DOI Number: 10.5958/2320-608X.2019.00043.X

To Evaluate Auditory Evoked Potentials in Non Alcoholic Liver Cirrhosis Subjects Attending a Tertiary Care Hospital: A Cross Sectional Study

Gowri Velayutham

Senior Assistant Professor of Physiology, Institute of Physiology and ExperimentalMedicine, Madras Medical College, Chennai

Abstract

Introduction: There is a definite relationship between the brain and the liver that has been known and the patients with liver cirrhosis frequently experience neurological problems. The commonest and most widely recognized is the syndrome of Hepatic Encephalopathy (HE). HE is generally taken as that refer to a collection of neuropsychiatric, neuropsychological and neurological disturbances that may arise as a complication of liver cirrhosis and which is reversible. The present study was designed to evaluate the involvement of central nervous system in non alcoholic liver cirrhosis by using auditory evoked potentials to assess conduction in auditory pathway. **Materials and Method:** 20 non alcoholic liver cirrhotic subjects were selected and 10 age and gender matched healthy subjects with normal liver functions from the Master Health Check Up. AEP Recording was done in electrophysiology laboratory of Physiology using Neuro Perfect Plus Medicaid Polyrite. **Results** :The parameter for the study was absolute wave latencies which was considered the important cortical wave latencies. Results were analysed by student's independent t-test using Statistical Package for Social Sciences 11.5 version. P value was calculated to test the statistical significance. The level of significance chosen for the study was 1% ($p < 0.01$). **Conclusion:** The finding of absolute wave latency prolongation in clinically non encephalopathic non alcoholic cirrhotic patients signify the presence of MHE. Therefore the ethanol induced demyelination thought to be the basic cause of AEPs is also over ruled. AEP is such a simple non invasive technique to be used as a prognostic marker and in follow up of even comatose patients. The emergence of MHE is significantly correlated with the severity of liver functions.

Keywords: *non alcoholic liver cirrhosis Auditory Evoked Potentials Neuropathy*

Introduction

There is a definite relationship between the brain and the liver that has been known and the patients with liver cirrhosis frequently experience neurological problems. The commonest and most widely recognized is the syndrome of Hepatic Encephalopathy (HE). HE is generally taken as that refers to a collection of neuropsychiatric, neuropsychological and neurological disturbances that may arise as a complication of liver cirrhosis and which is reversible. Minimal hepatic encephalopathy is the term now has replaced the previous terms of Latent or sub clinical hepatic encephalopathy. The older terms seems not to reflect the significant effects that influence the liver cirrhotic patient's life[1].There is really a need to evaluate the liver cirrhotic patients who are showing to be completely free from hepatic encephalopathy The very true incidence and prevalence of HE in the cirrhotic patients is difficult to establish, because of the considerable heterogeneity in etiology and disease severity. It is also difficult to diagnose the more subtle forms of HE such as stage I

Corresponding author:
Gowri Velayutham
Senior Assistant Professor of Physiology
Institute of Physiology and ExperimentalMedicine
Madras Medical College, Chennai-3.
Phone : 443431451
Email : gowrivelayutham07@gmail.com

and minimal HE[2]. The clinical electro diagnosis involves the recording, display, measurement and interpretation of action potentials arising from the central nervous system eg: evoked potentials. Evoked potentials are visual, auditory, somatosensory and P 300 event related have been proposed to be diagnostic techniques in evaluation and assessment of the brain related functional impairments like dementia, encephalopathy etc,. Halliday[3] stated evoked potentials can reflect neurotransmitter changes [4] in cortical and sub cortical neurons. Despite the controversy, Evoked Potentials remain an attractive possibility for the diagnosis of minimal HE. Brainstem Auditory Evoked Potentials (AEP) has extended the possibility of objective testing of hearing functions. This is an effective and simple method that requires less co operation of the patient and also measures specific part of the auditory pathway. It is not significantly altered by the consciousness, literacy, much common drugs and environmental factors.

Materials and Method

The present study was designed to evaluate the involvement of central nervous system in non alcoholic liver cirrhosis by using auditory evoked potentials to assess conduction in auditory pathway. In this cross-sectional study, the liver cirrhotic patients from liver clinic who had etiology of not using alcohol were considered. Ethical approval from the Institutional Ethical Committee was obtained for the study. 20 non alcoholic liver cirrhotic subjects were selected and 10 age and gender matched healthy subjects with normal liver functions from the Master Health Check Up. (case control ratio was 2:1)

Inclusion Criteria: Age group was 30 to 50 years, both genders, diagnosed liver cirrhosis subjects due to Hepatitis Virus B,D and E, Wilson's disease and cryptogenic aetiology.

Exclusion Criteria : Smokers, alcohol intake within last 6 weeks, occupational history with continuous noise back ground, hearing impairment, external or middle ear diseases, systemic diseases like diabetes mellitus, hypertension, primary psychiatric disorders, complete drug history of antibiotics to rule out ototoxic drugs, cardiac and renal disease , cochlear implant/ cardiac pacemaker.

The study subjects were allowed to relax and be comfortable. A clinical history about the liver cirrhosis was collected. The complete procedure and objectives of the study was explained to the subjects in their regional language. The written and informed consent was obtained before subjects entered the study. The complete examination of external ear was done for both ears, wax was removed and tests for hearing done. The basic parameters of subjects like height, weight, pulse including body temperature were recorded. Auditory evoked potentials were first recorded in few normal subjects of both genders with age ranging from 30- 50 years. In order to establish reliability of the method, several repetitions of brainstem auditory evoked potential recording were performed on different days and at different hours. After this preliminary investigation, BAEP in 20 nonalcoholic liver cirrhosis subjects were recorded. The subjects were instructed clearly to have shampoo head bath, avoid oil on hair, hair spray and metal accessories especially ear studs. Auditory evoked potentials comprise of 5 or more peaks within 10 ms of the stimulus [5].The gold plated copper disc (1 cm) electrodes filled with conducting paste for recording AEPs were used. The electrode impedance was kept below 5 kΩ. The BAEP is recorded from the ipsilateral ear referred to the vertex. Two channels recorded from ipsilateral and contra lateral mastoid processes were referred to as Oz and Cz respectively and ground as Fz. Vertex is the suitable location since waves II – V has good amplitude with little muscle artifact. AEPs were recorded using an amplification of 200,000-500,000. 2000 trials were averaged to get a good quality recording. A 10 ms epoch after the click stimulus is averaged, amplified and displayed on the computer monitor. The low filter is set at 100 Hz and high filter at 3000 Hz. AEPs were produced by a brief click stimulus, which is usually a square wave pulse of 0.1 ms duration. The pulse moves the ear phone diaphragm away from the subject's ear which is a rarefaction phase stimulus. Wave I amplitude is greater with rarefaction compared to condensation stimulus. Since recognition of wave I is very important, rarefaction click polarity was chosen. Clicks were usually presented 10- 70 times per second. A click rate of 11Hz was used. The click stimulates not only the ipsilateral ear, but also travels by bone and air conduction to stimulate the contra lateral ear at an intensity of 40- 50 dB lower than the ipsilateral ear. White noise at 30- 40 dB blocks the stimulation of contra lateral ear thus prevents false AEP responses. Recording was done in electrophysiology laboratory of Physiology using Neuro Perfect Plus Medicaid Polyrite. The left

and right ears were tested separately in the uniform laboratory temperature , in sitting posture reclined on a chair with their feet placed on wooden board. The body temperature was measured since hypo or hyperthermia may cause alterations in latencies of both absolute and inter peak. The disc electrodes were placed on scalp by 10- 20 standard system with conducting jelly. The skin and electrode impedance were checked. Since the potentials recorded are in far field, well displaced from the site of impulse generation, the wave forms recorded were very weak and hence amplified. This amplification is achieved by improving the signal: noise ratio. The automatic artefact rejection was used. The sweep velocity was 1 ms. The click acoustic stimuli at a rate of 11 pulse per second at an intensity of 90 dB hearing level to the ear stimulated and masking sound (white noise) of 40 dB in non stimulated ear was given through head phone supplied by Medicaid[6,7,8]. The continuous 1000 auditory click responses were summated, averaged and displayed. All the techniques of measurement, duration, instruments including research laboratory temperature were maintained uniformly throughout the study [9].The wave latency I, II, III, IV and V, inter peak latency I-III, I- V, III- V and amplitudes of waves were measured. The wave pattern in BAEP recording is 5 or more peaks within 10 ms of stimulus. Initial five peaks have clinical value [10]. The succeeding peaks VI- VIII are quite variable and are not clinically useful. In normal subjects waveform IV- V forms complex. Absolute amplitudes are too variable to be of any clinical use even in inter ear comparison. Hence the absolute wave latencies are taken into consideration in this study.

Findings

The total non alcoholic cirrhotic patients were 20 and they were age, gender matched with 10 healthy controls. All the data were expressed as mean ±SD .The study had a ratio of 2:1 ratio of cases with the control. The mean age was 44.00 ± 4.86 with BMI as detailed in table.1. There was no statistical difference between non alcoholic liver cirrhosis subject group and controls with regards to age and BMI. Auditory evoked potentials of both the ears were tested. The absolute and interpeak wave latencies were measured. The parameter for the study was absolute wave latencies which was considered the important cortical wave latencies. Results were analysed by student's independent t- test using Statistical Package for Social Sciences 11.5 version. P value was calculated to test the statistical significance. The level of significance chosen for the study was 1% ($p < 0.01$).

Interpretation: There is considerable prolongation of the important Absolute Wave latency III and V in nonalcoholic liver cirrhosis subjects which is statistically significant.

Table 1: Baseline characteristics of nonalcoholic liver cirrhosis subjects and controls:

Baseline characteristics	Cirrhosis subjects n = 20 Mean ± SD	Controls n = 10 Mean ± SD	P Value
Age(yrs)	44.00 ± 4.86	42.00 ± 4.16	1.00
Height(cms)	156.70 ± 10.25	153.70 ± 11.25	1.00
Weight(Kgs)	66.87 ± 9.22	60.87 ± 8.22	1.00
BMI(Kg/m^2)	27.14 ± 1.95	27.14 ± 1.95	1.00

BMI = Body mass Index

* P ≤ 0.05 Significant

Table 2 : Left ear Absolute latencies of nonalcoholic liver cirrhosis subjects and control group:

Variables Wave Latency (ms)	Cirrhosis subjects n = 20 Mean ± SD	Controls n = 10 Mean ± SD	P Value
I	1.44 ± 0.05	1.44 ± 0.05	0.62
II	2.72 ± 0.12	2.721 ± 0.12	0.76
III	3.78 ± 0.16	3.56 ± 0.07	< 0.001 *
IV	4.98 ± 0.09	4.89 ± 0.07	0.06
V	5.90 ± 0.34	5.66 ± 0.07	< 0.001 *

* P ≤ 0.05 Significant

Table 3: Right ear Absolute latencies of nonalcoholic liver cirrhosis subjects and control group:

Variables Wave Latency (ms)	Cirrhosis subjects n = 20 Mean ± SD	Controls n = 10 Mean ± SD	P Value
I	1.45 ± 0.05	1.44 ± 0.05	0.20
II	2.71 ± 0.13	2.72 ± 0.12	0.61
III	3.68 ± 0.16	3.54 ± 0.07	< 0.001 *
IV	4.89 ± 0.08	4.88 ± 0.07	0.41
V	5.89 ± 0.35	5.66 ± 0.07	0.001 *

* $P \leq 0.05$ Significant

Discussion

In the above study, AEP recorded in 20 non alcoholic cirrhosis subjects who fulfilled selection criteria and compared with 10 age and gender matched controls. Both the ears tested individually. These potentials reflect functional integrity of the sensory tract (auditory pathway) in the brain and help in identifying the sites impaired due to neurotoxic factors. Absolute wave latencies were considered mainly. In patients with minimal HE usually there will be no neurological findings detected but there may be subtle changes brought out by neuropsychological and neurophysiologic testing. The true prevalence of minimal HE in cirrhotic patients is variable, but expected to be more [11-14].Many studies have shown that these patients have poor quality of life and daily routine living activities [15]. There is no single method which will accurately measure the severity of HE. The techniques involved for assessing mental state involves consciousness, orientation, behavior , literacy and intellectual functions etc [15 ,16] Patients with MHE appeared to have no clinical symptoms. But they are vulnerable to overt HE. So the present study observed that the absolute wave latencies were much prolonged especially middle latencies (III, V) indicating the central neuropathy.

The liver supplies certain nutrients that the brain itself cannot produce. Liver also cleanses the blood off the substances that can damage the brain cells (neurotoxins). Although the brain is protected from neurotoxic substances by Blood Brain Barrier (BBB) , certain neurotoxins penetrate BBB by damaging it. So the previous studies were not clear in standing delineated the influence of alcohol on AEP and the real pathology of liver cirrhosis affecting the brain potentials considerably. The following hypothesis is derived supporting our study which is evidenced by prolongation of central absolute latencies especially. The detoxifying function of liver carried out through the portal vein in normal functioning liver. The main cause for the neurological deterioration is because of porto systemic shunting. There is lack of detoxification by liver and toxic substances rise in general circulation and increase the level of neurotoxins. These toxins first damage the nerve cells and second bring about the changes in structure of supporting glia especially astrocytes.

The essential functions of astrocytes are to take up neurotransmitters released by neurons and minerals as K which is released during brain energy metabolism. Astrocytes eliminate neurotoxins. The improper functioning of astrocytes leads to abnormal astrocytes as Alzheimer type II astrocytosis which cause physiological or functional delay in potentials. There is also loss of cerebral biochemical homeostasis on reason out that compromise of detoxifying function of cirrhotic liver.Since the astrocytes are1/3 rd of cortical volume, regulation of BBB, maintains brain neurons electrolytes and homeostasis with special effects of detoxification by itself. The prolongation results also from the cerebral overloading of neurotoxins such as ammonia, glutamate[17,18]. The levels of ammonia increases in central nervous system due to astrocyte damage also affects nerve signal transmission, brain energy metabolism and alteration in expression of gene that encodes key proteins.

Drawbacks:

The study has to improve the sample size to stand a better way to generalize the results into the whole population. A follow up study is needed to record AEP during every visit of the cirrhotic subjects get their viral load checked, status of oesophageal varices etc, too and to correlate with the parameters.

Conclusion

The finding of absolute wave latency prolongation in clinically non encephalopathic non alcoholic cirrhotic

patients signify the presence of MHE. Therefore the ethanol induced demyelination thought to be the basic cause of AEPs is also over ruled. AEP is such a simple non invasive technique to be used as a prognostic marker and in follow up of even comatose patients. The emergence of MHE is significantly correlated with the severity of liver functions. The non alcoholic cirrhosis patients might be at risk always whenever they perform complex motor activities such as operating heavy machinery or drivers during driving their vehicles.

Conflict of Interest: None declared

Source of Funding: No funding sources

Ethical Clearance: The study was approved by Institutional Ethical Committee

References

1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT, Hepatic Encephalopathy – definition, nomenclature, diagnosis, and qualification : final report of the working party at the 11th World Congresses of Gastroenterology ,Vienna 1998 .Hepatology 2002;35:716-21.
2. M G Davies, M J Rowan, J Feely Metabolic Brain Disease. EEG and event related potentials in hepatic encephalopathy (1991). Volume 6,Issue:4,Pages:175-186 Pub Med :1812391.
3. Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. Lancet 1972; 1:982-5.
4. Bodis-Wollner I, Onofry M. System disease and auditory evoked potential diagnosis in neurology: changes due to synaptic malfunction. Ann NY Acad Sci 1981; 388:327-48
5. Chiappa KH, Ropper AH. Evoked potentials in clinical practice (first of two parts). N Engl J Med 1982; 306:1140–50.
6. UK Misra J Kalita.In: An introduction to Electrodiagnosis signals amd their measurements. Clinical Neurophysiology 2nd edition Elsevier publishers: New Delhi.2006; Chapter 2: Page 11 - 21.
7. Colin Binnie, Ray Cooper, Francois Mauguiere, John Osselton, Pamela Prior and Brian Tedman. In : Evoked Potentials .Clinical Neurophysiology, Volume 1 Revised and Enlarged edition, Edited by: Elsevier. Netherland.2004;Part 3 : Page 353 – 415.
8. Michael J.Aminoff., In: Brainstem auditory evoked potentials ,Methodology,Interpretation and Clinical Application.Electrodiagnosis in clinical neurology ,fifth edition Elsevier publications Philadelphia,5th edition.2008 : chap 23: Page 490-492.
9. Colin Binnie, Ray Cooper, Francois Mauguiere, John Osselton, Pamela Prior and Brian Tedman. Clinical Neurophysiology, Volume 1 Revised and Enlarged edition, Edited by: Elsevier. Part 3 : Page 416 – 615.
10. Cynamon HA, Norcross K, Isenberg JN. Evoked potential abnormalities in children with chronic cholestasis. Hepatology 1988; 8: 1596 –1601.
11. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar- Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy .Am J Gastroenterol 2001;96:2718-23.
12. Das A, Dhiman RK, Saraswat VA, Verma M. Naik SR.Prevalence and natural history of Subclinical hepatic encephalopathy in cirrhosis.J Gasteroenterol Hepatol. 2001 ; 16: 531-5.
13. Slowik A.Ciecko-Michalska I, Bogdal J,Szczudlik. The diagnosis of Subclinical hepatic encephalopathy . J Gasteroenterol Hepatol . 2001 Mar; 16(3): 322-7.
14. Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA.HOP WC, Schalm SW. The prognostic significance of Subclinical hepatic encephalopathy . Am J Gasteroenterol . 2000 ;95: 2029-34.
15. Groeneweg M, Quero Jc, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC,Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. Hepatology. 1998 Jul;28(1):459.
16. Yang S-S, Wu C-H, Chiang T-R et al. Evoked potentials in subclinical portasystemic encephalopathy: a comparison with psychometric tests. Hepatology 1998; 27:357.
17. Sherlock S, Summerskill WHJ, White LP, Pear EA. Portal systemic encephalopathy. Neurological complications of liver diseases. Lancet 1954; 2: 453-7.
18. Harrison's Principles of Medicine Edition 15, Mc Graw Hill, Page 1923 Table 295 - 4.