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Different check sizes pattern-reversal visual evoked potentials study in patients with compensated hepatic cirrhosis

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Abstract---Background: Cirrhosis is a dynamic process starts after sustained inflammation, followed by necrosis of liver cells and fibrosis that occur as a normal wound healing response then nodular formation that eventually lead to hepatic dysfunction. Aim and objectives: Study the effect of hepatic cirrhosis on cerebral cortex and subcortical pathways using VEP, and Comparison between different VEP check sizes in detection of early encephalopathy among cirrhotics. Subjects and methods: This was a case/control study carried out on 45 cirrhotic patients, and 45 matched normal controls.

All subjects underwent full ophthalmological assessment prior to the conduction of the PVEP, after the approval of the ethical committee. Results: the studied cases had significantly more delayed latency and lower amplitude than the studied controls on both sides at both 1 degree and 15 minutes check sizes ($P\text{-value} < 0.05$), however 13 patients were detected by the 15 min check size to be abnormal on the contrary of the 1 degree check size that detected changes only in 6 patients. Conclusion: Vep 15 min is more sensitive in detecting early changes in cirrhotic patients, denoting that most of the hepatic encephalopathy changes are affecting the central visual field.

Keywords---visual evoked potentials, hepatic cirrhosis, minimal hepatic encephalopathy.

Introduction

Over the past two centuries, the term “cirrhosis” was a synonymous description for the end-stage of chronic liver diseases regardless the etiology (Ivanova, 2016). After many researches and clinical reports, cirrhosis terminology has gone far beyond the restricted view of being a mark of end stage liver disease; it is now known to be a heterogeneous condition that includes multi-stages with variable prognosis (Ivanova, 2016). Cirrhosis staging ranging from an early asymptomatic stage that is called compensated cirrhosis to a late progressive stage with many complications that is called decompensated cirrhosis (Samonakis et al., 2014). The rate of transition from the compensated and decompensated stages is almost 5%-7% per year (Ivanova, 2016).

One of the typical cirrhotic neurological complications is hepatic encephalopathy. It is a syndrome presented with a wide spectrum of neurological and psychiatric manifestations; in its mild form it is called minimal hepatic encephalopathy (MHE) (Samonakis et al., 2014). MHE is one of the most debilitating complications, it affects the quality of life of the patient in addition to increase the socioeconomic burden on the family members and caregivers Ridolaa et al., 2018. Neurophysiological investigations helps in assessment of the neuronal and electrogenesis via a functional point of view. Also, have been used for quantitative assessment and follow-up of several diseases El-Sherif et al., 2018.

Visual electrophysiology is a simple, non-invasive, objective and reliable method. However Visual evoked potentials (VEPs) were first described to assess abnormalities only in the visual system; they are now widely used in evaluation of different neurological and metabolic disorders Zhang et al., 2013. Visual Evoked Potentials (VEPs) are electrophysiological responses generated in the cortical and sub-cortical visual areas in response to stimulation of the retina with light Whatham et al., 2014. patterned stimuli are called “Pattern VEPs” (PVEPs) whereas unpatterned stimuli are called “flash VEPs” (FVEPs) Pojda-Wilczek et al., 2019.

The visual evoked potential (VEP) responses are recorded according to International society for the clinical electrophysiology of vision (ISCEV) standard

from the occipital electrode (Oz) as the active electrode and a mid-frontal electrode as the reference one (Fz) . Odom et al., 2016. The response consists of 3 components (often named “peaks” (referring to mean latency in msec, at which the response will occur after stimulation)), they are marked as N1 or N75, P1 or P100 (representing the most stable component of the response) and N2 or N145. N and P refers to as negative or positive deflection Jancic et al., 2016. The clinical interpretation of PVEP is mostly based upon the latency of P100 and to a much lesser extent on its P100 amplitude Jancic et al., 2016.

In 2014, Phurailatpam by using intracerebral recording in humans, they found that P100 appears to be generated by the pyramidal cells in layer IV of area 17. Imaging studies point to the source of the early phase of P100 peak in the dorsal extrastriate cortex of the middle occipital gyrus, whereas the late phase of P100 appears to be generated by the ventral extrastriate cortex of the fusiform gyrus. The VEP is primarily a reflection of activity originating in the central 3° to 6° degrees of the visual field Phurailatpam, 2014; or central 8-10 degrees of the visual field. Jancic et al., 2016 The central retinal projections are relayed to the surface of the occipital lobe, while the peripheral ones are directed to deeper regions within the calcarine fissure. hence, scalp electrodes that pick up the signals directly from the cortical tissue , receive mainly the central inputs, therefore VEPs tends to be attenuated or even unrecordable when the peripheral retina is stimulated. Phurailatpam, 2014

Large check sizes greater than 30 minute of arc will allow the recording of signals outside the central 3° but not beyond 10° of the visual field. Phurailatpam, 2014. Jeon et al., 2012 and Jancic et al., 2016 demonstrated that the responses to smaller checks are more sensitive to disorders of the visual pathway and they are also more affected by defocusing and amblyopia. The visual system processes information along multiple parallel channels. The optic tract starts from the optic chiasma and terminates in the lateral geniculate body. From the lateral geniculate body, visual information is transmitted to striate area 17 through two principal pathways. Magnocellular (M pathway), which is sensitive to low spatial frequency (large checks) and parvocellular (P pathway), which is more sensitive to high spatial frequency (small checks). Kothari et al., 2014 ; Abdelkader, 2016.

VEPs are influenced by optic nerve diseases, demyelinating processes, disorders of either subcortical or cortical neurons of brain hemispheres, metabolic abnormalities, traumatic brain injury and the use of psychoactive medications. Amodio & Montagnese,2015, the magnitude of the PVEP abnormality is correlated with other measures of injury severity such as the extent of cognitive impairment. Jancic et al., 2016. VEP recordings have been used in evaluation of hepatic cirrhosis and minimal hepatic encephalopathy. It showed promising results in detection of minimal hepatic encephalopathy El-Sherif et al., 2018.

Several researches have been done to investigate the role of VEPs in the detection of cortical affection among cirrhotic patients (Guerit et al., 2009; Amodio & Montagnese, 2015). El-Sherif et al. 2018, studied VEP and psychometric test in thirty patients with liver cirrhosis and no clinical evidence of HE . VEP showed prolonged P100 in 46.7% of patients while impairment of at least one psychometric test was documented in 50% of patients. In 2018, Abdelfattah et al.,

also used minimal state examination (MMSE), electroencephalography (EEG) and visual evoked potentials (VEP) for detection of MHE in 60 cirrhotic patients with no symptoms of overt encephalopathy, MHE was detected in 36.7%, 48.3%, 51.7% of the patients based on MMSE, EEG and VEP respectively. MHE is diagnosed by having one abnormal electrophysiological study or psychometric testing. El-Sherif et al. 2018. For the best of our knowledge no previous work studied the effect of 2 different checksizes .

Aim of Work

Detection of the effect of hepatic cirrhosis on cerebral cortex and subcortical pathways using VEP and comparison between different VEP check sizes in detection of early encephalopathy among cirrhotics .

Methodology

Subjects and Methods

This is a case/control study carried out on 45 cirrhotic patients, and 45 matched normal controls. Patients were recruited from the tropical and internal medicine clinics, Beni-Suef university hospital, between April 2019 and December 2020, after the approval of the ethical committee.

Ethics

All the individuals included in the study were informed about the procedures of the study, and all agreed to participate. The participants were informed of their rights to refuse participation or withdraw from the study without giving reasons. All information was treated with confidentiality. Prior starting of the research study , an approval was obtained from the ethical approval of the faculty of medicine, Beni-Suef University research ethical committee (REC)

Inclusion criteria

Patients with compensated liver cirrhosis, confirmed with clinical examination, laboratory tests and abdominal U/S with or without liver biopsy. 45 patients with hepatic cirrhosis and 45 healthy volunteers matched for age and sex. Males and females were included and age older than 18 years old.

Exclusion criteria

Patients with overt hepatic encephalopathy, patients with alcoholism, patients with neurodegenerative disorders as Parkinsonism or dementia, patients with other end organ failure e.g. renal, cardiac or respiratory, patients with hypernatremia or hypoglycemia, patients with ocular diseases that could affect visual function (e.g. lenticular or corneal opacities, glaucoma, uncorrected errors of refraction or diseases affecting gaze fixation) or have a history of ocular trauma or surgery, patients with systemic or metabolic illness known to affect vision (e.g. cerebrovascular diseases or diabetes mellitus), patients on psychoactive drugs or with a history of drug abuse, exposure to toxic substances, heavy metals, or any

substance known to affect vision and patients' refusal for participation in the study.

Methodology

All the patients had been through a full Assessment of the hepatic cirrhosis including previous history of hepatic encephalopathy. Thorough clinical examination including manifestations of liver cell failure and portal hypertension

The subjects (both patients and controls) were subjected to the following:

1. Ophthalmological assessment: Thorough history taking regarding the presence of any ocular, neurological or systemic disease that could affect vision, visual acuity testing and ophthalmological examination: for exclusion of anterior or posterior segment disorders.
2. Neurophysiological assessment:
The tests carried out in the Neuro diagnostic research center (NDRC), Beni-Suef University Hospital, using Roland Consult device (*Roland Consult Electrophysiological Diagnostic Systems, Germany*). All the tests were recorded at the same session.

Visual evoked potentials (VEPs)

The test was done according to ISCEV standard Odom et al., 2016. The patient sat on a comfortable chair at a distance of about 60-70 cm from the monitor after correction of vision if needed.

Electrode Type

Gold disc electrodes were used for recording. The skin was prepared by cleaning using abrasive gel (Nuprep), and 10-20 paste was used to ensure good electrical connection. The electrode impedance was kept below 5 k Ω .

Electrode placement

According to the International 10/20 electrode placement system .The active electrode was placed on the scalp over the visual cortex at Oz with the reference electrode at Fz. A ground electrode was placed on the forehead.

Stimulus pattern

The standard pattern stimulus used was a black and white checkerboard on a 20 inch monochrome screen. Two check element sizes were used: 1° and 15 min. Each eye was stimulated separately (monocular stimulation). A fixation point was used and positioned at a corner of four checks which was located at the center of the field.. Full field stimulation is performed. The stimulus was pattern reversal (The black and white checks change phase abruptly). Computerized signal averaging is used to extract the time-locked VEPs after a reversing checkerboard stimulus.

Luminance and contrast

The mean luminance of the checkerboard was 50 cd/m² and contrast between black and white squares was 100%

Analysis of data

The pattern-reversal VEP waveform consists of N75, P100, and N135 peaks. These peaks are designated as negative and positive followed by the typical mean peak time. The P100 is usually a prominent peak, it is recommended to measure its amplitude from the preceding N75 peak (peak to peak), and the implicit time of P100 (latency) is measured from the stimulus onset to the peak of the wave.

Results

The mean value for age in cirrhotic patients was 50.9±7.3 years (ranging from 36-62 years), and in the control group was 48.13± 6.47 years (ranging from 38 to 60 years). the distribution of sex was 24(53.3%) for males and 21(46.7%) for females in the patients group, while in the control group the distribution of males was 23(51.1%) and the females was 22(48.9%).

Table (1) Baseline characteristics of the studied groups

Characteristics	Cases (no=45)	Controls (no=45)	P-value
Age (mean± SD)	50.9±7.3	48.13 ± 6.47	0.064
Sex			0.833
Males	24(53.3%)	23(51.1%)	
Females	21(46.7%)	22(48.9%)	

Table (4) showed that both groups were well matched and there was no statistically significant difference between cases and controls regarding their age, and sex (P-value>0.05). There was one case with autoimmune hepatitis (2.2%), one case (2.2%) with HBV and majority of cases had HCV (95.6%). Figure (2)

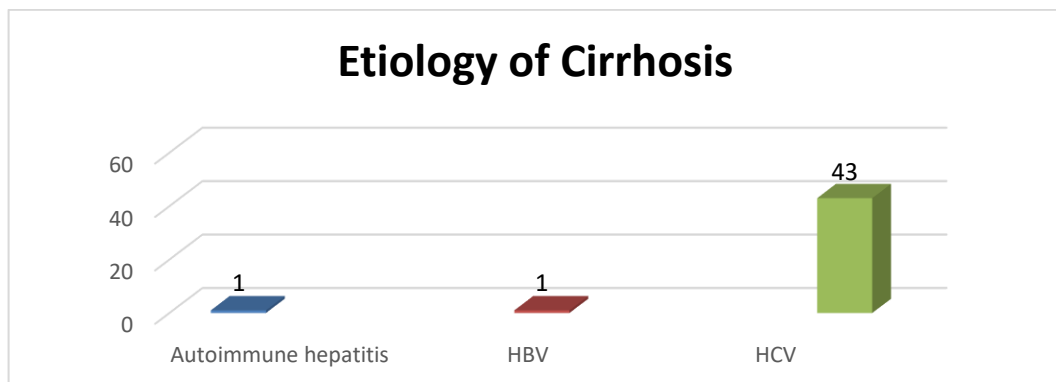


Figure (1) Etiology of cirrhosis among the patients group

The P100 responses were obtained on two check sizes 1degree and 15 minutes. The mean value of P100 latencies in cirrhotic patients were 105.7±7.9 and

105.9±8.3 for the right and left eyes respectively, while in controls they were 102.5±4.9 and 102.6±5.4 for the right and left eyes. The mean value of P100 amplitude in cirrhotic patients were 11.3±3.5 and 11.5±3.5 for the right and left eyes respectively, while in controls they were 12.4±4.6 and 12.7±4.6 for the right and left eyes. As showed in table 2.

Table (2) Comparison between cases and controls regarding their VEP latency and amplitude at 1 degree

VEP 1 degree (mean±SD)	Cases (no=45)	Controls (no=45)	P-value
Rt latency	105.7±7.9	102.5±4.9	0.027*
Lt latency	105.9±8.3	102.6±5.4	0.026*
Rt amplitude	11.3±3.5	12.4±4.6	0.187
Lt amplitude	11.5±3.5	12.7±4.6	0.156

*P-value is significant.

Table (2) showed that the studied cases had significantly more delayed latency than the controls on both sides at 1 degree (P-value<0.05). However, the amplitude didn't differ significantly between both groups in both sides (P-value>0.05). The mean value of P100 latencies in cirrhotic patients were 114.3±8.9 msec and 115±9.5 msec for the right and left eyes respectively, while in controls they were 106.5±4.2 msec and 106.9±4.3 msec for the right and left eyes. The mean value of P100 amplitude in cirrhotic patients were 11.9±3.7 µv and 11.9±4 µv for the right and left eyes respectively, while in controls they were 14.1±5.7 µv and 14.3±5.5 µv for the right and left eyes. As shown in table 3.

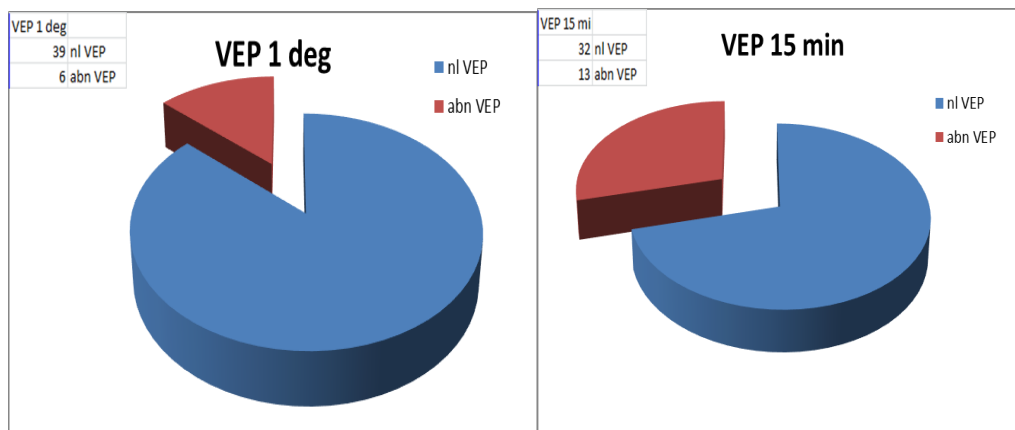
Table (3) Comparison between cases and controls regarding their VEP latency and amplitude at 15 minutes

VEP 15 minutes (mean±SD)	Cases (no=45)	Controls (no=45)	P-value
Rt latency	114.3±8.9	106.5±4.2	<0.001*
Lt latency	115±9.5	106.9±4.3	<0.001*
Rt amplitude	11.9±3.7	14.1±5.7	0.030*
Lt amplitude	11.9±4	14.3±5.5	0.022*

*P-value is significant.

Table (3) showed that the studied cases had significantly more delayed latency and lower amplitude than the studied controls on both sides at 15 minutes (P-value<0.05).

6 cirrhotic patients (out of 45) had abnormal VEP 1 degree, and 13 patients were abnormal by VEP 15 min. as shown in figure (2)



Figure(2): showing the number of abnormal patients detected by each check size (1 degree and 15 min).

Discussion

Hepatic encephalopathy is a clinical syndrome with a wide range of variability extending from minimal impairments of intellectual function only detectable by specific psychometric testing (minimal hepatic encephalopathy MHE), to obvious neuropsychiatric abnormalities up to profound coma (overt hepatic encephalopathy OHE) (Butterworth, 2019). Prevention of OHE development is very important because a first episode of overt hepatic encephalopathy is associated with a short survival of 23% at 3 years (Weissenborn, 2019, Tapper et al., 2020). Treatment of MHE is therefore important as a potential prophylaxis for overt hepatic encephalopathy (Rose et al., 2020).

MHE had been diagnosed when a psychometric test and/or neurophysiological study (VEP, BAEP, SSEP, EEG) were altered (Amodio and Montagnese 2015; Formentin et al., 2021). Many published researches had investigated the role of VEP, SSEP, BAEP and EEG in diagnosis of HE. Zhang et al, 2013; El-Sherif et al. 2018. For the best of our knowledge , no previous studies had investigated 2 different check sizes in pVEP (large and small check sizes) in cirrhotic patients. Forty-five patients with compensated hepatic cirrhosis were enrolled for our study, both males and females were included. Compared to 45 healthy controls that were matched for age and sex. No significant difference between both groups regarding age, sex was found.

The Egyptian Demographic Health Survey (EDHS) that was conducted in 2015 showed that about 6 million patients have the burden of HCV (El Kassas et al., 2018). This could explain the high incidence of virus C among our patients as an etiology of liver cirrhosis (43 cases, 95.6%), with only one case with virus B infection (2.2%), and one case with autoimmune hepatitis (2.2%). The cirrhotic and control groups were tested with PVEP and two different check sizes (1 degree, 15 minute) were examined. For both check sizes, there was significantly delayed latency in the cirrhotic patients in comparison to healthy controls. There was no significant interside difference regarding latency or amplitude in both eyes among the cirrhotic patients.

Moreover, 15 min check size VEP showed significantly small amplitude among the cirrhotic patients when compared to controls. These findings signify the sensitivity of using the 15 min check size in detecting abnormalities that couldn't be detected by the 1 degree check size VEP. Both the original and more recent EP investigations for cirrhotic patients were confined to latency impairment (Zhang et al., 2013; El-Sherif et al. 2018; Abdelfattah et al., 2018). According to our calculated cutoff, 6 patients were found to be abnormal in PVEP 1degree check size with only latency abnormality, and 13 patients were found to be abnormal in PVEP 15 min check size (with delayed latency abnormality in all cases, and amplitude abnormality in only 3 cases). All our patients were compensated cirrhotics (child A) and that explain the fairly low prevalence of MHE among them 28.8% by VEP 15 min and 13.3% by VEP 1 min. Many researchers reported similar findings; the prevalence of MHE was between 30% to 84% according to the type patients, methods, control groups, and the severity of liver disease in the cirrhotic population (Maldonado-Garza et al., 2011).

In our study, the 15 min check size had revealed additional information than the 1 degree check size and that could delineate the different area of perception of both check sizes. The Large check sizes 1 degree (60 min) mainly perceive signals from the peripheral field outside the central 3° but not beyond 10° of the visual field Phurailatpam, 2014, while smaller check sizes mainly perceive signal from the foveal area (central visual field) Kothari et al., 2014. Jancic et al., 2016 demonstrated that the responses to smaller checks are more sensitive to disorders of the visual pathway. That is highly correlated with our PVEP results, as the 15 min check size (mainly measure the central visual field) revealed more affection than the 1 degree check size (that mainly measure the peripheral visual field).

These findings map out the effect of encephalopathic changes on the visual field with more affection of the central visual field than its periphery. Changes in EPs amplitude reflect changes in the synchronization and in the amount of the activated neurons over these cortical areas. Amodio and Montagnese, 2015. Numerous studies have explored MHE-related brain structural and functional abnormalities like decrease glucose uptake, reduced cerebral oxygen consumption and cerebral blood flow (Zhang et al. 2012). We inferred from our results that VEP small checks has been able to find early impairment in cirrhotic patients that still show no overt evidence of hepatic encephalopathy, and early detection of these patients can prevent further progression into overt hepatic encephalopathy.

Conclusion

Subclinical encephalopathic changes in cirrhotic patients can be detected by pVep (especially the small check sizes patterns (15 min), that is proven to be superior than the large check sizes. And that proves that most of the encephalopathic changes are affecting the central visual field and the regions of their relay over the occipital cortex.

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