurological or psychological troubles. None of them consumed alcohol at any time of their life.

All patients and controls were subjected to routine liver function tests including total bilirubin, serum albumin, total globulin, SGOT, SGPT, alkaline phosphates, prothrombine time and ammonia nitrogen (Table 2).

Pure tone audiometer: Amplaid, model 309 was used with:

- Silent cable: Amplisilence, model E.
- Multisensory evoked potential: Amplaid, model MK 15.
- Headphone TDH 41. Electrodes, silver disc.

Pure Tone Audiometry

This test was carried out for all subjects of the study including air and bone conduction at frequencies from 250-8000 Hz air conduction and from 500-4000 Hz for bone conduction.

By this test, only subjects with normal hearing threshold, i.e. 25 dBHL at all tested frequencies, were included in the study.

Table (1) : Reaction Time to Sound (RT) and Accuracy* in Patients of Group (II) and the Controls.

Sub.	group I		group IIa		group IIb	
No.	RT in m.s.	Accuracy	RT in m.s.	Accuracy	RT in m.s.	Accuracy
1	311	100	380	100	401	80
2	318	100	323	100	400	100
3	380	100	311	100	402	100
4	310	100	374	100	430	100
5	320	100	389	100	470	80
6	343	100	374	100	405	100
7	390	100	351	100	430	100
8	396	100	318	100	580	70
9	371	100	397	90	403	100
10	350	100			451	80
11	341	100			407	100
12	379	100			412	90
13	315	100			424	90
14	363	100			571	80
15	362	100			400	
16	310	100			409	100
17					435	100
18					472	80
19					420	100
20					511	90
21					551	80
23					410	100
24					513	100
25					438	70
26					471	80
27					549	100
28					433	80
29					418	100
30					440	90

* Accuracy is the number of correct responses expressed as a percentage of the total stimuli.

Table (2): Bicohemical Measures of Hepatic Dysfunction for the three Groups (Serum Values).

Group		Total bilirubin (mg/d)	Albumin (g / L)	Total globulin (g / L)	SGOT (i.u. / L)	SGPT (i.u. / L)	Alk. phos. (i.u.)	Proth. time (sec)	Amm. nitr. (mg /L)
Group IIa	**Mean**	3.20	28.78	39.00	83.89	71.11	228.78	22.56	0.31
	S.D	1.50	4.73	2.91	18.20	14.49	33.25	3.44	0.07
Group IIb	**Mean**	4.17	26.33	42.03	94.77	82.40	232.60	22.17	0.45
	S.D	1.64	4.58	3.61	26.39	24.11	46.96	3.57	0.07
Group III	**Mean**	5.84	24.00	46.92	160.08	141.85	284.23	24.31	0.52
	S.D	1.48	3.42	5.90	56.10	49.40	76.69	4.30	0.04

Evoked Potential Recording :

The patient was instructed to keep calm in the supine position with his eyes closed.

Scalp electrodes and paste as the conducting medium were placed on the head according to the standard international 10-20 method.

Results

The values for results of wave latencies of P 300 and BAEPs latencies in the studied groups are presented in tables (3-5).

Event - Related Potential P 300 wave Latency:

The latency of P 300 wave was increased in the cirrhotic patients" group II and III" when compared with the controls "group I". (Table 3).

The differences were statistically significant ($p < 0.001$) when the control group was compared with the cirrhotic encephalopathic groups of either subclinical or overt encephalopathy"groups IIb and III respectively".

The difference was insignificant ($p < 0.05$) between the controls" group I " and the cirrhotic non-encephalopathic patients "group IIa".

The difference in P 300 wave latency was statistically highly significant ($p < 0.0001$) between the cirrhotic non-encephalopathic patients "group IIa" and the cirrhotic patients with" sub-clinical" hepatic encephalopathy "group IIb" (Table 4).

Brain Stem Auditory Evoked Potentials "BAEPs":

The values of the interpeak latencies I-III and III-V, and the absolute latency of wave V show statistically significant differences ($p < 0.026$, 0.006 & 0.002 respectively) between the controls" group I" and patients with overt hepatic encephalopathy "Group III" (Table 3). While no statistically significant differences were found when values of BAEPs were compared between group I and II (Table 3) or between groups II and IIb (Table 4).

Table (5) presents the sensitivity, specificity, accuracy and the positive and negative predictive values of P 300 and BAEPs in detecting cases of "subclinical" and overt hepatic encephalopathy respectively. Upper limit of normal for P 300 latency and BAEPs was taken as mean + 2.S.D. of control group.

The P 300 latency had a 58.97% accuracy with a positive predictive value of 10% in the assessment of patients with "subclinical" hepatic encephalopathy. While it had 100% accuracy with a positive predictive value of 100% in the assessment of overt hepatic encephalopathy. BAEPs has much lower diagnostic values in assessing both subclinical and clinical encephalopathy (Table 5).

Table (3) : Mean and Standard Deviation (S.D.) for the Evoked Potentials in Different Groups.

Test	Group I		Group IIa			Group IIb			Group III		
	Mean	S.D.	Mean	S.D.	*P*	Mean	S.D.	*P*	Mean	S.D.	*P*
P 300	341.68	19.22	353.44	16.27	0.15	380.73	11.77	0.000*	410.38	12.00	0.000*
I-III	2.19	0.20	2.16	0.20	0.72	2.23	0.24	0.602	2.46	0.38	0.026*
III-V	2.02	0.25	2.00	0.21	0.84	2.02	0.22	0.904	2.44	0.46	0.006*
V	5.19	0.36	5.85	0.37	0.93	5.95	0.30	0.676	6.60	0.67	0.002*

* = Significant

The "P" values calculated by comparing the different groups with the controls "group I".

Table (4): Mean and Standard Deviation (S.D.) for the Evoked Potentials in Groups II a and IIb

Test	Group I		GroupIIa		*P*
	Mean	S.D.	Mean	S.D.	
P 300	353.44	16.27	380.73	11.7	0.000*
I-III	2.16	0.20	2.23	0.24	0.452
III-V	2.00	0.21	2.02	0.22	0.777
V	5.85	0.37	5.95	0.30	0.747

* = Significant

Table (5) : Accuracy of P 300 and BAEP s in "Subclinical" and overt he Patic Enecepathy

Test	Sens.	Spec.	Accur.	PVP	PVN
Subclinical HE:					
P 300	46.66 %	100.00 %	58.97 %	100.00 %	36.00 %
I-III	16.66 %	94.44 %	34.61 %	90.90 %	25.37 %
III-V	0.00 %	100.00 %	23.07 %	0.00 %	23.07 %
V	0.00 %	100.00 %	23.07 %	0.00 %	23.07 %
Overt HE:					
P300	100.00 %	100.00 %	100.00 %	100.00 %	100.00 %
I-III	61.45 %	94.44 %	75.00 %	94.12 %	62.96 %
III-V	53.85 %	100.00 %	72.73 %	100.00 %	60.00 %
V	42.31 %	100.00 %	65.91 %	100.00 %	54.55 %

Sens. = Sensitivity
Spec. = Specificity
Accur. = Accuracy
PVP = Positive predictive value
PVN = Negative predictive value

Discussion

Hepatic encephalopathy "HE" represents a group of neurologic signs and symptoms accompanying advanced, decompensated liver disease of all types [1]. The identification of patients with HE has important therapeutic and prognostic implications.

Early diagnosis may improve patient management and, hopefully, the patient's quality of life [3]. Detection of cases with "subclinical" hepatic encephalopathy "SHE" is potentially important as it may be associated with impaired functional capacity and job performance [1]. Schomerus et al [5] have estimated that 60% of patients with SHE in their study were unfit to drive. Clinical diagnosis at this stage depends on a high index of suspicion, and thorough examination of mental status does not "objectively" detect the incidence of SHE [4].

Psychometric tests are useful screening tests in the clinical context, and when doubt exists, electrophysiological tests should be used [3]. However, the electroencephalogram provides a non specific index of electrical brain dysfunction that has been empirically related to the degree of encephalopathy. In general, the electrical waves progressively decrease in frequency and increase in amplitude as encephalopathy becomes more advanced but exactly what is being measured and its relationship to the cause and degree of hepatic encephalopathy in interpretation, although computerized techniques may minimize this problem.

In our study, psychometric assessment elucidated that only 9 patients (23%), out of 39 patients with liver cirrhosis without overt HE, showed normal results in psychometric testing (Table 1).

This means that there is a high incidence of patients (77%) that were apparently normal, yet the psychometric tests detected them as having SHE. These results are in agreement with those of Gitlin et al [7] who stated that three quarters of their patients with cirrhosis, and seemingly normal neurological and mental status, fail pscychometric test. They also claimed that impairment in performance is more marked than verbal skills. Morgan and Stranger [8] found that only 18% of 71 cirrhotic patients attending an out patient clinic gave normal psychometric test, 48% had subclinical and had 34% overt encephalopathy.

However, the performance of psychometric tests is influenced by the patients' intelligence and his cultural and educational level. Studies of the visual and somatosensory responses have indicated that evoked responses (ER) may be sensitive indicators of central nervous system dysfunction in the early stages of HE [9, 10].

Although HE does appear to affect early brainstem components of the auditory evoked responses [10], later components have not been systematically investigated to any great extent [11].

Of great potential interest is the P 300 component because there is general agreement that its latency provides a good measure of stimulus processing time within the central nervous system independent on the time required for response selection and execution [12, 13, 3].

Brainstem auditory evoked potential BAEPs and event related potential P 300 wave latency, as objective markers of SHE, were used in our study.

BAEPs demonstrated a statistically significant delay in interpeak latencies I-III and III-V and the absolute latency of wave V in patients with overt HE when compared with the controls ($p < 0.026$, 0.006 & 0.002 respectively).

However, no significant differences were found between the cirrhotic nonencephalopathic patients (Group IIa) and patients with SHE (Group IIb) when compared to each other (Table 4) and between either of them when compared to the controls (Table 3). These findings are consistent with those reported by Sandford et al [14] Chu and Yang [5] and Davies et al [16].

In contrast, our findings contradicted those of Mehandiratta et al [17] who reported that BAEPs were found to be sensitive parameters for the detection of SHE.

As regards the auditory P 300 wave latency, our study clarified that a statistically significant difference in wave latencies was found between patients with either overt HE (Group III) or subclinical HE (Group IIb) and the controls ($p < 0.0001$) (Table 3).

The difference in latencies was not found to be statistically significant between patients with (Group IIa) and the controls.

Of note, a statistically highly significant difference ($p < 0.0001$) was found when the records of the P 300 wave latency were compared in patients with SHE (group IIb) and patients with liver cirrhosis without encephalopathy (group IIa) (Table 4). This would suggest that P 300 wave latency would play a role in the detection of SHE among patients with overt HE, while the test was found to be 58.97% accurate in detecting cases of SHE (Table 5).

These findings are in line with the results reported by Davies et al [3,16].

The delays in the P 300 wave latency may indicate that encephalopathic patients have a deterioration in their stimulus evaluation abilities [3].

These tests appear to provide a simple and "objective" index of central nervous system dysfunction in HE.

So, P 300 wave latency may have a role in assessment of patients in and out the hospital and in follow up of their response to therapy. However, it's not yet known whether the delay in P 300 wave indicates that patients with SHE are at risk of developing overt encephalopathy and might justify prophylactic treatment, or only reflects

cognitive dysfunction that could affect job performance.

One may come to the conclusion that P 300 wave latency is extremely helpful in detecting cases with SHE, and consequently it may be considered the best index of the occurrence of SHE in patients with liver cirrhosis.

Therefore, this test may be performed for each patient with this diagnostic possibility to help identify those at risk of developing overt encephalopathy.

On the other hand, BAEPs are better reserved to assess and follow-up patients with more advanced encephalopathy.

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