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ORIGINAL ARTICLE

EVALUATION OF CRITICAL FLICKER FREQUENCY IN DETECTING AND MONITORING MINIMAL HEPATIC ENCEPHALOPATHY

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ABSTRACT: BACKGROUND: Minimal hepatic encephalopathy (MHE) is defined as presence of abnormal neuropsychological and/or neurophysiological tests in cirrhotic patients without clinical signs of overt HE. Detecting MHE with available tests is time consuming, semi-objective, dependent on psychomotor skills of the patient and requires qualified personnel for administering test. Of late Critical Flicker Frequency (CFF) has emerged as a new diagnostic test for detecting MHE which obviates the above problem. **AIM:** To find out the prevalence of MHE in a group of adult cirrhotic patients with no overt HE, at a tertiary health care center using CFF analysis and assess changes in the same after four weeks of oral L-ornithine L-aspartate (LOLA) administration in subset with abnormal CFF. **METHODS:** 25 adult patients with cirrhosis, diagnosed on basis of clinical parameters & lab investigations, were invited to participate in the study. In patients without signs of overt encephalopathy (N=20) CFF analysis was done by HEPAtonorm analyzer. Cut off of 39 Hz was used, below which result was taken as abnormal and diagnostic of MHE. Patients with abnormal result (n=10) were given oral LOLA 30gm/day for 4 weeks. Repeat CFF analysis was done after 4 weeks in 13 patients, comprising 10 patients with abnormal and 3 patients with normal result in first study. Results were analyzed using non-parametric statistical tests. **RESULTS:** Of 20 patients without overt HE (M: F-12:8) (Median age 43 years [25-73yrs]) etiology was alcohol/cryptogenic/viral (B/C) in 4/7/9 (3/6), Child's status A/B/C in 5/7/8 respectively. The prevalence of MHE in cirrhotic patients was found to be 50% (10/20) and all of them had advanced cirrhosis (Child B/C). Subgroup of patients with MHE treated with LOLA for 4 weeks showed improvement in CFF test results repeated after 4 weeks (p=0.008) while those with no MHE showed insignificant change in their CFF after 4 weeks (p=0.85), signifying reproducibility & lack of learning effect. **CONCLUSIONS:** CFF measurement is a simple and reliable tool for detection of MHE. It also has high degree of reproducibility & lack of learning effect on repeated testing in the same patient. It provides an objective parameter for assessment of improvement in MHE by pharmacological intervention. CFF should be used more often to diagnose and monitor MHE in patients with advance cirrhosis.

KEYWORDS: Minimal hepatic encephalopathy, Critical Flicker Frequency.

INTRODUCTION: BACKGROUND: One of the main complications of cirrhosis is encephalopathy which can be classified to Minimal (previously called Subclinical encephalopathy) and overt hepatic encephalopathy. Minimal hepatic encephalopathy (MHE) is defined as the presence of abnormal neuropsychological and/or neurophysiological tests in cirrhotic patients without clinical signs of overt HE.[1] Borderline between normality and pathology is difficult to assess, the subtle motor and cognitive deficit in MHE are of socio medical and prognostic relevance and may impair fitness to drive, earn living and overall quality of life (QOL).[2,3,4] In view of this, simple & objective method for diagnosing MHE is required and of late critical flicker frequency (CFF) is being increasingly used for

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same. Of various therapies available for treating MHE –ammonia lowering agents are preferred, one of which is L-ornithine L-aspartate (LOLA).

AIM: To find out the prevalence of MHE in a group of adult cirrhotic patients with no overt HE, at a tertiary health care center using CFF analysis and assess changes in the same after four weeks of oral L-ornithine L-aspartate (LOLA) administration in subset with abnormal CFF.

METHODS: Patients: From a pool of adult cirrhotic patients seen in Liver Clinic of Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, on a given day, 25 patients were invited to participate in the study. Of these, patients without overt HE (N=20) were administered CFF test. Cirrhosis was diagnosed on a clinical basis involving laboratory tests and clinical examination.

Exclusion Criteria:

1. Presence of overt HE on clinical examination.
2. Acute gastrointestinal hemorrhage or spontaneous bacterial peritonitis during past 7 days.
3. Active alcohol consumption in any amount over past six months.
4. Significant non-hepatic disease such as decompensated heart, respiratory, or renal failure, poorly controlled diabetes mellitus.
5. Overt or amnestic neurological disease (Except HE), such as Alzheimer's disease, Parkinson's disease and non-hepatic metabolic encephalopathy.
6. Patients on medication including psycho active drugs, such as antidepressants or sedatives
7. Ophthalmologic disorder, diabetic retinopathy with involvement of fovea and red-green visual blindness.

Other concomitant medications including lactulose were allowed and not discontinued. Informed consent was taken from each patient.

Determination of Critical Flicker Frequency (CFF): CFF was assessed by HEPAtonorm analyzer (R & R Medi-Business, Freiburg Germany). Intrafoveal stimulation with a luminous diode (wave length 650 nm, luminance 270 cd/m,^{2} luminous intensity 5.3 mcd) was achieved through concave-convex lens system, which allowed light accommodation to a virtual picture of light source at 12 meters in the distance. Light pulses with 1:1 ratio between the visual impulse and the interval were used with decreasing frequency in gradual step of 0.5Hz/sec from 60Hz downward. CFF was determined as the frequency when the impression of fused light switched to flickering one. After brief instructions & dark adaptation of 15 minutes and training period–flicker frequency was measured 9 times of which two extreme values were discarded & median of 7 values was calculated. Whole procedure took 15-20 minutes in each patient. CFF analysis was done between 9AM to 5PM in a quiet room with constant light quality.

Repeat CFF assessment was done in subgroup (n=13) after 4 weeks interval. Of those retested, 10 had abnormal (Received LOLA for 4 weeks) & 3 had normal CFF at baseline.

All examination was performed by the same investigator (AB) who was blinded to patient's clinical characteristics. Cut off of 39 Hz was used, below which result was taken abnormal or diagnostic of MHE.[5]

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Assessment of HE Severity: A total of 20 patients underwent clinical assessment before CFF at baseline and after 4 weeks (Subgroup of 13 patients).Patients grading of HE severity was performed on basis of West –Haven criteria by same investigator (VR) who was blinded for the CFF results.

LOLA Administration: Subgroup of those patients whose CFF was found abnormal Group A (N=10), were given 30gms of oral LOLA preparation per day in divided doses for 4 weeks duration. Other medications including lactulose was allowed both in normal (n=3) & abnormal CFF group (n=10).

Statistical Analysis: CFF analysis was done as automatic measurement done on Windows Xp (Microsoft Corp., Redmond, WA) based software (CFF-003 version 3.1). Data processing was performed using SPSS software (version 12, SPSS Inc.). Data was expressed as median & range. Mann-Whitney 'U' test, Wilcoxon's Signed Rank test and Fisher's Exact's test were used. p value<0.05 was taken as significant.

RESULTS: Of 20 patients without overt HE (M: F 12:8) (Median age 43 years [range 25-73]) etiology was alcohol/cryptogenic/viral (B/C) in 4/7/9 (3/6) respectively.

There were 5 Patients with Child's a Cirrhosis & 15 with Advanced Cirrhosis (Child's Status B/C):

- Prevalence of MHE in cirrhotic patient without overt encephalopathy was 50%. Of the 20 patients analyzed by CFF test, 10 patients had abnormal CFF values or MHE.
- Median age of the patients with MHE (group A, n= 10) was comparable to those without MHE (group B, n=10) (43 vs. 50 years) (p=0.48).
- Median CFF in group A was significantly lower than that in group B (34.5 vs. 40.5 Hz) (p<0.001).
- Median Child's score in group A was significantly higher than that in group B (10.5 vs. 6.5) (p<0.001). All patients with MHE had advanced liver cirrhosis (Child's status B/C).
- All patients in group A treated with LOLA (n=10) for 4 weeks showed significant improvement in CFF compared to baseline (p=0.008).Overall 80% patients with MHE normalized after therapy.
- Three patients with normal CFF assessment at baseline who were retested after 4 weeks showed no significant difference (p=0.85), suggesting stable disease, lack of any learning effect and reproducibility of results.

DISCUSSION: Cirrhosis and its complications are one of the leading causes of morbidity in Indian population and rest of the world. Hepatic encephalopathy (HE) is a frequent complication of cirrhosis and its appearance indicates a poor prognosis.[6,7,8] HE is classified in to 4 grades according to West Haven criteria according to presence and severity of neuropsychiatric symptoms on clinical evaluation.[9] A significant proportion of cirrhotic patients exhibit MHE, a condition in which patients with cirrhosis, regardless of its etiology, demonstrate a number of quantifiable neuropsychiatric & neurophysiological defects yet have normal mental and neurological status on clinical examination.[1]

Apparently a patient suffering from MHE is normal to his family members and colleagues but suffers from minor cognitive and psychomotor defects which over all leads to impairment in quality

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of life and probably survival. Detection of overt HE is made clinically and does not provide major diagnostic challenge, diagnosis of MHE is requires wide array of tests.

Because of its prognostic and socioeconomic relevance[2,3,4] interest has focused on MHE which describes a poorly defined syndrome in grey zone between normality and overt encephalopathy. Various workers have shown that MHE impairs daily living, work capacity, quality of life. Patients with MHE are more prone to developing overt encephalopathy and probably have reduced long term survival.[10] So it seems only natural that clinicians all over the world have been trying to treat MHE with various available modalities like non-absorbable disaccharides, oral antibiotics and LOLA, but lack of effective tool to document the efficacy of these therapeutic measures has been a major hindrance in long term continuation and monitoring the effects of these measures.

Currently neuropsychological, neurophysiological & neuroimaging tests are used for diagnosis of MHE. Neuropsychological tests are most widely used among above methods[1]. Various workers have attempted to characterize MHE using battery of tests, one of the most comprehensive attempts to understand the neuropsychological characteristics of MHE was performed by Hamster et al, who applied more than 30 psychometric tests.[11,12] Subsequently Weissenborn popularized PHES (Psychometric hepatic encephalopathy score) which included composite score based on Number connection Test (NCT-A&B), serial dotting test, digit symbol test, line drawing test.[13] Results of psychometric tests are hampered by training effect, proband education, necessity of age matched controls, psychomotor skills of the patient, time & expertise required for administering these tests. Standardized and acceptable definition of MHE by means of psychometric test is still missing[1] which may explain wide range of MHE prevalence (20-80%) in literature.[14-16]

Neurophysiological tests such as spectral electroencephalogram (EEG), visual evoked potential (VEP), Somatic evoked potential (SEP), Event related potentials (P300) requires sophisticated equipment & analysis, results are affected by etiological cause of cirrhosis. They have overall lower specificity than neuropsychological tests.[17] Neuroimaging tests requires further standardization, are expensive and presently not suitable for routine clinical use.[1] No study till present has been able to directly compare all available existing modalities for their sensitivity & specificity in detecting MHE. Hence on the whole there has been no reliable gold standard for diagnosing MHE. Most authors however recommend a battery of tests including psychometric (two or more, one of which usually is NCT) with one or more neuro-physiological test for diagnosing MHE.[1,17]

Due to time consumed in carrying out battery of tests, none of them has been systematically used to follow the course and monitor the effect of any therapy on MHE. Many of the above problems can be circumvented by use of simple, automated neuro-physiological test of CFF analysis to diagnose MHE, which is a reproducible parameter It's results are not affected by education status, age, time of the day when administered, training effect or inter-observer variability.[5,17] CFF decreases in parallel with extent of psychometric and mental impairment in cirrhotic patients, can be done in less than half an hour, does not require high level of expertise to administer, relatively inexpensive & compact handy instrument which can also be used to longitudinally follow the course of particular patient with MHE, effect of any therapy & its modification according to results obtained on serial evaluation.

Studies on pathogenesis of HE suggests that low grade astrocyte swelling is the early pathogenic event and triggers HE symptoms by altering glioneural communication. Such event may also take place in retina and may underlie so called hepatic retinopathy, in which Muller cells may exhibit morphological changes similar to Alzheimer's type-II astrocytes.[18]

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Based on this principle CFF has been applied to quantitate and monitor low grade encephalopathy and current evidences suggest that CFF analysis not only reflects efficiency of visual apparatus, but also the functional efficiency of cerebral cortex.[19]

Tests used for diagnosing MHE especially neuropsychological tests have a major drawback of learning effect. It can be circumvented to an extent by administering parallel version of the test in follow-up study of the same patient. Except NCT most neuropsychological tests do not have validated parallel version[13,17,20,21] Neurophysiological tests like CFF analysis lack this draw back as response is based only on integrity of reflex arc & cortical functions. In our study repeat CFF analysis was performed on patients without MHE after 4 weeks showed no significant change over baseline, conforming lack of any learning effect.

By using 39 Hz as cutoff value,[5] 50% of cirrhotic patients without overt HE were found to have MHE. This value is slightly higher than reported by other workers[6,7,8,16] in their study. This might be due to the fact that majority (75%) of our study group comprised of advanced cirrhosis (Child B/C). CFF values changed or remain same consistently in parallel with evolution of HE severity in individual patient, suggesting single parameter is suitable for monitoring fluctuations in response to therapy as LOLA in our group of patients.

Ammonia lowering therapies have been treatment of choice for overt encephalopathy but its benefit in MHE is difficult to assess objectively. Non-absorbable disaccharides (Lactilol & lactulose) and antibiotics have been used for treatment of overt encephalopathy but their role in MHE is doubtful and recent meta-analysis by Nielsen et al[22,23] found no significant effect of non-absorbable disaccharides on hepatic encephalopathy compared to placebo, though antibiotics fared slightly better. L-ornithine L-aspartate (LOLA) is a salt of natural amino acid ornithine & aspartic acid. It has ammonia lowering capacity as it stimulates urea cycle (Carbamoyl phosphate synthetase-I) and provides substrate for glutamine synthetase, which removes ammonia via glutamine cycle active in muscle, kidney & perivenous hepatocytes.

Beneficial effect of LOLA in terms of improvement in performance status in psychometric tests and decrease in levels of blood ammonia has been consistently shown in patients with MHE in various double blind placebo controlled randomized trials.[24,25,26,27,28] Though to document its efficacy in longitudinal course no study till present has used CFF analysis which is why we performed this study to document its role in monitoring therapy of MHE. Our study showed benefit of oral LOLA over four weeks as assessed by normalization in 80% and improvement in CFF result of all patients with MHE.

LIMITATIONS: CFF threshold may depend on intensity of light source or physical parameters of the apparatus and is important to be kept constant. Though normal values are available for Caucasian population[5], same needs validation in population of Indian origin.

Our study consisted of small number of cirrhotic patients, test results of this study needs to be proven in larger group with more heterogeneous composition (Viz more patient comprising of Child A status & encephalopathy caused by shunt etc) to demonstrate consistency & reproducibility of CFF results. Due to logistical constraints, results of CFF analysis could not be compared with other neuropsychological & neurophysiological tests which are required to demonstrate its sensitivity and specificity in diagnosing MHE.

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TO CONCLUDE: CFF measurement is a simple and reliable tool for detection of MHE. It also provides an objective parameter for assessment of improvement in encephalopathy by any pharmacological intervention done (LOLA in our study) in a particular group of patients and comprehensively following course of encephalopathy over an extended period. It also has high degree of reproducibility & lack of learning effect on repeated testing in the same patient. CFF should be used more often to diagnose and monitor MHE in patients with advance cirrhosis.

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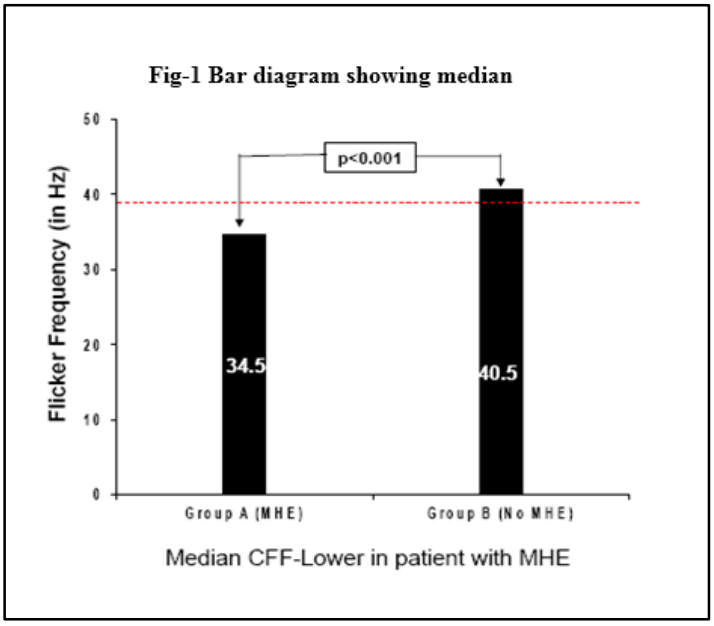

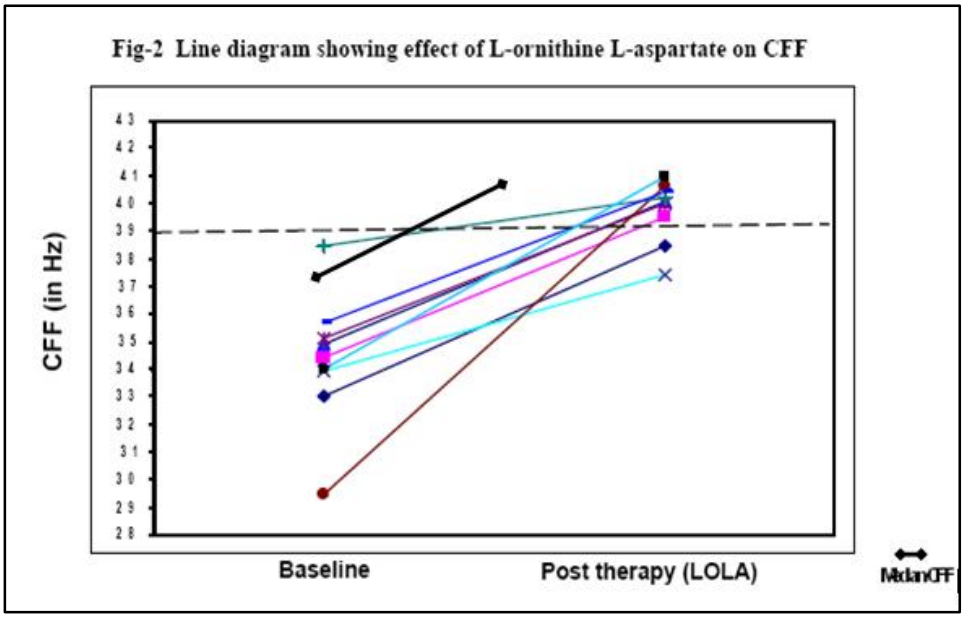

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