# Auditory P300 Event-Related Potential in Detection of Subclinical Hepatic Encephalopathy in Children

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**Abstract**

Subclinical hepatic encephalopathy (SHE) is difficult to assess. Thus, the aim of this study is to evaluate the role of auditory P300 event-related potentials (P300 -ERP) in assessing SHE in children with chronic liver disease (CLD). Twenty children suffering from CLD with no clinical evidence of hepatic encephalopathy (HE) aged (6 - 15) years were selected for the study from the Specialized Hepatology Outpatient Clinic, Children Hospital, Ain Shams University. They were matched for age, sex, education and social class with 20 healthy children to act as controls. Both groups were subjected to medical and neuropsychiatric history and clinical examination; complete blood picture, liver function tests, hepatitis markers, urine and stool analysis and abdominal ultrasonography. They were subjected to psychological testing using Wechsler Intelligence Scale for Children (WISC-R), Benton test, Trail Making Test. as well as auditory P300-ERP was performed at the Institute of Psychiatry, Ain Shams University. Results: All (100%) of patients were diagnosed by P300 as having SHE while 80% were diagnosed by all the psychometric tests together. Benton test, Trail Making Test part B, digit symbol and coding were abnormal in 70%, 45%, 40%, and 35%, respectively. In CLD patients the mean P300 peak latencies were significantly increased while the amplitudes were significantly shortened than controls. Severity of liver disease and presence of portal hypertension were related to the increased latencies of P300, while duration of disease was not correlated with latency but with amplitude. Digit span was significantly correlated with P300 at Cz and Pz ($r = .48, .54$ respectively). All latencies N100, P100, N200 and P200 were not affected by CLD. It is conclude that auditory P300-ERP is a sensitive measure to detect SHE in CLD children. Typical changes include latency prolongation and decreased amplitude. All patients showed abnormal results on P300 testing, which is likely reflecting early impairment of cognitive function in CLD in the form of impairment in attention and short term memory as well as information processing. Auditory evoked P300 potentials are more sensitive than psychometric testing alone. The correlation of P300 with the severity of liver disease suggests that these problems may become more severe as the underlying disease progress.

## Introduction

Patients suffering from chronic liver disease (CLD) show abnormalities in the central nervous system. Clinical manifestations of hepatic encephalopathy (HE) include a decreased intellectual function, personality disorders, an altered level of consciousness, and neuromuscular dysfunction *(Groeneweg et al., 1998)*. Traditionally HE is graded into four clinical stages of severity, ranging from abnormal behavior to coma *(Sherlock and Dooley, 1998)*. In addition to clinical grading of HE, a subclinical stage has been described, in which patients with CLD, regardless of its cause, show a number of quantifiable neuropsychological and neuro-physiological defects, yet have a normal mental and neurological status on global clinical examination *(Gitlin et al., 1986 and*

*Watanabe, 1998).* The prevalence of this subclinical hepatic encephalopathy (SHE) has been reported in adults to vary from 30% to 84%, depending on the kind and number of tests and population used *(Quero et al., 1996*). Despite the subtle nature of subclinical encephalopathy, it may have a profound effect on the performance of these subjects, especially in those individuals who have perform intellectual tasks *(Edwin, 1999).*

Neuropsychological tests were used in the diagnosis of SHE particularly and digit symbol, digit span and block design which are subtests of Wechsler Intelligence Scale and Trial Making Test (TMT) part B. However, neuro-psychological testing is biased by education, intelligence, compliance, age, and learning effects. Because early diagnosis and treatment of SHE have been suggested to be critical for the preservation of cerebral function, efforts have been made to apply other, more objective and reliable methods in the diagnosis of HE *(Geissler et al, 1997).*

Various neurophysiological investigations including electro-encephalography (EEG) and evoked potentials have tried to quantify the neurological alterations, which occur during HE and identify early signs in clinically asymptomatic patients. However, conventional EEG sensitivity reflects only the clinical but not the subclinical stages of HE *(Gallai et al., 1995).* Furthermore, stimulus-dependent evoked potentials (visual, brain stem and somatosensory) were relatively insensitive for detecting early HE *(Watanabe, 1998).*

The P300 event-related potential is an objective measure of selective attention and mental tracking, it is regarded as the neurophysiological correlate of cognitive functions such as decision making, information processing and short-term memory *(Lishman, 1998).*

In the literature, very few studies were done using P300 event - related potential in-patients with CLD. They detected minor cognitive deficits in patient with no clinical HE *(Hollerbach et al., 1997).* However, none were done, to our knowledge, in children.

Thus, the aim of the study to evaluate the role of auditory P300 event-related potential in assessing SHE in children with CLD by detection of SHE using P300-ERP, and determine its prevalence. Also, to assess diagnostic value in relation to neuropsychological tests and to other components of auditory ERP as well as its relationship with parameters of liver disease as severity, presence of portal hypertension and duration of illness.

## Subjects and Methods

### Subjects

*Patient group*: Twenty CLD children were selected from the Hepatology Specialized Clinic Children's Hospital, Ain Shams University with age ranged (6-15) years old. They were 12 males and 8 females. They suffered from CLD with different etiologies. The Wilson disease child had no neurological or psychiatric manifestations. All the patients had no apparently HE on clinical examination.

***Control group:*** They were composed of 20 healthy children matched to the patient group in age, sex, education and social class. They had no liver disease or a history of hepatitis or Schistosomiasis.

Both patients and control were co-operative patients, with intact auditory function, with no past or present history of significant

neither medical nor neuro-psychiatric disease.

## Methods

*Both patients and controls were subjected to the following:*

1- Full history and thorough clinical examination, the patient group showed history of liver disease, physical signs of liver impairment and clinical evidence of HE.

2- *Complete psychiatric examination*

3- *Laboratory investigations*:

- Complete blood picture.
- Liver function tests serum enzymes - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) - total serum bilrubin, serum albumin, prothrombin time,
- Hepatitis viral markers.
- Urine and stool analysis

*4-Abdominal ultrasonography*

5- For *patients only: Upper endoscopy and histopathological examination of liver biopsy specimens.*

*6- Assessment of severity of liver disease:*

The Child-Pugh score and Child grading were used to assess the severity of liver disease. Three biochemical variables (serum albumin, bilirubin and prothrombin time) in addition to the two clinical characteristics (presence or absence of ascites and clinical signs of encephalopathy) determine the Child-Pugh score. Each variable is given 1 to 3 points, leading to scores ranging from 5 (excellent liver function) to 15 points (poor liver function). Grade A = 5 - 6 points, Grade B = 7 - 9 and Grade C = 10 - 15 points. In this study 11 were class A and 9 were class B *(Sherlock and Dooley, 1998).*

*6- Neuropsychological tests using:*

*A- Wechsler Intelligence Scale for Children-Revised (WISC-R)*: It is formed of two scales

*1.Verbal Scale*: composed of Comprehension subtest to assess common sense and verbal reasoning; arithmetic subtest to assess problem solving; similarities subtest to measures ability to make verbal abstraction; and digit span subtest to assess short-term memory and attention.

*2.Performance Scale: composed of* picture completion subtest to measures perceptual reasoning; block design subtest to measures visuospatial ability; coding subtest (equivalent to adult digit symbol subtest) to measures the motor speed and accuracy *(Wechsler,1998).*

*B- Benton Test (Visual Retention Test):* Assess visual perception abilities and memory for geometric forms. It puts stress on the memory capacity. Age range between 8 - 15 years *(Anastazi, 1990).*

*C- Trail Making test for children*: It is composed of 2 forms A and B. Its age range is (9 - 15) years. It is a neuropsychological test particularly used for diagnosis of organic brain damage. This test measures cognitive motor abilities. It measures the visuospatial ability. A low score indicates a good performance. Normal values are expressed as the mean 2 ± standard deviation *(Retain, 1986).*

This test battery takes more than an hour to be performed.

*6- Auditory P300 Event-Related Potentials (ERPs):*

The main principal of the test to detect cognitive abnormalities (dysfunction) is that the incoming sensory stimuli are associated with brief changes in brain potentials, and these can be detected when suitable averaging stimuli are used to demarcate them from the background EEG activity. Successive epochs of EEG are summated and averaged by computer while repeated auditory stimuli being presented to the subject.

ERPs were recorded with the oddbali paradigm consisting of the presenting of target and frequent stimuli via a binaural modality through earphones. The active disc scalp electrodes were set at Fz, Cz and Pz.

The children were informed that they would hear low pitched (1000 - HZ) tones interspersed occasionally with high - pitched (2000-HZ) tones, and that they were required to silently count the high pitched tones. They were told that at the end of the trial. They would be asked how many high tones they heard. Subjects were assessed for hearing threshold first.

Latency was calculated as the point of maximum deflection from the onset of stimulus. The following components were measured for amplitude (micro-volts = uv) and latency (milliseconds = ms): N100, P200, N200 and P300. ERP curve is composed of a negative wave (N100) occurring between 70 - 150 ms and a positive wave (P200) between 7150 - 225 ms. In the average response to frequent stimuli P300 is a positive wave between 280 - 480 ms; and N200 is the most negative wave immediately preceding P300 in the average response to rare stimuli *(Lishman, 1998).* A peak latency or amplitude of higher than 2 SD than that of healthy controls were considered abnormal *(Hollerbach et al., 1997).* It takes ten minutes to be performed.

*Statistical analysis:*

The Computer Package SPSS version 8 was used to analyze the data. All the results were expressed as means and standard deviations (SD). Comparisons of means were made by student t test for parametric data while Kruskal-Wallis test for the non-parametric. To correlate between two continuous variables the Pearson correlation coefficient (r) was computed. The P value was considered significant at the level $p <. 05$.

**Results**

*Table (1)* shows the clinical and biochemical characteristics of the CLD children.

*Table (2)* shows the percentage of abnormal event-related potential and psychological tests. It has to be noted that 3 cases that had normal Pz P300 latency did not perform Trail making test nor the Benton test (they were below the age). Only one patient had a normal P300 latency in all its regions however she had abnormal P300 amplitude. P300 was abnormal in 100% of patients. Benton test, TMT part B, coding and digit span were abnormal in 70%, 45%, 40% and 35%, respectively. About 80% of CLD patients had at least an abnormal psychometric test. The healthy children did not show abnormal results on tests performed.

*Table (3)* shows the means and standard deviation of the latencies of N100, P200, N200 and P300 of chronic liver disease children. There were no significant differences between the means of the two groups in all latencies except P300 at all the zones. There were significance difference

between both groups as regards the amplitude at Fz and Cz.

*As regard to severity of liver diseases* according to modified Child classification, 11 patients were Child A (less severe) while 9 were Child B (more severe). There were significant differences between the means of the two groups in all zones of P300 *(table 4)*. Also, there were significant differences between both groups in the latencies of the central zone of P200 (p =. 017). On the other hand, there were no significant differences as regards the remaining latencies and the P300 amplitude as well as all the psychometric tests.

The CLD children were divided into two groups according to the presence (n=13) or absence (n=7) of *portal hypertension*. There were no significant differences between the two groups as regards the latencies of N100 and P200, amplitude of P300 as well as the psychometric tests. However, there were significant differences between both groups as regards to the latency of parietal zone (p = .01) of N200. Also, there were significant differences between both groups as regards the latency of the central and parietal zones of P300 (p =. 019 and .012 respectively) but not that of the frontal zone (p = .08).

*Correlation between P300 and psychometric tests:*

There were no significant correlation between the latencies of P300 and the psychometric tests in all the areas except the Digit Span sub-test which was negatively correlated to the latency of parietal zone (r = - .49 p = .028).

There was no correlation between the duration of disease in years and all the psychometric tests (total, verbal, performance IQ on the WISC test and all its sub-scales, as well as the Trail making test (A and B) and the Benton visual test.

*Table (5)* shows the correlation between the duration of disease and auditory P300 event-related potentials.

**Table (1): Clinical and biochemical data for children with chronic liver disease**

| | MEAN | SD |
|---|---|---|
| *Age* years | 9.55 | 2.98 |
| *Duration of illness* years | 4.6 | 2.98 |
| *liver function tests* | | |
| AST(IU/L) | 91.6 | 99 |
| ALT(IU/L) | 93.4 | 111 |
| Total Proteins | 6.8 | .7 |
| Albumin (g %) | 3.3 | .8 |
| Biluribin (mg %) | 1.6 | 2.2 |

**Table (1) Continue**

| | FREQUENCY | % |
|---|---|---|
| *Sex* | | |
| Males | 12 | 60 |
| Females | 8 | 40 |
| *Etiology* | | |
| Alpha 1-antitrypsin | 1 | 5 |
| Wilson Disease | 1 | 5 |
| Autoimmune hepatitis | 5 | 25 |
| Post hepatitis B | 3 | 15 |
| Biliary atresia | 1 | 5 |
| Cryptogenic | 5 | 25 |
| Portal vein thrombosis | 4 | 20 |
| ***Severity*** | | |
| Child A | 11 | 55 |
| Child B | 9 | 45 |
| *Former upper GI bleeding* | | |
| *No* | 16 | 80 |
| *Yes* | 4 | 20 |
| *Portal Hypertension* | | |
| No | 7 | 35 |
| Yes | 13 | 65 |

**Table (2): Prevalence of abnormal auditory event-related potential and neuropsychological tests and the diagnosis of SHE in chronic liver disease patients without clinical signs of HE**

| | No | Abnormal |
|---|---|---|
| Latency | | |
| N 100 | | |
| Fz | 20 | 4(20%) |
| Cz | 20 | 2(10%) |
| Pz | 20 | 0(0%) |
| P200 | | |
| Fz | 20 | 0(0%) |
| Cz | 20 | 0(0%) |
| Pz | 20 | 0(0%) |
| N200 | | |
| Fz | 20 | 0(0%) |
| Cz | 20 | 0(0%) |
| Pz | 20 | 6(30%) |

**Table (2) continue:**

| | | |
|---|---|---|
| **P300** | | |
| Fz | 20 | 7(35%) |
| Cz | 20 | 14(70%) |
| Pz | 20 | 17(85%) |
| **P300 Amplitude** | | |
| 4(20%) | 20 | 7 (35%) |
| 2(10%) | 20 | 0(0%) |
| 2(10%) | 20 | 2(10%) |
| **P 300 (Fz,Cz,Pz)** | | |
| Latency | 20 | 7 (35%) |
| Amplitude | 20 | 0(0%) |
| Latency and amplitude | 20 | 2(10%) |
| **WISC-R** | | |
| **Verbal subtests** | | |
| Comprehension | 20 | 0(0%) |
| Arithmetic | 20 | 1(5%) |
| Similarities | 20 | 0(0%) |
| Digit span | 20 | 7(40%) |
| **Performance subtests** | | |
| Picture completion | 20 | 2(10%) |
| Block design | 20 | 0(0%) |
| Coding( digit symbol) | 20 | 8(40%) |
| **Trail Making Test** | | |
| A | 11 | 1(9%) |
| B | 11 | 5(45.5%) |
| **Benton Test** | 10 | 7(70%) |
| **Psychological Test** | | |
| Digit span + coding | 20 | 11(55%) |
| Digit span +coding +TMT B+ Benton test | 20 | 16(80%) |

**Table (3): Comparison between patients and healthy children as regards to auditory event-related potential and neuropsychological tests**

| | MEAN ± SD | | T TEST | P VALUE | SIG |
|---|---|---|---|---|---|
| | PATIENTS | CONTROLS | | | |
| **N100 (ms)** | | | | | |
| Fz | 113.05 ± 36.1 | 107.8 ± 12.9 | 0.65 | 0.4310 | NS |
| Cz | 101.15 ±28.25 | 107.5 ± 26.4 | 1.56 | 0.2190 | NS |
| Pz | 85.00 ± 20.26 | 97.5 ± 12.1 | 2.37 | 0.1337 | NS |

**Table (3) continue:**

| | | | | | |
|---|---|---|---|---|---|
| **P200 (ms)** | | | | | |
| Fz | 170.90 ± 34.77 | 179.1 ± 31.6 | 0.51 | 0.485 | NS |
| Cz | 156.55 ± 26.35 | 170.9 ± 30.3 | 1.97 | 0.1708 | NS |
| Pz | 144.8 ± 32.47 | 162.8 ± 20.3 | 2.76 | 0.1666 | NS |
| **N200 (ms)** | | | | | |
| Fz | 251.85 ± 41.12 | 249.6 ± 59.9 | 0.02 | 0.890 | NS |
| Cz | 224.85 ± 27.30 | 225.3 ± 31 | 0.00 | 0.957 | NS |
| Pz | 225.45 ± 39.05 | 209.0 ± 22.0 | 1.64 | 0.210 | NS |
| **P300 (ms)** | | | | | |
| Fz | 321.75 ± 43.43 | 239.6 ± 45.6 | 34.04 | 0.000001 | **HS** |
| Cz | 294.55 ± 47.18 | 228.4 ± 26.8 | 5.48 | 0.0260 | **S** |
| Pz | 307.25 ± 45.0 | 221.4 ± 20.7 | 7.75 | 0.0098 | **HS** |
| **P300 Amplitude (*uv*)** | | | | | |
| Fz | -0.6 ± 3.4 | 4.5 ± 3.5 | 24.08 | 0.000014 | **HS** |
| Cz | 0.915 ± 2.02 | 4.0 ± 3.2 | 13.29 | 0.000729 | **HS** |
| Pz | 3.01 ± 3.49 | 1.4 ± 3.3 | 0.01 | 0.926 | NS |
| **WISC-R** | | | | | |
| Verbal IQ | 102.85 ± 11 | 1056 ± 9.2 | .78 | .443 | NS |
| Performance IQ | 92.1± 9.4 | 102.6 ± 10.5 | 2.9 | .006 | **HS** |
| Total IQ | 97.35 ± 11.7 | 102.8 ±10.3 | 1.53 | .134 | NS |
| **TMT (sec)** | | | | | |
| A | 49.5 ± 33.6 | 27.9 ± 6.2 | 2.1 | .06 | NS |
| B | 105.5 ± 60 | 35.3 ± 8.6 | 3.1 | .005 | **HS** |
| **Beton Test** | | | | | |
| **Correct** | -1.3 ± 1.7 | 1.2 ± .42 | 4.5 | .002 | **HS** |
| **Error** | 3.0 ± 2.2 | -2.2 ±.78 | 7.15 | .000 | **HS** |

**Table (4): Comparison of Latency of P300 as Regards to the Severity of Liver Disease According to Modified Child's Classification**

| P300 | MEAN ± SD | | P VALUE | SIG |
|---|---|---|---|---|
| | Child A (n= 11) | Child B (n = 9) | | |
| ***Latency (ms)*** | | | | |
| Fz | 304.27 ± 40.74 | 343.11 ± 38.38 | .05 | **S** |
| Cz | 268.09 ± 42.23 | 326.89 ± 30.33 | .004 | **HS** |
| Pz | 283.9 ± 42.32 | 335.78 ± 35.13 | .011 | **S** |
| ***Amplitude (uv)*** | | | | |
| Fz | -.67 ± 3.5 | .511 ± 2.5 | .552 | NS |
| Cz | 1.34 ± 2.2 | .39 ± 1.7 | .412 | NS |
| Pz | 3.45 ± 4.3 | 2.47 ± 2.4 | .456 | NS |

Child A: score between (5 - 6) less severe, Child B: score between (7 - 10) more severe

**Table (5): Comparison of Latency of P300 as Regards to the Presence of Portal Hypertension**

| P300 | MEAN ± SD | | P VALUE | SIG |
|---|---|---|---|---|
| | Portal H (n= 13) | No Portal H (n = 7) | | |
| ***Latency (ms)*** | | | | |
| Fz | 304.27 ± 40.74 | 343.11 ± 38.38 | .08 | **S** |
| Cz | 268.09 ± 42.23 | 326.89 ± 30.33 | .019 | **S** |
| Pz | 283.9 ± 42.32 | 335.78 ± 35.13 | .012 | **S** |
| ***Amplitude (uv)*** | | | | |
| Fz | -.67 ± 3.5 | .511 ± 2.5 | .552 | NS |
| Cz | 1.34 ± 2.2 | .39 ± 1.7 | .412 | NS |
| Pz | 3.45 ± 4.3 | 2.47 ± 2.4 | .456 | NS |

**Table (6): Correlation between Duration of Liver Disease and Auditory P300 Event-Related Potentials**

| P300 | Correlation coefficient | Significance |
|---|---|---|
| ***Latency (ms)*** | | |
| Fz | 0.02 | NS |
| Cz | -.02 | NS |
| Pz | 0.2 | NS |
| ***Amplitude (uv)*** | | |
| ***Fz*** | 0.25 | NS |
| ***Cz*** | 0.48 | **S** |
| ***Pz*** | 0.54 | **S** |

* Correlation is significant at the 0.05 level

**Discussion**

The generation of P300 potential is associated with functions such as attention and short - term memory during cognitive tasks. The P300 potential has been found to be abnormal in metabolic and degenerative encephalopathy *(Ruzicka et al., 1993)*.

In the present study, we found a significant increase in mean latency of the P300 in the diseased than healthy controls. The P300 latency is correlated with the time necessary to complete the cognitive task. The latency increase of this potential is due to the fact that patients take longer time to process the stimulus than controls This denotes attention and memory impairments *(Gallai, 1995)*.

It was confirmed in the current study a distinct increase in the P300 peak latencies in 19 out of 20 patients (95%) (abnormal prolonged P300 latency above 2SD of normal control) with no clinical evidence of HE. Our finding differ from those of *Weissenborn and his collogues 1990*, who were the first to examine patients with non-alcoholic cirrhosis of liver by using auditory P300 potentials. These investigators found abnormally prolonged P300 latencies in 30% of their patients with no overt HE. Also, *Gallai (1995)* found that 54.5% with patients with no clinical HE had significantly increased P300 peak latency. However, other studies *(Davies et al., 1990)* found increased P300 latencies only in patients with clinically overt HE.

The higher prevalence of P300 abnormalities in this study than the others could be due to that other studies were done in adults while this study was done in children. The developing brain of the child might be more vulnerable to the cerebrotoxic effects of the liver disease *(Stewart et al., 1992)*. Also, malnutrition that is common in chronic liver disease *(Shepherd, 1999)* has a deleterious effect on the growing brain in children particularly anemia *(Wasantwisut, 1997)*, zinc *(Black, 1998)* and vitamin E *(Stewart et al., 1992)*. Also, it might be that P300 detect cognitive impairment more sensitive in children than in adults.

The maximal P300 amplitude was significantly lowered in patients with CLD in the frontal and central cortical regions (Fz: $p < .0000$; Cz: $p < .0007$, respectively). This is in accordance with the study done in adults by *Hollerbach and his colleagues (1997)*. Reduction in P300 amplitude has been related to cognitive deficits *(Lishman, 1998)*.

These, the changes in P300 parameters indicate brain dysfunction even with no clinical evidence of hepatic encephalopathy the so-called subclinical hepatic encephalopathy (SHE).

In this study, there were no significant differences between CLD and healthy children as regards all latencies N100, P100, N200 and P200 except the auditory P300 event-related evoked potential.

Psychometric testing is a well-known method for diagnosing and measuring SHE. About 80% of CLD children had abnormal psychometric testing (at least one test abnormal, on the commonly used tests in the diagnosis of SHE. Benton test, Trail Making test part B, coding and digit span were abnormal in 70%, 45%, 40% and 35%, respectively.

Although, psychometric tests has been established as a standard tool for the diagnosis of SHE (*Hollerbach et al., 1997)*. Some 20% of patients were normal in all

the psychometric tests administered. However, 100 % showed abnormal results during P300 testing (both latency and amplitude), which is likely to reflect early impairment of cognitive function. Thus, auditory P300 event-related potential is more sensitive than psychometric tests in detecting SHE.

All patients with CLD who had no encephalopathy on clinical examination and on psychometric testing proved to have cerebral dysfunction as measured by auditory P300 event-related potential. Neuroimaging studies had supported these findings, *Geissler et al., (1997)* reported that all patients with cirrhosis had abnormalities of cerebral metabolism detected by proton magnetic resonance spectroscopy and magnetic resonance imaging.

The clinical importance of early detection of brain dysfunction remains to be determined. It is possible that neuropsychologic impairment in SHE might be reversible to a greater extent by treatment with agents such as lactulose or branched chain amino acids or with earlier liver transplantation *(Ross et al., 1994)*. Thus, the ability to detect SHE in CLD children may make the auditory P300 event-related potential of diagnostic value, providing an opportunity for preventive therapies.

In the current study, the centro-parietal areas were the most affected centers in-patients of subclinical hepatic affection. This is not manifested only by P300 affection but also by the affection of coding and digit span sub-tests, Benton visual retention test and Trail making test part B, which need the integrity of parietal lobe functions *(Strub and Black, 1997)*.

In this study, patients with liver disease were found to have a good correlation between digit span (subscale of attention and immediate memory) and P300 latency. This could be that P300 is an objective measure of selective attention and short-term memory *(Lishman, 1998)*.

The intellectual deficit pattern revealed that differences in verbal IQ were minimal and non-significant, while differences in performance IQ were significant. This is in accordance with other studies *(Gitlin et al, 1986 and Sood et al., 1989)*. This could be the reason why patients with liver disease with cognitive dysfunction were not detected clinically *(Gitlin et al, 1986)*.

The neuropsychological defects found in SHE may have a negative effect on patients' daily life, In addition, these defects are considered to be a preclinical stage of clinical manifest of HE *(Quero et al., 1996)*.

According to the traditional concept, HE can be explained as the consequence of 2 major components: vascular rearrangement (ie portosystemic shunting) and hepatocellular insufficiency. Thus, both factors were examined *(Sherlock and Dooley, 1998)*.

As regards to severity of liver disease, in this study, we failed to find a significant relationship between severity of liver disease and all the psychometric tests used. This is in accordance with several other studies *(Gitlin et al, 1986; Sood et al., 1989; and Farid, 1998)*. Despite that children with grade A (less severe) had better means in all the psychometric tests used than grade B yet they did not attain a significant difference.

However, in this study, there were significant increases in the auditory evoked

P300 latencies in children with more liver impairment as assessed by modified Child's classification. This could be due to that P300 is much more sensitive tool in children than the psychometric tests. The increased latency means that the patients take longer time to process the stimulus. This indicates more cognitive impairment and brain dysfunction with the more severe group (grade B). However, *Hollerbath et al. (1997)* reported in adults that P300 latency was independent from the severity of liver disease. The reason for this difference could be due to the difference between adults and children. The correlation of P300 with the severity of liver disease suggests that these problems may become more severe as the underlying disease progress.

As regards to presence of portal hypertension, there were significant differences between both groups as regards the latency of the central and parietal zones of P300 ($p = .019$ and .012 respectively) but not that of the frontal zone ($p = .08$). As the P300 generators are more from the centro-parietal zones *(Knight, 1997)*. However, there were no significant differences as regards to all the psychometric tests used. This could be explained by that P300 is more sensitive in detecting cognitive dysfunction.

There were no significant correlation between duration of liver disease and all of the neuropsychological tests and the auditory P300 latencies.

However, there were significant correlations between duration of disease and the P300 amplitude at the central and parietal zones. Patients with longer duration of disease had shortened amplitude. Further research is needed to clarify this finding. It has to be taken with caution, as chronic liver disease may be asymptomatic for a long time before seeking medical advice.

Neuropsychological testing is biased by education, intelligence, compliance, age and learning effects. Also, Benton test can not be applied before 8 years of age while the Trail Making test not before 9 years. On the other hand, auditory P300 event-related potential could be applied at a younger age. This is an advantage of it over the psychometric tests. Since it is more sensitive, objective, less time consuming and has a larger spectrum of age. Hence, it is recommended that those children with chronic liver disease should be examined with P300 for early detection SHE. These deficits or cerebral dysfunction could make these children vulnerable to learning disabilities. Early detection of this vulnerability could result in early intervention with the possibility of remediation for future patients *(Stewart et al., 1992)*. Assessment for learning difficulties should become a routine part of the schooling of chronic liver disease. This is especially important as pediatricians and child psychiatrists focus on 'quality of life ' issues for children.

Thus, it was concluded that all patients with chronic liver disease who had no encephalopathy on clinical examination proved to have cerebral dysfunction as measured by auditory P300 event-evoked potential. P300 evoked potential is a very sensitive objective measure to detect functional cognitive impairment in cirrhotic children with subclinical hepatic encephalopathy. Typical changes include latency prolongation and decreased frontal and central peak amplitude. Auditory P300 evoked potentials are more sensitive than psychometric testing alone in detection of SHE. Severity of liver disease and presence

of portal hypertension were associated with prolonged latency while long duration of disease is associated with shortened amplitude. Severity of liver disease is an important variable in predicting the severity of cognitive dysfunction as shown in this study.

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## الجهد المستثار المرتبط بالحدث السمعي ب ٣٠٠ لاكتشاف اعتلال الدماغ الكبدي غير الظاهر إكلينيكيا لدي الأطفال

نظرا لصعوبة قياس اعتلال الدماغ الكبدي غير الظاهر إكلينيكيا فقد هدفت هذه الدراسة الى تقييم دور ب ٣٠٠ من الجهد المستثار المرتبط بالحدث السمعي في اكتشاف و قياس اعتلال الدماغ الكبدي غير الظاهر إكلينيكيا لدى الأطفال المصابين بمرض الكبد المزمن. تم اختيار عشرون طفلا من عيادة الكبد التخصصية بمستشفى

الأطفال جامعة عين شمس مصابين بمرض الكبد المزمن مع عدم وجود دليل إكلينيكي على إصابتهم باعتلال الدماغ تتراوح أعمارهم من ٦ إلى ١٥ عاما. و تم اختيار عشرون طفلا من الأصحاء يتماثلون في العمر و الجنس و التعليم و المستوى الاجتماعي مع مجموعة المرضى. و قد تعرضت المجموعتان إلى أخذ تاريخ و فحص طبي و نفسي مع عمل فحص إكلينيكي شامل بالإضافة إلى إجراء اختبارات معملية تتمثل في وظائف الكبد و صورة دم كاملة و تحليل بول وبراز و أشعة تلفزيونية على البطن. و قد أجريت اختبارات نفس عصبية منها اختبار وكسلر لذكاء الأطفال، و اختبار بنتون للذاكرة البصرية، واختبار اقتفاء الأثر، كما تم قياس الجهد المستثار المرتبط بالحدث السمعي ب٣٠٠ في معهد الطب النفسي بكلية الطب جامعة عين شمس.

و قد وجد إن جميع الأطفال المرضى (١٠٠%) قد تم تشخيصهم باعتلال الدماغ الكبدي غير الظاهر إكلينيكيا باستخدام ب٣٠٠، بينما تم تشخيص (٨٠%) منهم فقط عندما استخدمت جميع المقاييس النفسية في آن واحد. و قد كشف استخدام كل من اختبار بنتون و اقتفاء الأثر و الشفرة و إعادة الأرقام عن أداء غير طبيعي لدي ٧٠%، ٤٥%، ٤٠%، ٣٥% من الأطفال المرضى على الترتيب.و قد تبين أن شدة مرض الكبد ووجود ارتفاع في ضغط الدم البابى لهما علاقة بزيادة طول ب٣٠٠، و أن هناك علاقة بين طول فترة المرض و شدة ب٣٠٠. كما أن جميع الموجات ن١٠٠، ب١٠٠،ن٢٠٠، ب٢٠٠ لم تتأثر بمرض الكبد المزمن.

لذا فأننا نخلص إلى: أن ب ٣٠٠ من الجهد المستثار المرتبط بالحدث السمعي لهو وسيلة دقيقة لاكتشاف اعتلال الدماغ الكبدي غير الظاهر إكلينيكيا في الأطفال المصابين بمرض الكبد المزمن. و تشمل التغيرات في ب٣٠٠ على زيادة زمن الكمون (تأخر الاستجابة) و قصر مداها لدى جميع المرضى بما يعنى بداية قصور في الوظائف المعرفية تتمثل في قصور في الانتباه و الذاكرة القريبة و تجهيز المعلومات في مرضى الكبد المزمن. أن ب٣٠٠ من الجهد المرتبط بالحدث السمعي يعد اكثر حساسية من الاختبارات النفسية، و أن العلاقة بين ب ٣٠٠ و شدة المرض تنبئ بزيادة هذا القصور عندما تسوء حالة الكبد.

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