EVALUATION OF VISUAL EVOKED POTENTIAL AND BRAINSTEM AUDITORY EVOKED POTENTIAL IN MIGRAINE

Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the

Regulations for the award of the degree of

M.D.(PHYSIOLOGY)

BRANCH – V

Thanjavur Medical College and Hospital

The Tamil Nadu Dr.M.G.R. Medical university

Chennai, India

April 2015

CERTIFICATE

This is to certify that this Dissertation entitled **" Evaluation of Visual Evoked Potential and Brainstem Auditory Evoked Potential in Migraine "** is a bonafied work done by Dr. R.Sowmiya , under my guidance and supervision in the Department of Physiology , Thanjavur Medical College , Thanjavur during her Post graduate course from 2012 to 2015.

Dr.K.MAHADEVAN,M.S,
The Dean ,
Thanjavur Medical College,
Thanjavur – 613004.

Dr.R.VINODHA,M.D.,
Professor and HOD,
Thanjavur Medical College,
Thanjavur – 613004.

CERTIFICATE

This is to certify that this Dissertation entitled **" Evaluation of Visual Evoked Potential and Brainstem Auditory Evoked Potential in Migraine "** is a bonafied work done by Dr. R.Sowmiya , under my guidance and supervision in the Department of Physiology , Thanjavur Medical College , Thanjavur during her Post graduate course from 2012 to 2015.

Dr.R.VINODHA,M.D.,
Professor and HOD,
Thanjavur Medical College,
Thanjavur – 613004

DECLARATION

I solemnly declare that this Dissertation **" Evaluation of Visual Evoked Potential and Brainstem Auditory Evoked Potential in Migraine "** was done by me in the Department of Physiology , Thanjavur Medical College and Hospital , Thanjavur under the guidance and supervision of my Professor **Dr.R.VINODHA,M.D.,** Department of Physiology ,Thanjavur Medical College , Thanjavur between 2012 and 2015.

This Dissertation is submitted to the TamilNadu Dr.MGR Medical University , Chennai in partial fulfillment of University requirements for the award of M.D. Degree (Branch – V) in Physiology.

Dr.R.Sowmiya,
Postgraduate student ,
Thanjavur Medical College,
Thanjavur – 4.

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA-613 001

(Affiliated to the T.N.Dr.MGR Medical University, Chennai)

INSTITUTIONAL ETHICAL COMMITTEE

CERTIFICATE

Approval No. : 004

This is to certify that The Research Proposal / Project titled

EVALUATION OF VISUAL EVOKED POTENTIAL AND BRAINSTEM AUDITORY EVOKED POTENTIAL IN MIGRAINE

submitted by Dr. R. SOWMIYA **of**

Dept. of PHYSIOLOGY **Thanjavur Medical College, Thanjavur**

was approved by the Ethical Committee.

Thanjavur

Dated : 06.12.2013

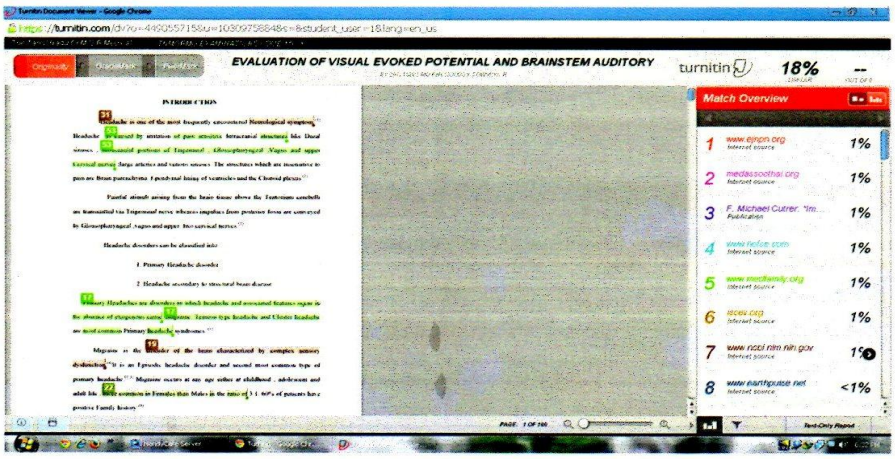
THANJAVUR MEDICAL COLLEGE THANJAVUR-4

Secretary

Ethical Committee

TMC, Thanjavur.

ANTI PLAGIARISM – ORIGINALITY REPORT



ACKNOWLEDGEMENT

I express my sincere gratitude and thanks to my **Professor & HOD Dr.R.VINODHA,M.D.,** Thanjavur Medical College , Thanjavur , for the constant unfathomable guidance, immense support, constructive suggestions and for being a great source of inspiration throughout the period of study.

I would like to thank the Dean , Thanjavur Medical College , Thanjavur , for granting me permission to conduct this research study at Thanjavur Medical College & Hospital , Thanjavur.

I sincerely thank Head of Department of Neuromedicine for permitting me to carry out the study in the outpatient of Department of Neuromedicine.

I express my thanks and gratitude to all my patients who co-operated to undergo the study.

CONTENTS

S.NO	TITLE	PAGE NO.
1	INTRODUCTION	1
2	AIM AND OBJECTIVES	4
3	REVIEW OF LITERATURE	5
4	MATERIALS AND METHODS	50
5	RESULTS	61
6	DISCUSSION	95
7	CONCLUSION	100
8	BIBILOGRAPHY	
9	ANNEXURES	

ABSTRACT

Evaluation of Visual Evoked Potential and Brainstem Auditory Evoked Potential In Migraine

Aim : The present study was undertaken to investigate the visual and brainstem auditory functions in Migraine patients.

Materials And Methods : The subjects were recruited from Out patient Clinic of Department of Neuromedicine, Thanjavur Medical College & Hospital , Thanjavur based on International Headache Society classification for Migraine. Subjects with history suggestive of other types of headache, TTH , cluster headache , sinusitis and subjects with Visual field defects , Auditory deficits are excluded from the study . Forty subjects (16 with Aura & 24 cases – Migraine without aura) in the mean age group of 19 to 52 yrs & forty age / sex matched controls with no history of Headache were selected for the study. Informed written consent was obtained from the subject. Ethical committee approval was obtained from the Institution before commencing the study. A detailed history of Headache duration, frequency and history suggestive of aura and history to rule out other types of headache were noted. Ophthalmologic examination was done to determine visual acuity, Field of Vision, extraocular movements and pupillary diameter. The results were analysed statistically using student 't' test .

Results : There was significant prolongation of P100 & N145 latency ($p<0.05$) in both Migraine with aura and without aura compared with controls. BAEP recording shows significant prolongation of latency of Wave I, III & V and the Interpeak latency I-III, III-V & I-V in Migraine with aura. In Migraine without aura, there was significant prolongation of Wave I, III & V and only III-V IPL & I-V IPL. ($p<0.05$).

Keywords : Migraine , Aura , Visual evoked potential , Brainstem auditory evoked potential.

INTRODUCTION

INTRODUCTION

Headache is one of the most frequently encountered Neurological symptom.[1] Headache is caused by irritation of pain sensitive Intracranial structures like Dural sinuses , intracranial portions of Trigeminal , Glossopharyngeal ,Vagus and upper Cervical nerves ;large arteries and venous sinuses. The structures which are insensitive to pain are Brain parenchyma, Ependymal lining of ventricles and the Choroid plexus.[2]

Painful stimuli arising from the brain tissue above the Tentorium cerebelli are transmitted via Trigeminal nerve whereas impulses from posterior fossa are conveyed by Glossopharyngeal ,vagus and upper two cervical nerves.[2]

Headache disorders can be classified into

1. Primary Headache disorder

2. Headache secondary to structural brain disease

Primary Headaches are disorders in which headache and associated features occur in the absence of exogenous cause. Migraine, Tension type headache and Cluster headache are most common Primary headache syndromes. [3]

Migraine is the disorder of the brain characterized by complex sensory dysfunction.[4]It is an Episodic headache disorder and second most common type of primary headache.[2,3] Migraine occurs at any age either at childhood , adolescent and adult life , more common in Females than Males in the ratio of 3:1. 60% of patients have positive Family history.[5]

Migraine has a great impact on mental , physical , functional and socioeconomic aspects of patient ‘s life.[6] Migrainous have higher lifetime risk of Depressive disorder, Panic disorder, OCD , Generalised Anxiety disorder , phobias and Suicide attempts than the normal subjects.[7]

The Diagnosis of Migraine was based on headache characteristics and associated symptoms which is subjective.[2] Routine Clinical Examination and Testing for Visual function also appears to be normal in Migraine patients. So, Electrophysiological and Psychophysical tests have been carried out in Migraine patients.[6]

The Migraineous brain is hyperexcitable not only during the attack but also in between attack i.e., the interictal phase. There is specific involvement of visual system in Migraine patients. Migraineous aura is visual in about 82 to 90% of cases.[6]Due to frequent occurrence of visual symptoms and due to impairment of Visual processing in Migraine many studies are oriented towards evaluation of VEP changes in Migraine patients which is a simple and Non-invasive test .[8]

Migraine attacks also originate due to abnormal Nociceptive Neuromodulator centers especially the Monoaminergic sensory control systems located in the Brainstem. Neuro-otological symptoms like vertigo, phonophobia, tinnitus, unsteadiness and hearing loss are also common in Migraine. There is a mild bilateral and reversible auditory & vestibular hypofunction during Migraine attack. So, BAEP can be done to assess the function of Brainstem structures traversed by auditory pathways.

Functional and Electrophysiological alterations in cortical functioning also found, an association between Cognitive impairment and Migraine attack.[7]

Hence, Electrophysiological tests like Visual Evoked Potential and Brainstem Auditory Evoked Potential are done in Migraine patients to better understand the pathogenesis of Migraine and to utilize these tests for Diagnosis and Effective management of Migraine.

AIM AND OBJECTIVES

AIMS AND OBJECTIVES

1. To investigate and compare the visual function and Auditory function in Migraine patients and healthy controls.
2. This study was undertaken to evaluate Electrophysiological parameters VEP and BAEP in Migraine patients with and without Aura compared with controls.
3. To evaluate the role of VEP and BAEP in the diagnosis of Migraine.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Migraine is worldwide common, chronic, incapacitating Neurovascular disorder, characterized by attacks of severe headache, Autonomic nervous system dysfunction and an Aura involving neurologic symptoms. Individuals with Migraine appear to process Auditory and Visual information differently from those without Migraine.[7]

HISTORY:

It was Arateus of Cappadocia in the 2nd century AD first identified many of the features of Migraine. Galen in 200 AD named illness using the Greek , as Hemicrania to describe periodic disorder that comprises paroxysmal and blinding hemicranial pain from which the term corrupted to latin "Hemigranea and Migranea" and finally the French translation "Migraine" was obtained in the 18th century.[9]In 1988, the International Headache Society published Guidelines for classification of Headache types. Then, Stewart and Lipton published the American Migraine study.[10]

EPIDEMIOLOGY:

The Lifetime prevalence of Migraine is about 20% in Females and 6% in Males. Migraine may begin at any Age, from early Childhood, although peak age of onset is Adolescent and early Adulthood. [2] Over 90% of sufferers have their first attack by 30yrs of age and commonly affects the working individuals in the population. [1]This chronic illness is widespread among the population, 10% diagnosed & 5 % undiagnosed with seriousness varying from mild distress to chronic daily headache.

ETIOLOGY:

Etiology of Migraine is largely unknown. Proposed causes are

1. Family history suggests Genetic predisposition, positive history is present in 60 to 90 % of cases. One type of Migraine called Familial Hemiplegic Migraine is due to mutation in a gene for P/Q type calcium channel on Chr.19 and a gene encoding Sodium – Potassium ion pump on Chr.1. The calcium channels cause serotonin release in the Midbrain. So, dysfunction of these channels, impair serotonin release and predispose to Migraine attack. The release of CGRP , a Neuropeptide also play a role in Migraine as it is a potent vasodilator.[2]
2. Female preponderance suggests Hormonal influence. Some women have Migraine only around the Menstrual period called Menstrual Migraine which is more intense and last longer.[11]
3. Dietary precipitants – diet such as cheese , chocolate and red wine can precipitate an attack of Migraine.[5]
4. Stress - often trigger an attack in about 70% of cases. Stress may be of Endogenous (eg.Hormone), Exogenous, psychological stress like Emotional, socioeconomic and social stress. These repeated stressors lead to changes in the brain state , characterized by Cortical Excitability , changes in brain Morphology and changes in Behavior.[11]
5. Headache can be initiated or amplified by various triggers like glare , bright lights , sounds or other afferent stimulation ; Hunger, Excess stress , physical exertion , stormy weather or barometric pressure changes , excess sleep or

lack of sleep , alcohol or other chemical stimulation can precipitate an attack.[3]

Acute Migraine attack depends upon the individual‘s inherent level of Vulnerability to an attack. The lower the threshold, the greater the vulnerability for Migraine.

CLASSIFICATION :[12]

Several varieties of Migraine are present.

1. Migraine without Aura (common Migraine)
2. Migraine with Aura (classic Migraine)
3. Complicated Migraine
4. Hemiplegic Migraine
5. Ophthalmoplegic Migraine
6. Basilar Migraine
7. Facioplegic Migraine
8. Retinal Migraine

1. COMMON MIGRAINE:

Migraine without Aura accounts for 80% of cases. A prodrome may occur 24hrs preceding the headache. Prodromal features are hunger, thirst, euphoria, mania, depression, psychomotor slowing or irritability.[10]

In General pain in Migraine is Unilateral, Pulsating, Fronto temporal in distribution usually accompanied by anorexia , Nausea and vomiting.

Patients are intolerant to

- Light (photophobia)
- Sound (phonophobia)
- Odours (osmophobia)[2]

In Children Migraine is characterized by episodic abdominal pain, motion sickness and sleep disturbances.[2]

2. CLASSIC MIGRAINE:

Migraine with Aura is seen in only about 15 to 25% of cases. Migraine auras are focal Neurologic symptoms that precede, accompany or follow an attack. Aura usually evolves over 15 – 20 mins lasts less than 60 mins and involves visual, sensorimotor, language or brainstem disturbances.[2]

Aura symptoms present as

1. FORTIFICATION SPECTRA:

In the Early phase, there is isolated Paracentral Scotomas which slowly expands in to C shape scotoma. It appears colored as the scotoma moves towards the periphery of the involved half of the visual field then gradually it disappears over the horizon of the peripheral vision. This process occurs for 20 – 25 mins. This phenomenon called Fortification Spectra, is due to cerebral structural anomaly.[9,10]

2. Positive visual symptoms such as Shimmering (wavy lines) , tiechopsia and metemorphopsia – distortion of form ,size ,position of objects or environment in part of visual field.[13]
3. Positive sensory symptoms like tingling and dysphasia or aphasia.[13]

4. Weakness, confusion, dysphagia, tinnitus and hemiparesis.

Headache may begin before or simultaneously with aura.[10] There is an association between Migraine especially with Aura and development of Stroke. Migraine is an independent risk factor for stroke. The mechanism involved in developing stroke is Hyperaggregability of the platelet and reduction in the cerebral blood flow in Migraine with aura.

Thus, patients with Migraine are found to develop stroke with increased motor deficit on the basis of Rankin Disability scale which was found to be significantly worse in Migraine patients.

2. COMPLICATED MIGRAINE :

This term refers to Migraine attacks with major neurologic dysfunction i.e., Migraine with hemiplegia or coma which is different from an attack of Aura. In these patients neurologic dysfunction outlasts the headache by hours to 1 or 2 days. Structural brain disease should be ruled out.[2]

3. HEMIPLEGIC MIGRAINE :

Hemiplegic Migraine is a rare Autosomal dominant disorder , mutation in a gene for P/Q type calcium channel located in chromosome 19 is characterized by hemiparesis during the prodromal phase of Migraine which resolves in 20 to 30 mins then contralateral headache begins.[10] A serious form appears as hemiplegia, affecting same side, that persists for days to weeks after head pain subsides.

Dysarthria and aphasia present in 50% of patients. Hemihypesthesia is present in all cases. CSF analysis shows pleocytosis and elevated CSF protein concentration.[9]

4. BASILAR MIGRAINE:

The incidence of Basilar Migraine is common in Children in whom severe episodic headache is preceded by signs of bilateral occipital lobe, brainstem or cerebellar dysfunction like diplopia, ataxia, vertigo and dysarthria. Bilateral sensory and motor disturbances can occur. [(2)]The episodes begin with total blindness which is accompanied or followed by other symptoms. Symptoms persist for 30mins then followed by occipital headache. Sensorial alterations like confusional states will be present for 5 days which may be mistaken for psychotic reactions.[(9)]

5. FACIOPLEGIC MIGRAINE:

Facioplegic migraine also called Lower half headache or Facial Migraine pain is restricted to nose, cheek, gums and teeth on one side of the face. Sometimes transient facial palsy seen. Episodic throbbing Pain often turning into sharp, continuous, deep and dull aching type that last for minutes to hours is characteristic of Facioplegic Migraine. Tenderness and pulsations over the carotid artery and swelling of the soft tissues over the carotid are present on the side of the pain.[(9,12)]

6. OPHTHALMOPLEGIC MIGRAINE:

In Ophthalmoplegic Migraine in addition to attacks of headache there is unilateral third nerve palsy associated with ptosis , dilated pupil and diplopia. Patient presents with periorbital pain for 1 to 4 days as the pain subsides ptosis and palsy occurs. This ophthalmoplegia persist for several days to even 2 months.[(9)]

7. RETINAL MIGRAINE:

It is a rare variant of Migraine. There is sudden transient monocular blindness followed by retro- orbital headache.[12]

PATHOGENESIS OF MIGRAINE:

Migraine can be initiated either by Central mechanisms - by afferent stimulation from central centers in cortex , thalamus and the hypothalamus or by peripheral afferent stimulation via Trigeminal nerve or C1 – C3 nerve roots. Local defects in the Endogenous pain control system prevents inhibition of pain stimulation in the spinal nucleus of Trigeminal nerve.

Mechanism of Migraine can be divided into three phases: Brainstem generation is the first phase ; the second phase is Vasomotor activation in which arteries within and outside the brain contract or dilate ; Third phase is the Activation of the cells of the Trigeminal nucleus caudalis which release vasoactive neuropeptides at the terminations of Trigeminal nerve on blood vessels resulting in soft tissue swelling and tenderness of blood vessels during Migraine attacks.[9]

CONCEPT OF NERVE STORMS:

In 1873, Liveing published the concept of Nerve Storms. According to him the clinically apparent circulatory phenomena of Migrainous attacks were caused by repeated cerebral discharges or Nerve storms.[9]

VASCULAR HYPOTHESIS OF MIGRAINE:

In 1930, Graham & Wolff put forward this hypothesis, they proposed that the

headache phase of Migraine attacks was caused by extracranial vasodilatation and that Neurologic symptoms are produced by intracranial vasoconstriction.[9]

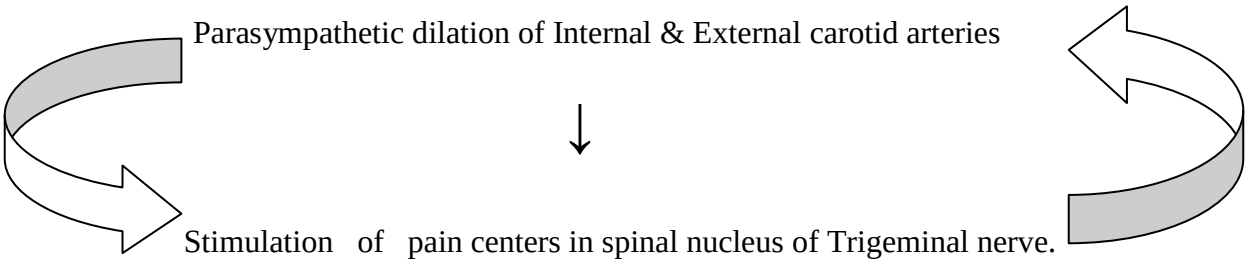
The basis for pain in Migraine is the activation of trigeminal vascular system. First division of Trigeminal nerve innervating the large intracranial vessels and the dura forms the Trigeminal vascular system.[13]

TRIGEMINALVACULAR SYSTEM (TVS):

The TVS arises from the dense plexus of Nociceptors, that innervate the cranial vasculature and the duramater. The central projections from these plexus travel via the trigeminal ganglion which synapse on second order neurons in the dorsal horn that form Trigeminal Cervical Complex (TCC) [14] which is illustrated in Fig 1.

Activation of these sensory afferents releases neuropeptides that act on cerebrovasculature and the spinalcord. The TCC has ascending connections with brainstem areas like Locus coeruleus and Periaqueductal grey, thalamus and the hypothalamus through there ascending tracts. In addition to these the projections are connected to parasympathetic system via superior salivatory nucleus and sphenopalatine ganglion. Activation of this system causes neuronal activation in pontine and brainstem regions.[10]

TRIGEMINAL VASCULAR REFLEX:[10]



Activation of cells in the Trigeminal nucleus releases vasoactive neuropeptides like CGRP , Neurokinin A , substance P and 5-HT serotonin that causes painful meningeal inflammation and vasodilation. These neuropeptides also activates serotonin receptors and nerve endings on small dural arteries, resulting in neurogenic inflammation. These processes in turn stimulate perivascular nerve endings, with resultant orthodromic stimulation of the trigeminal nerve and pain is referred to its distribution.[2]

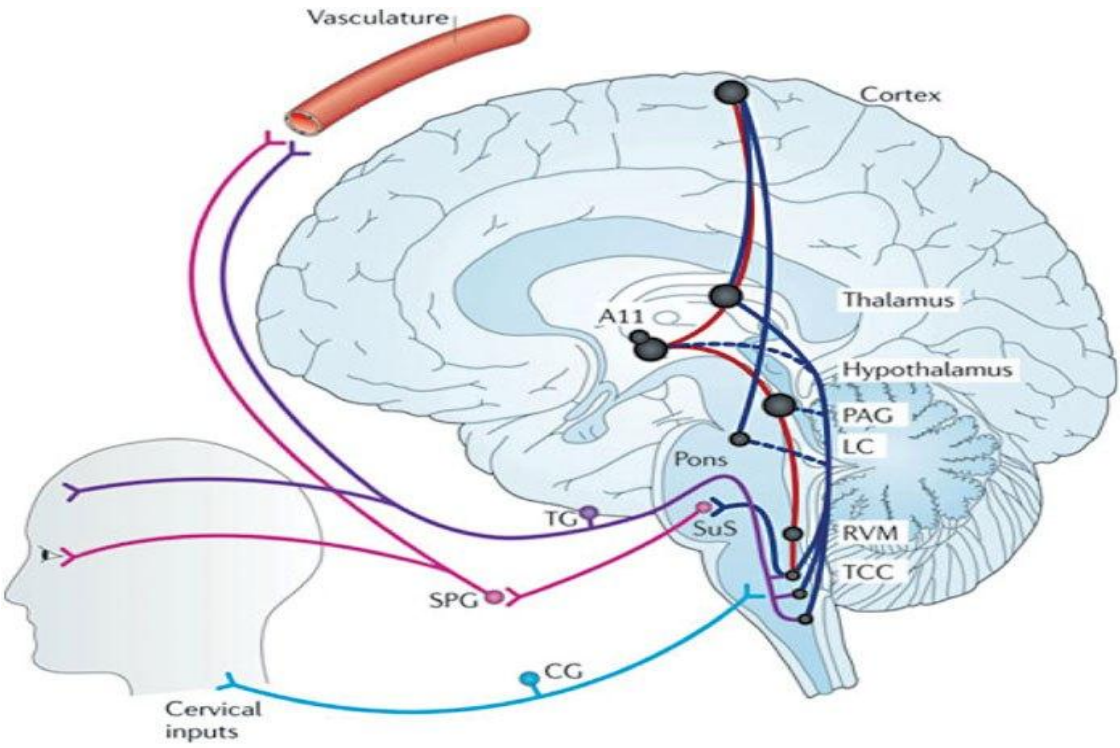


Fig .1 TRIGEMINAL CERVICAL COMPLEX

CORTICAL SPREADING DEPRESSION THEORY:

The pathophysiology of Aura in Migraine can be explained by cortical spreading theory of Leao. According to this theory, the underlying mechanism for aura is the disturbance of the cerebral cortex.[15]

CSD is a short lasting depolarization wave that moves across the cortex at a rate of 3-5 mm /min. A brief phase of excitation heralds the reaction which is immediately followed by prolonged nerve cell depression. Aura represents a spreading front of electrical excitation followed by depression of activity of the cortical cells. Thus, CSD is a wave of neuronal depolarization followed by depressed activity spreading slowly anteriorly across the cerebral cortex from the occipital cortex [14,15] as shown in the figure no.2.

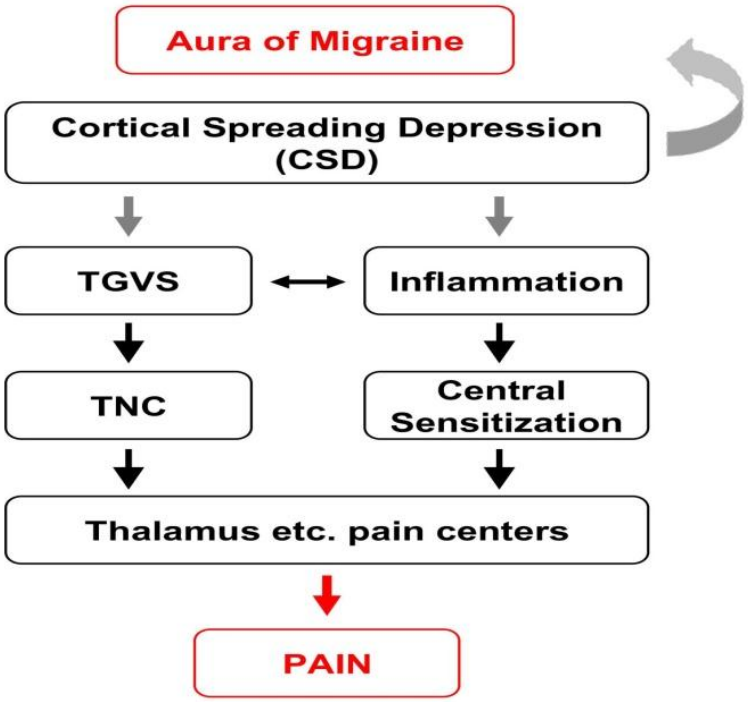
In CSD there is change in the local pathway, cellular environment that produces subtle functional changes in neural performance. Precortical deficits in Migraine group are due to changes in ocular vasoregulation, that results in functional abnormalities either due to hypoperfusion or changes in local cellular environment.

During attacks of Classic Migraine , studies of regional cerebral blood flow showed cortical hypoperfusion which averaged 25 to 30% and progresses anteriorly in a wave like fashion . This hypoperfusion persists for 4 to 6 hrs does not cross the central sulcus and progresses to the frontal lobe via insula. Perfusion in the subcortical region was found to be normal. In few patients focal ischemia was sufficient to cause symptoms.[9]

In attacks of common Migraine , there is no abnormalities in the regional cerebral blood flow . So, these changes in the blood flow are due to alterations in the cerebral neuronal function . Brainstem acts as a Generator for these cortical events.[9]

ROLE OF POTASSIUM:

Potassium plays a central role for CSD that any disturbance in K^+ homeostasis predispose the brain to CSD. In the Brain K^+ homeostasis or clearance system depends on the capacity of glial cells . In humans , the lowest glial neuronal cell ratio is in the primary visual cortex , therefore CSD starts in the visual cortex and most of the auras in Migraine are visual.[15]



OTHER MECHANISMS:

Other systems like Serotonergic , Nor adrenergic and Dopaminergic pathways; Hypothalamic and deep brainstem structures and hormones like estrogen are also involved in the expression of Migraine.

Thus, Migraine can also occur due to neuronal sensitization , neurogenic inflammation leading to many neurochemical changes.[10]

There is dysfunction of neuromodulatory structures in the brainstem such as Locus coeruleus, dorsal raphe nucleus and peri aqueductal grey matter. Locus coeruleus , the major Nor adrenergic nucleus is activated during the acute attack of Migraine. Locus coeruleus dysfunction lead to distractibility and anxiety in Migraine patients.[4]

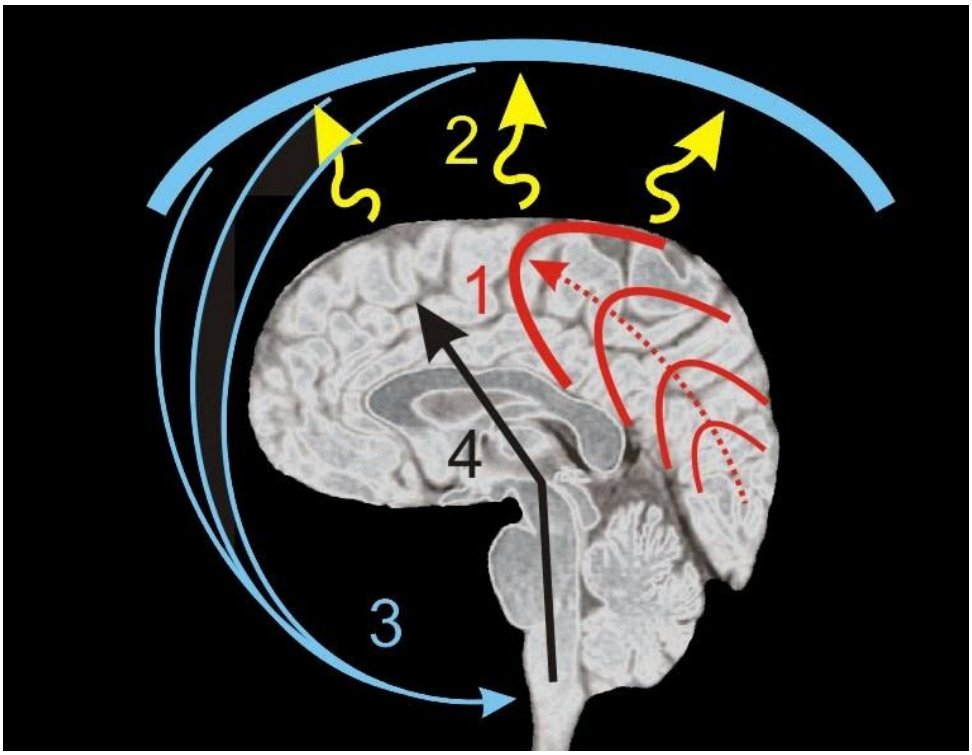


Fig 2 CORTICAL SPREADING DEPRESSION

1. Cortical spreading depression
2. Release of neuropeptides
3. Activation of brainstem
4. Perception of pain.

Electrical stimulation near dorsal raphe nucleus provoke Migraine. Projections from these nucleus terminate on the cerebral arteries and alter cerebral blood flow. The Dorsal raphe also projects to the neurons in the lateral geniculate body, superior colliculus , retina and visual cortex. This explains the anatomical and physiological basis of circulatory and visual characteristics of Migraine. In addition to this the dorsal raphe nucleus stops firing during sleep so sleep ameliorates Migraine.[9] Dysfunction of brainstem not only account for somatosensory component of Migraine but also for the auditory , olfactory and visual components.[10]

X – Y IMBALANCE IN MIGRAINE:

There are two parallel visual pathways, Contrast processing – X system and Luminance Processing Y system. In Migraine patients there is an imbalance between these two pathways with predominance of Luminance processing Y system. X - system receives input mainly from the foveal and perifoveal areas via parvocellular pathway whereas Y – system receives from the retinal periphery via magnocellular pathway .[16]

Abnormality of these two pathways is due to impairment of GABAergic inhibitory interneurons or Dopaminergic transmission. Rieke Oelkers et.al using Pattern reversal VEP, proposed that the P1 component is attributed by the X- system and the N2 component by the Y – system. In Migraine patients, there is prolongation of N2 latency which is due to imbalance between these two pathways which play a role in Migraine pathophysiology.[17]

Interictal Y predominance increases the sensitivity to visual stimuli in Migraine patients. This imbalance also plays a role in habituation behavior i.e. defective habituation in Migraine patients during long periods of pattern reversal stimulation.[18]

MIGRAINE AND COGNITIVE FUNCTION:

Migraine was found to be associated with cognitive impairment which was demonstrated on tests of perception, psychomotor ability, attention and verbal memory.

Mini Mental State Examination :(MMSE)

There is significant difference between patients and controls as regards MMSE. Controls perform better than the Migraine patients. This was explained due to cumulative effects of Migraine attacks which result in subtle CNS dysfunction that occur due to repeated vascular insult.[7]

COGNITIVE RESERVE THEORY:

This theory states that brain injury or damage result in cognitive deficit, after a certain threshold of damage has been achieved. Thus, cognitive deficits are more apparent after a long history of Migraine.[7]

Event related potential (ERP) Component P300 was considered as a cognitive Neuro -electrical indicator of CNS activity. They reported longer P300 latency and lower P300 amplitude which suggests that Migraine is a central disorder, which has deficit in attention or memory.[7]

In another study by Karen E.Waldie et.al. proposed that there is cognitive impairment specific to Migraineurs but from Early age .So, they suggest that Migraine is

associated with Atypical Neurodevelopment in utero or in infancy.[19] Thus , Migraine children have poor Academic performance and generalized impairment in attention.

DIAGNOSTIC CRITERIA :[10]

Based on International Headache Society Classification, Migraine can be diagnosed as:

Criteria for Migraine without Aura(Common Migraine)

A. Atleast 5 attacks lasting 5- 72 hrs

B. Headache has atleast two of the following characteristics ,

- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by routine physical activity

C. Atleast one of the following during headache :

- Nausea or vomiting
- Photophobia
- Phonophobia

CRITERIA FOR MIGRAINE WITH AURA (CLASSIC MIGRAINE):

A. Atleast two attacks

B. Aura must exhibit atleast three of the following characteristics:

Fully reversible and indicative of focal cerebral, cortical or brainstem dysfunction

- Gradual onset
- Lasts less than 60 mins
- Followed by headache with a free interval of less than 1 hour
- Headache may begin before or simultaneously with the aura.

MIDAS (Migraine Disability Assessment Score)[20]

MIDAS is used to assess the extent of patient‘s severity and disability.

MIDAS QUESTIONNARIE

INSTRUCTIONS: Please answer the following questions about ALL headaches you had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headache?_____ days
2. How many days in the 3 months was your productivity at work or school reduced by half or more because of your headache ?_____days
3. On how many days in the 3 months did you not do household work because of your headache? _____days
4. How many days in the 3 months was your productivity in household work reduced by half or more because of your headache ?_____days
5. On how many days in the 3 months did you miss family, social or leisure activities because of your headache? _____days.

A. On how many days in the 3 months did you have a headache ?_____days

B. On a scale of 0 – 10, on average how painful were these headaches?_____.

Migraine Disability Assesment Score[2]

Grade I – Minimal or No disability:0- 5

Grade II - Mild or Infrequent disability : 6 – 10

Grade III – Moderate disability : 11- 20

Grade IV – Severe disability : >2

GENERAL EXAMINATION:

General Examination of the subjects including the vital parameters like Pulse rate, respiratory rate, blood pressure have been done. In addition to this Visual acuity, Examination of Eye, Ear, Nose and Paranasal Sinuses are carried out.

NEUROLOGICAL EXAMINATION:

Neurological Examination performed in the subjects to rule out the secondary causes for headache.

ELECTROPHYSIOLOGICAL STUDY:

EVOKED POTENTIAL:

Evoked potential studies are actually an extension of neurological Examination. Evoked potentials are electrical signals generated by the nervous system in response to visual, Auditory, tactile or any other peripheral stimuli.[21]These studies

reveal the existence and location of neurological lesions. A slow in conduction reflects inflammation or demyelination in the respective pathway. Evoked potential studies also detect clinically silent lesions. These studies like EEG are tests of function and are not Etiologically specific.[22,23]

Visual evoked potential, Brainstem auditory evoked potential and somatosensory evoked potentials belong to afferent evoked potentials whereas Motor evoked responses to electrical or magnetic stimulation reflect multiple synapses between cortex and peripheral muscle are efferent evoked potentials. [23]

Neurophysiological studies can also be used to assess the integrity of reflex functions and their central connections. Thus, Evoked potential techniques are non-invasive have better resolution, that permits to study the functional changes in the CNS.

VISUAL EVOKED POTENTIAL (VEP):

Visual Evoked Potential are electrical potential differences recorded from scalp in response to visual stimuli. VEPs are the summed electrical signals generated by Occipital areas 17 , 18 and 19 in response to visual stimulation.[24] VEPs depend on the functional integrity of the central vision at any level of the Visual pathway , so it assess the integrity of the entire visual system.[25]

Physiological Basis of VEPs:

Retinal ganglion cells classified into X, Y & W cells. X cells are small cells that mediate the colour vision i.e., the cone function. They have small receptive field

concentrated in the central retina (central visual field). X ganglion cells provide substrate for pattern VEPs and exhibit lateral inhibition via geniculate pathway.

Y ganglion cells are large mediate rod function. They have large receptive field and concentrated in the peripheral retina. These cells provide substrate for Flash VEPs via extra geniculate pathway. Activities from the peripheral retina reach the deeper regions of the visual cortex whereas stimulation from the central vision reach the surface of the occipital cortex.

VEPs are elicited by a temporal change in the Visual stimulation. Three types of stimuli are used to record VEP:

1. Luminance (Light) Flashes
2. Pattern Onset / Offset
3. Pattern Contrast Reversal [23]

TRANSIENT LUMINANCE FLASH VEPs:

Flash VEPs are recorded in response to a strobe light or a flashing light - emitting diode (LED) Display or goggles. Recent studies suggest that flash VEPs primarily reflect the activity of striate and extrastriate cortex.[26] They are elicited by a brief flash that subtends a visual field of atleast 20 degree in a dim illuminated room . Flash VEPs are more variable than the Pattern reversal VEP.[25]

Thus Flash VEPs are recommended only in patients with dense media opacities, poor visual acuity, poor fixation. Infants are usually tested with Flash VEP.[27]

PATTERN ONSET/OFFSET:

In Pattern Onset / Offset, the checkerboard pattern is exchanged with a diffuse gray background. The luminance of diffuse background and the checkerboard pattern must be equal.[21]Pattern Onset / Offset VEPs show greater inter-subject variability than the Pattern reversal VEP. This stimulus pattern is effective for the detection of Malingering and for evaluation of patients with Nystagmus.[25]

PATTERN REVERSAL VEP:

Pattern Reversal VEP is the most sensitive and reliable method of recording VEP. The stimulus is change of Black squares to white and white squares to black repeatedly at a specified number of reversals per second. VEP is generated by Foveal and Parafoveal components. Monocular full-field stimulation is used. [22] PRVEP is less variable than the pattern onset /offset and flash VEPs.[26]

WAVEFORM OF VEP:

The Waveform consists of N75, P100 and N145 peaks. The peaks are designated as Negative and Positive followed by the mean peak time.P100 waveform is generated in the occipital cortex due to activation of primary visual cortex and thalamocortical fibre discharge. N145 reflects the activity of the visual association areas 18 and 19. N75- P100 peak to peak amplitude and P100 amplitude are measured. The mean luminance of the pattern should remain constant throughout the contrast reversals. [28]

Waveform of VEP depends upon the temporal frequency of the stimulus. At rapid rates of stimulation i.e., when the light flashes or pattern reversals are repeated frequently

at regular intervals (at 10 Hz or higher) a simpler waveform is obtained. This is called Steady state response.

If the light flash, pattern onset /offset or contrast reversals occurs infrequently (at 1 Hz or less) the entire waveform is obtained. This is called a Transient Response.[23]

MULTIFOCAL VEPs:

Multifocal VEP measurement is a new technique to evaluate the visual function. Here , VEPs are measured simultaneously from many areas of the visual field .The patient is instructed to view a display containing about 60 sectors each sector with a checker board pattern. These VEPs are used to assess disease progression in optic neuritis and multiple sclerosis and to exclude Non – organic visual loss. Multifocal VEPs compared with Multifocal ERG to differentiate diseases of retina from disease of ganglion cell and optic nerve.

Factors affecting VEP: [24]

Factors that affect VEP are:

1. **Age :**

   Amplitude of the VEP is stable in adult life. In the first decade, the amplitude is larger and the mean amplitude is double the adult value. These changes are due to age related changes in both retina and in the visual pathway.

2. **Gender :**

   P100 latency is longer in adult males than the females. This is due to longer

head size and low body temperature in males. P100 amplitude is greater in females than in males. These changes are thought to have a hormonal influence.

3. **Eye dominance :**

   The P100 wave in the dominant eye is shorter and the amplitude is greater than in the Non dominant eye. The amplitude is greater in Right hemifield stimulation in Right handed persons. This is due to neuroanatomic asymmetries in the striate cortex.

4. **Eye movement :**

   Eye movement reduces the P100 amplitude. Latency is not affected by eye movement.

5. **Visual acuity:** The VEP amplitude reduces with reduction in visual acuity. Latency of P100 wave was found to be normal.

6. **Drugs :**

   Drugs that cause constriction of the pupil increases the latency of P100 wave whereas mydriatics decreases the latency.

CLINICAL APPLICATION OF VEP[22]

VEPs are used in the clinical assessment of

- Demyelinating disease like Multiple sclerosis
- Ischemic optic neuritis
- Spinocerebellar degenerations
- Nutritional and toxic amblyopias
- Optic nerve tumours.

VEPs are used to assess the integrity or maturation of the visual pathway in premature infants and preverbal children. Thus, VEPs are most sensitive in diagnosing Optic nerve lesions anterior to the optic chiasm but also detect Retro-chiasmatic or postchiasmatic abnormalities.

AUDITORY EVOKED POTENTIAL:

Auditory evoked potentials are signals produced in the Auditory nerve and the Brainstem after acoustic stimulus. It was Jeweet and colleagues who correctly described the sequence of ABR waveform components.[29]

Auditory evoked potentials can be divided into

1. Short latency component
2. Middle latency AEPs
3. Long latency AEPs

SHORT LATENCY AEPs:

These are series of Neurogenic potentials recorded within 10ms after the stimuli is provided. Short latency AEPs are commonly called Brainstem Auditory Evoked Potential or Far field electrococleography.[30]

Relatively easy to record and the waveforms and latencies are not highly variable among subjects. BAEP are unaffected by subject‘s degree of attention and identical in both waking and sleep state.[30]

MIDDLE LATENCY RESPONSE: Middle latency AEPs are recorded within 80 to 100ms and the peak latencies range from 12 to 65ms .Generators of this response are

located in the thalamus and Auditory cortex. Middle latency AEPs depends on the attention and arousal of the subject.[30]

LONG LATENCY RESPONSE:

These responses are generated by Postsynaptic potentials within areas of cerebral cortex. They are used as probes for cognitive process. Long latency AEPs are used especially in patients who are uncooperative and in legal cases where Non-organic loss should be excluded.[29]

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP):

BAEPs are the potentials recorded from the Ear and scalp in response to a brief auditory stimuli that asses the conduction through the auditory pathway from the auditory nerve up to Midbrain.[31] Transduction of acoustic stimulus by the ear cells create an electrical signal that appear as evoked potential and is carried through the auditory pathway to the brainstem and from there to the cerebral cortex. [32]

BAEPs are recorded within 10ms after the acoustic stimulus. Stimulus is delivered to one ear via headphones while the contralateral ear is masked with continuous white noise at an intensity of 30 to 40db which is below that of the BAEP stimulus.[28]

The stimulus is usually a square wave pulse. If the electrical square pulse causes the diaphragm of the earphone to move toward the patient‘s ear then condensation click is produced. Reversing the polarity produces a rarefaction click .The amplitude of the waveforms are affected by the type of the stimulus. [30]

WAVES OF BAEP:

Five to seven waveforms are recorded within 10ms of auditory stimulus. Wave I originates from the peripheral portion of the eighth cranial nerve adjacent to the cochlea, Wave II arises from cochlear nucleus, Wave III from superior olivary nucleus, Wave IV originates from the lateral lemniscus and Wave V from inferior colliculi. [32]

Wave I is the first prominent upgoing peak in the ipsilateral ear recording channel. It is reduced or absent from the contralateral ear recording channel where as Wave II is more prominent in the contralateral channel recording. Wave III is the prominent upgoing peak, Wave IV is a small wave, sometimes it may be absent or appear as a bifid wave along with Wave V which is the most prominent wave in the recording of BAEP. [32]

Interpeak latencies: [28]

The interpeak latencies measured are I-III, III- V & I- V. They are measured as the distance between the peaks of both waves.

I - V IPL measures conduction from the proximal part of 8th cranial nerve up to the Midbrain. Normal value is 4ms. Prolonged in conditions like demyelination and degenerative diseases. **I-III IPL** represents conduction from the eighth nerve into the core of the lower pons. Normal value is 2.5ms. prolonged in conditions like tumours of the eighth nerve and at pontomedullary junction. **III - V IPL** represents conduction from the lower pons to the midbrain. Normal range is 1.9 – 2.4ms.

Factors affecting BAEP: [31]

Factors that affect BAEP are:

1. **AGE:** Age has an distinct effect on BAEP Waveform latency . Till the age of 18months BAEP is age dependent. Older adults have slightly prolonged I-V IPL than the younger individuals.
2. **GENDER :**

   Females have shorter latency and larger amplitude than males. It is due to higher core body temperature and shorter length of the brainstem auditory pathway.
3. BAEP waveforms are resistant to the effect of various Drugs.

CLINICAL APPLICATIONS OF AUDITORY EVOKED POTENTIAL: [28,33]

- Used to assess conduction through the auditory pathway up to midbrain.
- To assess severity of hearing deficits.
- To assess functioning of middle portion of brainstem and localization of brainstem dysfunction.
- Identification and quantification of hearing loss in children who are uncooperative for audiometry.
- Used for intra operative monitoring of auditory nerve.

Other findings in evoked potentials are cortical evoked potential and nociceptive blink reflex in Migraine patients with and without aura demonstrate lack of habituation during repeated stimulation due to CNS dysfunction.[34]

FINDINGS OF EVOKED POTENTIALS IN MIGRAINE PATIENTS:

VISUAL EVOKED POTENTIAL:

EL- Shater et al.,[35]

Studied, PRVEP in 30 Migraine patients (11 patients with aura & 19 patients without aura) P100 latency was significantly prolonged in Migraine with aura cases not in without aura patients when compared with controls. There is no significant difference in P100 amplitude between patients and controls. They demonstrated that there is subtle neuronal damage within the visual system of migraine patients especially in patients with aura. This may be due to recurrent cerebral hypoperfusion and due to cortical hyperexcitability between attacks.

Laila EL Mosly et al.,[7]

Evaluated the effect of Migraine on quality of life in females and associated changes in evoked potentials . They recorded VEP in 30 Migrainous females and reported that P100 latency was prolonged in Migraine patients but there was no significant difference in P100 amplitude. The prolongation was due to occipital cortex dysfunction that plays a role in the pathogenesis of Migraine and found to have a structural basis.

Pedro.F.Moreira Filho , Adalmir M.Dantas [36]

Studied PRVEP in 27 Migraine patients without aura. The study revealed that there is a significant increase in the latency of P100 wave when compared with controls. On this basis they concluded that VEP–PR can be used for investigation in Migraine patients without aura.

Bockowski.L et al., [37]

Measured VEP in 51 children , 12 with aura and 30 patients without aura and 9 with other variants of Migraine .They showed that P100 latency was significantly prolonged than in the controls and Amplitudes N1 – P100 and P100 – N2 were significantly larger. These abnormalities were related to cortical spreading depression and due to alterations in the central neurotransmission.

N.Ashjazadeh . B.Varavipour [38]

Done VEP in 53 Migraine cases (27 with aura, 26 are with common Migraine). They demonstrated that only in patients with classic Migraine P100 latency was significantly prolonged when compared with controls whereas there is no significant difference in P100 – N140 peak to peak amplitude between patients and controls reported it to be due to hyper excitability of the brain and due to synaptic delay.

Nofal M Khalil , Nigel J Legg ,Duncan J Anderson [6]

Studied PRVEP in 92 Migraine patients. The mean latency of P100 wave was increased significantly in both Migraine with aura and without aura patients. P100 amplitude was increased by 23 % in both Migraine with aura and without aura patients of short duration while it was decreased by 21% for a duration of 30yrs or more. This decline is due to subtle neuronal damage in the visual system from repeated transient ischemia.

Akbar Hamzei Moghaddam et al.,[8]

Recorded VEP in 30 classic Migraine patients and revealed that there was reduction in the amplitude of P100 and increase in P100 latency during an attack as well as after aura. This reduction in amplitude is due to spreading depression wave and that hypo perfusion wave is continued for 4- 6 hrs after an aura. So it persists after an attack also.

Boylu E et al., [39]

Studied VEP in 41 Migraine patients and reported that the latencies of N75, P100 and N145 were significantly prolonged than the controls whereas the N75 – P100 peak to peak amplitude in the study group were lower when compared with controls. So, they suggest that there is persisting dysfunction of pre cortical visual processing which may be relevant in understanding the pathogenesis of Migraine.

Kennard et al.,[40]

Studied VEP in Migraine patients and reported longer P100 latency in Migraine patients with aura. They suggested that prolonged latency have a structural basis due to ischemic damage from repeated attacks. Hyperexcitability of the brain is the cause for changes in P100 latency.

Khalil et al.,[41]

Reported that there is prolonged P100 latency but the study suggested that prolonged latencies are constitutional, perhaps due to synaptic delay.

Bramanti et al .,[42]

Studied about positive correlation of prolonged latency with disease duration and frequency of the attack in Migraine patients. The study reported that P100 latency altered significantly in patients with numerous attacks and longer duration of Migraine, they suggested that prolongation is due to ischemic damage from repeated attacks.

Polich et al., & Schoenen et al .,[43]

Reported that the alteration of P100 latency in Migraine patients was found mainly in Migraine patients with aura and it was significantly correlated with prolonged aura.

Golla & Winter[44]

Was the first to reveal the changes in VEP to repetitive flash stimulus in Migraine patients. They demonstrated VEP in 113 Migraine without aura cases and found significant difference between patients and controls.

Richey et al.,[45]

Measured VEP in 50 patients (29 without aura & 21 with aura). They reported that there is no alteration in the latencies and amplitude was decreased in Migraine patients.

Lehtonen et al., [46]

Studied, VEP to flash stimuli in 33 patients (19 without aura, 14 with aura) they reported that latencies were greater in Migraine patients than the control group.

Mariati et al .,[47]

Obtained VEP - PR in 20 Migraine patients with visual aura and without aura. They observed an increase in the P100 latency in Migraine patients where as amplitude results are quite dispersed among patients and controls. They suggested that alterations in the monoamine neuromediators occur during the interictal period.

Benna P et al ., [48]

Measured VEP in Migraine petients .VEP parameters are normal in Migraine patients when compared with the patients with Vertebro basilar TIA. Thus, PRVEPs are useful in evaluating the damage caused by any noxa, but it cannot clearly emphasize factors predisposing to specific pathology.

Drake ME et al ., [49]

Recorded VEP in 50 patients with common Migraine. The waves N1, P1 and N2 latencies were longer in Migraine patients than in controls and VEP amplitudes were minimally greater. No significant differences were found between patients and controls.

BRAINSTEM AUDITORY EVOKED POTENTIAL:

D Kaushal , S Sanjay Munjal , M Modi , N Panda [50]

Evaluated BAEPs in 25 Migraine patients. They reported prolongation of latencies of Waves I, III & V and I-III & I- V interpeak latencies. These findings suggest

involvement of Brainstem structures as well as activation of brainstem in Migraine patients.

Firat Y et al ., [51]

Measured auditory brainstem responses in pediatric population during the period of an attack and asymptomatic period of Migraine. There is prolongation of wave V and I –V Interpeak latency during the attack in Migraineurs. This indicate that there is a transient impairment of auditory brainstem function in Migraine patients.

Schlake HP et al ., [52]

Reported that in Migraine patients the peak latencies are pathologically delayed but there was no significant difference between patients and controls. However side differences of all the peaks were significantly increased in Migraine patients than the controls. These results indicate that there is permanent impairment in the brainstem function in Migraine patients.

Anil K Dash et al ., [53]

Studied audiovestibular functions in cases of Migraine patients with and without vertigo. BAEP revealed that there is significant prolongation of latencies of wave I, wave III & V and interpeak latencies I- III , III-V & I- V. The study concluded that BAEP abnormalities are the earliest indicator of impending auditory involvement in patients with Migraine.

Laila EL Mosly et al., [7] Evaluated the effect of Migraine on quality of life in females and associated changes in evoked potentials. They measured BAEP in 30 Migraine

patients and reported that there was prolongation of wave III & wave V latency and I-III and I- V interpeak latency but no significant change in III – V interpeak latency both during an attack and in the interictal phase.

Bayazit Y et al ., [54]

Studied BAEP in Migraine patients , they reported abnormal BAEP findings with increased latency of waves I , III & V and the interpeak latency III-V.

Yang Y ,Li P , Ye HC [55]

Explored personality test and BAEPs in 30 Migraine patients. They reported that the latencies of wave I , III & V and the Interpeak latencies of III- V are prolonged and related this prolongation to brainstem dysfunction.

Zgorzalewicz M et al ., [56]

The study evaluated BAEP in children with primary headaches. They reported significant prolongation of latencies of wave III & IV in Migraine children when compared with TTH. This study suggests that brainstem contributes to the pathophysiology of Migraine.

Sherifa A Hamed , Amal Mohammed Elatter [57]

Evaluated vestibular function in 58 Migraine patients and reported prolonged latency of wave III and I-III, III -V& I - V interpeak latencies. This study suggests that in cases chronic Migraine, there is permanent vestibular damage either peripheral or central vestibular pathways.

Drake ME et al ., [49]

In this study BAEP was measured in 50 common Migraine cases. They found that there was significant prolongation of I – V and III - V interpeak latency in Migraine patients. This study suggests dysfunction of brainstem centers possibly related to endorphin or serotonin neurotransmission.

Benna et al ., [48]

Studied BAEP in 20 Migraine patients in which they reported no alterations in BAEP Parameters in Migraine Patients.

HABITUATION IN MIGRAINE: [24]

It has been reported that PRVEP recording in Migraine patients, based on periods of stimulation, the normal habituation pattern was found to be replaced by potentiation in the Interictal period. Defective habituation was present not only for visual processing but also for auditory evoked responses and event related potentials.

This lack of Habituation depend on chemical connections from the brainstem that include serotonin, dopamine, Noradrenaline, acetylcholine and histamine.These transmitters diffusely innervates the layer IV pyramidal cells and the interneurons in the sensory cortices and have regular , tonic , pacemaker activity. Low pre activation level in the sensory cortex and low activity in the raphe cortical serotonergic pathway causes increased thresholds and a supra threshold activation before reaching a saturation or ‘ceiling effect ’. This is responsible for the initial low amplitude waves then followed by high amplitude curves during long periods of stimulation.

Defective habituation had a deleterious effect on metabolic homeostasis in the brain parenchyma. However habituation was thought to protect the cerebral cortex against sensory overload.

OTHER IVESTIGATIONS:

CT / MRI: [58]

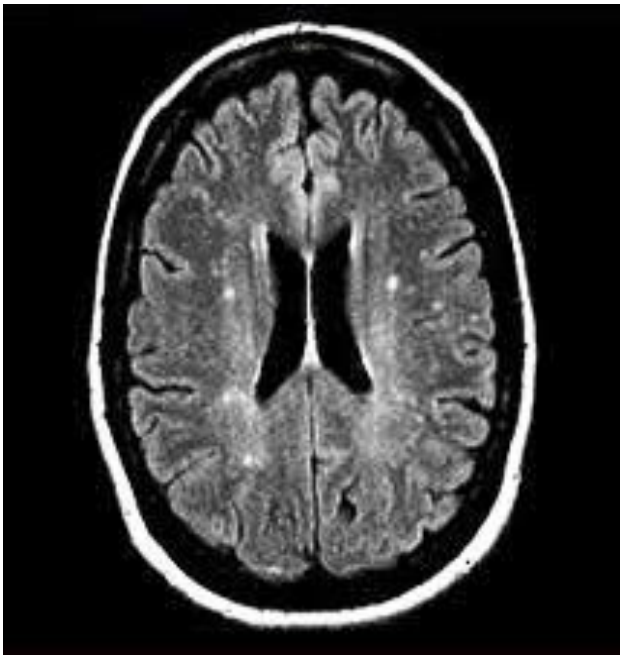
CT / MRI scans are often done in Migraine patients to rule out the secondary causes of headache. CT scan in Migraine patients especially with complicated Migraine reveal cerebral infarction or occlusion commonly in the Posterior cerebral artery is involved producing a deep Parietotemporal infarct. In some cases, Frontotemporal infarct in the territory of Middle cerebral artery has also been reported. The prognosis, functional recovery was found to be good. CT findings in other forms of Migraine are normal.

MRI: [59]

MRI in Migraine patients demonstrated White matter lesions (Fig 3). Anatomical changes are reported in both white matter and to some extent in the gray matter also. These cannot be used as a reliable marker for the diagnosis of Migraine. WMLs are not specific, it may be due to Ischemia, Demyelination and Connective tissue diseases. Significance of presence of WMLs is that Migraine patients are more prone to develop Ischemic stroke especially with Deep white matter lesions (DWMLs) .

Pavese et al ., studied T2 weighted MRI in Migraine patients and found that 19.3% of Migraneurs had DWMLs , So this study documented that Migraine is a risk factor for Cerebral ischemia.

Fig . 3 DWMLs in cerebral cortex



Auditory aura in patients with Migraine manifest in the form of auditory hallucinations but the condition is very rare. A patient with auditory aura was evaluated with MRI and found that there was a lesion in the lateral lemniscus along the auditory pathway. This peduncular lesion represent a migrainous infarct due to vasoconstriction.

This study revealed that either damage to the ascending reticular systems or loss of brainstem control of descending cortical process may be responsible for such changes in Migraine patients.[60]

PET STUDY :[61]

PET Study in Migraine patients revealed significant brainstem activation particularly in the dorsal Pons and Rostral medulla. Other areas which appear activated

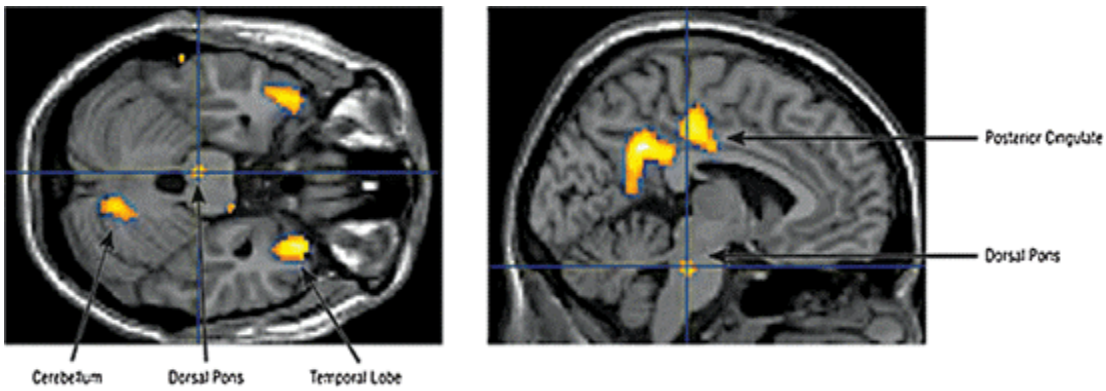


Fig 4 PET STUDY IN MIGRAINE

are anterior cingulate, bilateral Insula , bilateral Cerebellar hemispheres , prefrontal cortex and putamen as shown in Figure 4. PET study taken following treatment with Sumatriptan, showed that dorsal pons remained active even after the treatment. There is an imbalance in activity between brainstem nuclei regulating anti nociception and vascular control.

REGIONAL CEREBRAL BLOOD FLOW (rCBF): [62]

Cerebral blood flow falls by about 20% during attack in Migraine with aura reaching 40 – 50 ml /100g/min. This was explained as due to reduced level of metabolic activity during CSD. In the least perfused areas, the flow has been decreased to 16-23 ml / 100g /min. This degree of hypoperfusion, definitely produces transient hypoxia and neurological deficits due to damage to that area from repeated ischemia. The final pathway for this cell damage follows Neurotoxicity, from the action of Excitatory

aminoacids that results in neuronal damage through prolonged activation of NMDA receptors.[6]

In 1980, Olesen and his coworkers used Xenon blood flow techniques to study the changes that occur during an aura. The study revealed that rCBF reduced mainly in the posterior regions of the brain, hypoperfusion was also seen in Frontal cortex. This decreased blood flow persisted for one hour. After one hour rCBF either normalized or remain decreased in the focal regions. This decrease in blood flow was not sufficient to cause ischemia and was termed just as spreading oligemia.

rCBF was measured by using SPECT during Migraine attacks. Patients with common Migraine showed normal cerebral blood flow pattern during an attack. In patients with classic Migraine most patients displayed unilateral hypoperfusion and few revealed normal perfusion. These changes are not related to distribution of cerebral arteries but to cerebral metabolism with increase in the lactate levels.[59] Studies of cerebral blood flow suggests that there are areas of focal ischemia surrounded by hyperemia during Migraine attack. They also demonstrated elevated GABA and cAMP after an Migraine attack which represents cerebral ischemia occurs during an attack.

ELECTRO NYSTAGMOGRAPHY (ENG): [63]

ENG reveals horizontal deviations, indicating impairment of vigilance in Basilar type of Migraine in whom vestibule cochlear functions are impaired. In other types of Migraine ENG was found to be normal.

CSF ANALYSIS IN MIGRAINE :[64,65]

CSF in Migraine patients, in classic and common Migraine reveal normal cell count and normal CSF pressure both during and in between attacks but the total protein content was lower than in the controls. The CSF 5-hydroxy indole acetic acid (5- HIAA) was found to be higher in Migraine patients during attacks. 5–HIAA is the end product of serotonin metabolism, this suggests that serotonin plays an important role in the pathophysiology of Migraine.

FUNCTIONAL NEURO IMAGING: [66]

Perfusion weighted Imaging (PWI)–Gadolinium based fMRI technique was applied to study about Migraine aura. PWI is sensitive to microvascular changes, minimally Invasive and has higher spatial resolution than radionuclide based techniques. fMRI evaluates both hemodynamic changes and metabolic parameters at the same time.

They proposed that relative cerebral blood volume and relative cerebral blood flow decreased in Migraine patients on average of 35% and 19% respectively while the mean transit time was increased by 32% in the gray matter of the occipital cortex opposite to the affected visual hemifield. Hemodynamic changes are not seen in other areas like thalamus, frontal & temporal cortex or brainstem during an attack of aura.

Additional information was obtained from Magnetization Transfer Imaging (MTI) and Diffusion Tensor imaging (DTI).[59]

MTI in Migraine patients showed that the WMLs are due to ischemia with relative gliosis, there is no infarction. There is no significant difference between patients and controls using this technique.[59]

DTI detect ischemic tissue with higher resolution and sensitivity than the conventional MRI. Here the histograms of the average mean diffusivity (D) of the normal appearing white matter (NAWM) Was lower in Migraine patients than the controls. This damage may be due to recurrent ischemia or secondary to Wallerian degeneration of axons projecting into NAWM from the WMLs. They also suggested that cortical reorganization occurs due to deep WMLs. Though, White matter lesions are most commonly seen anatomical changes in Migraine, it cannot be considered as a bio- marker for the diagnosis of Migraine.[59]

Complications of Migraine:

- Chronic Migraine
- Status Migrainosus
- Persistent aura without Migraine
- Migrainous Infarction
- Migraine triggered Seizures.

TREATMENT: [2]

The aim in Migraine treatment is to reduce the severity, frequency and duration of an attack and to improve the life quality of the patient.

- Non – pharmacologic treatment
- Management of Acute attack
- Preventive therapy.

NON –PHARMACOLOGIC TREATMENT: [10]

This includes Identification and avoidance of headache triggers, regulated lifestyle, stress management that includes Yoga, Meditation, Hypnosis, balanced diet and Biofeedback relaxation. All these measures decrease neuronal irritability and reduce the frequency of attacks. If these measures fail, pharmacologic treatments are necessary.

MANAGEMENT OF ACUTE ATTACK: [2,3]

Acute treatment should begin as soon as possible after the onset of headache. Repeated use of analgesics should be avoided because it exacerbates the pain. Mode of treatment depends on the severity of attacks. Mild attacks need oral therapy that yields 50 to 70% efficacy. During attacks the Gastrointestinal motility will be reduced so, drug absorption will be impaired. If the oral agents fail then rectal administration of Ergotamine, subcutaneous triptans are given. In Classic Migraine, Ergotamine is given either sublingually or rectally to abort the attack during the prodromal phase. Severe attacks require Parenteral therapy.

Three major classes of drugs used are

a. Anti inflammatory drugs
b. 5 HT receptor agonists
c. Dopamine receptor antagonists

Anti inflammatory drugs:

NSAIDs reduce both severity and duration of Migraine attack. For effectiveness it should be taken early during an attack. A combination of Acetaminophen, Aspirin and Caffeine can be used for effective therapy. Major side effects are dyspepsia and gastrointestinal irritation.[3]

5 HT RECEPTOR AGONISTS:[67]

These drugs can be administrated via oral, nasal or parenteral depending upon the severity of the attack. Triptans act on $5HT_{1b}$ receptors and produces constriction of cranial vessels, through $5HT_{1D}$ receptors they inhibit peripheral trigeminal afferents that innervate the vessels and the duramater. Peripheral inhibition also involves inhibition of CGRP release thereby reducing the trigeminally mediated inflammatory process.

ORAL ROUTE :

Ergotamine and Dihydroergotamine are non selective 5 HT receptor agonists. Triptans are selective agonists. Triptans commonly used are Sumatriptan , Naratriptan , Zolmitriptan and Frovatriptan . Monotherapy with triptans are not effective so, co-administration of NSAIDs with triptans are recommended. Triptans are avoided when there is any vascular disease and Ergotamine group of drugs are contraindicated in pregnancy, hypertension, ischemic heart disease and peripheral vascular disorders. [3]

NASAL ROUTE:

Nasal formulations available are Dihydroergotamine and Zolmitriptan, they provide faster and more effective relief.

PARENTERAL:

Parenteral administration of Dihydroergotamine and sumatriptan were approved. Following Administration, peak plasma levels reach by 3mins via I.V. route , 30mins after I.M. and 45mins after subcutaneous route.[3]

DOPAMINE ANTAGONISTS:

Dopamine antagonists are used as adjunctive in Migraine therapy. Addition of dopamine antagonists like Metaclopramide increase gastric absorption of other drugs also. Parenteral drugs like Chlorpromazine, Prochlorperazine and Metaclopramide provide acute relief from Migraine.[13] CGRP antagonists are effective in acute treatment eg. Telcagepant.

OTHER MEDICATIONS: [3]

The combination of Acetaminophen, dichloralphenazon and isometheptene can be given orally. Butorphanol nasal preparation can be used in selected group of persons. Narcotics are beneficial in acute management of pain. The main drawback is that it causes craving or withdrawal and can aggravate the attack. So they are limited to patients with severe headache not responding to other therapies.

PREVENTIVE THERAPY: [3]

Preventive therapy is initated in patients with increasing frequency of Migraine attacks or in those who are not responding to the current treatment. Drugs used are Amitriptyline , Propranolol , Timolol , Sodium valporate , Topiramate and Methysergide. These drugs should be taken daily and have the capacity to stabilize

Migraine. The probability of success with single Anti – Migraine drug is 50- 75 %. Thus, these drugs can alter the natural history of Migraine.

Relaxation technique in Migraine: [68]

Lifestyle and behavior modification programmes can significantly lower the frequency as well as the severity of Migraine attacks. Meditation along with deep breathing can be used as adjuncts to routine anti Migraine treatment.

PROGNOSIS:

Prognosis in Migraine patients is highly variable. Severity decreases with age, whereas in patients with aura without headache severity increases with age. Modification of trigger factors can improve the condition. In some cases Migraine can turn in to chronic, defined type with 15 days headache/month particularly in obesity and low socio economic state condition.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study, a case control study was conducted in the Research laboratory, Department of Physiology, Thanjavur Medical College & Hospital, Thanjavur. The study period extended from August 2013 to June 2014. The subjects were recruited from the Out-patient clinic of Department of Neuromedicine. The study group comprises of 40 Migraine patients who are subdivided in to 16 patients – Migraine with Aura and 24 patients – Migraine without Aura , 4 males and 36 females of age group 19 to 52 yrs were selected according to International Headache Society Diagnostic Criteria for Migraine.

Patients with history suggestive of other types of headache, TTH, cluster headache, sinusitis and subjects with Visual field defects, auditory deficits are excluded from the study.

Out of 40 controls, 6 males and 34 females of age group of 19 to 55yrs with mean age of 35.45 ± 9.9 years with no history of headache, healthy controls were included in the study.

INCLUSION CRITERIA:

Patients in the age group of 19 to 52 yrs diagnosed as Migraine with episodes of headache for atleast 2 yrs and atleast 2 attacks per month in the last quarter year were included in the study.

EXCLUSION CRITERIA:

Subjects with

- Neurological diseases
- Ophthalmic diseases
- ENT & Systemic diseases
- Visual and Auditory deficits.

Ethical Committee approval was obtained from the institution before commencing the study. The nature of the study was explained to the subjects, an informed written consent was obtained from the subjects prior to the study.

A detailed history of Headache duration, frequency and history suggestive of aura and history to rule other types of headache were noted. Ophthalmologic examination was done to determine visual acuity, Field of Vision, extraocular movements and pupillary diameter. All patients had Visual acuity 6/6 or corrected with optical lenses and none had any visual disorder.

ELECTROPHYSIOLOGICAL ASSESSMENT:

The following elctrophysiological parameters are studied in cases & controls.

- Visual Evoked Potential (VEP)
- Brainstem Auditory Evoked Potential (BAEP)

All the parameters (Latency & Amplitude) were recorded using Four channel polygraph , Digital intex colour monitor , 17 ” model no: IT – 173 SB.

Method of recording VEP: [32]

Electrodes are placed using 10-20 electrode placement system.

Visual evoked potential:

The subjects were informed about the procedure of the VEP test and informed consent was obtained from the subject.

Pre test instructions: [28]

- The subject is asked to avoid applying hair oil or spray after the last hair wash.
- If the subject uses optical lenses, glasses should be worn during the test.
- The subject is instructed not to use any miotics or mydriatics 12hrs before the test.
- The room should be quite and comfortable.

Procedure:

The patternshift Visual evoked potential was measured separately for Right eye and Left eye . It involves the following steps:

- The skin is prepared by abrading and degreasing before applying the electrodes for proper contact of electrodes.

- ACTIVE ELECTRODE:

  Placed at Oz - 10% from the inion using EEG paste as per 10-20 international system for electrode placement.

- REFERENCE ELECTRODE : Reference electrode is placed at FPz position.

- GROUND ELECTRODE: Ground electrode is placed at vertex Cz as shown in Fig no.7.

- The subject is instructed or made to sit at a distance of 1m from the VEP screen. (Zebronics CRT monitor showing pattern reversal stimuli in checker board pattern with reversal rate 2/sec , contrast 50-80 % , check size 28-32 of arc and average number of trials – 100)

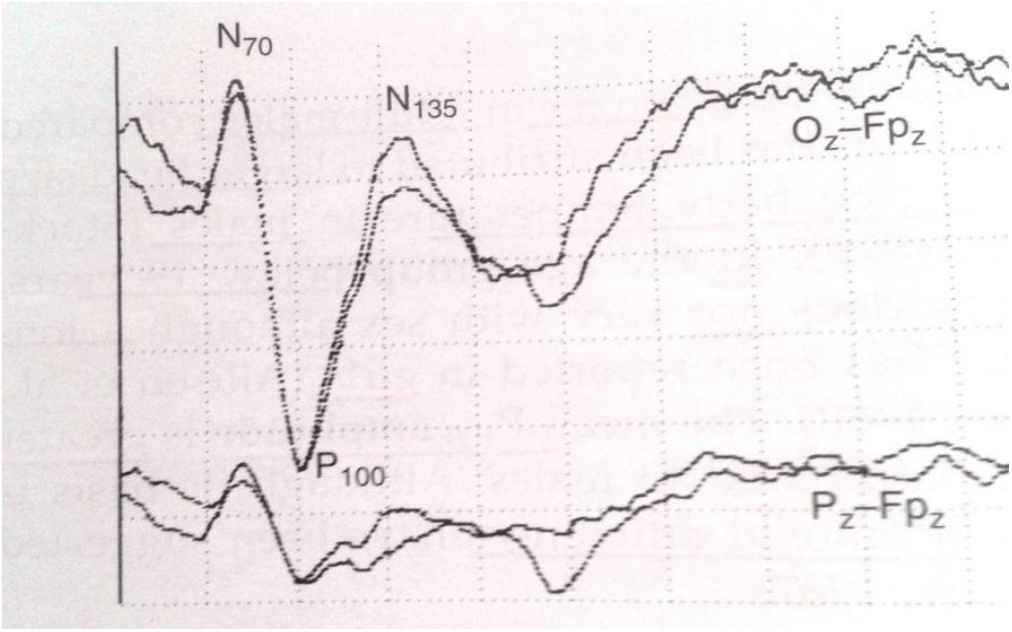
  A waveform is obtained. VEP latencies (N75, P100 & N145 in ms) are marked as in Fig 5.

RECORDING OF VEP

(Instrument setting for VEP)

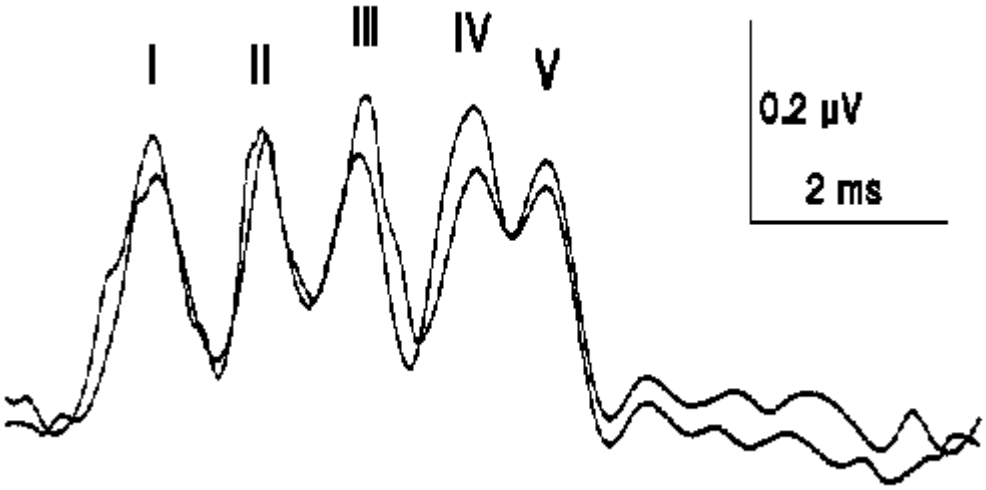
Settings	VEP
Sweep	20msec
Sensitivity	10µv
Low cut	2Hz
High cut	200Hz
Pulse	1/sec
Pulse width	0.1msec
Notch	Off
Recordings	100 average was recorded using checker board pattern stimulus

Fig 5 Normal VEP Waveform



Parameters	**Mean value**
P100 latency(ms)	96.9 ±3.6
Amplitude(μv)	1.5 ± 0.5
Duration(ms)	55.9 ± 7.7

Fig 6 Normal BAEP Waveform



WAVEFORM	GENERATORS
I	VIII Nerve
II	Cochlear nucleus
III	Superior olivary nucleus
IV	Lateral lemniscus
V	Inferior colliculi

Brainstem auditory evoked potential:

The subject was explained about the procedure of the test and informed consent was obtained.

Pre test instructions: [31]

- The subject is asked to avoid applying hair oil or spray after the last hair wash.
- Examination of external ear and hearing tests (Rinne‘s & Weber test) are done.
- Room should be quite and comfortable.

Procedure:

The procedure is explained to the subject. It involves the following steps..

- The skin is prepared by abrading and degreasing before applying the electrodes for proper contact.
- Electrodes are placed according to 10 – 20 electrode placement system.

  Channel 1 is placed at Cz - Ai (ipsilateral ear)

  Channel 2 is placed at Cz - Ac (contralateral ear)
- Ground electrode is placed 20% from the Nasion – Fz position.
- Auditory stimulus in the form of click sound is delivered through the headphones.

  Clicks are delivered at a rate of 8-10 /sec

  Intensity of the stimulus is set at 60db

  About 100 averages were recorded as in Fig 8.

RECORDING OF BAEP

(Instrument setting for BAEP)

Settings	BAEP
Sweep	5msec
Sensitivity	10µv
Low cut	100Hz
High cut	10kHz
Pulse	11/sec
Pulse width	0.1msec
Notch	On
Decibel	60db
Recordings	100 average was recorded using click stimulus

BAEP waveforms Wave I, II, III, IV& V are obtained as in the Fig 6.

Statistical Analysis:

Electrophysiological parameters were analysed by using statistical package SPSS version 20. The statistical analysis was done using unpaired student ‘t ’ test.

VEP RECORDING

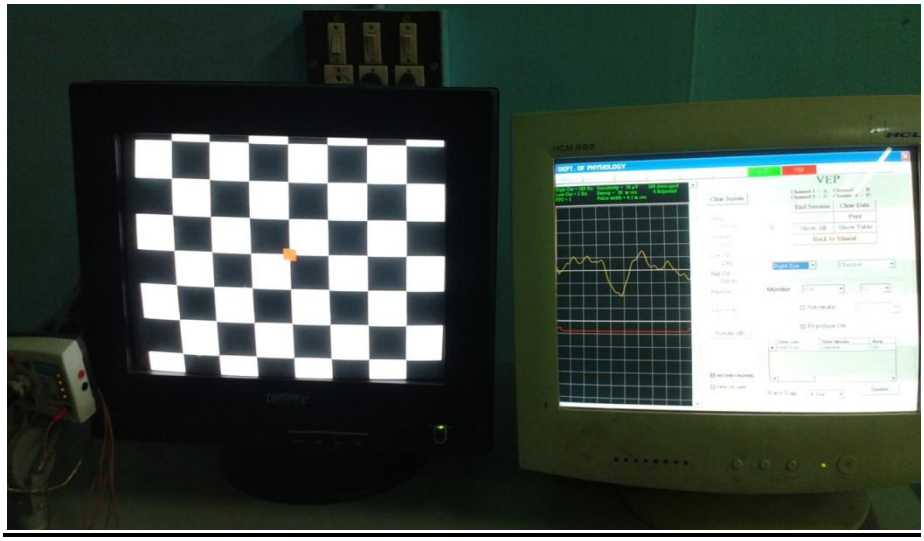


Fig 7

BAEP RECORDING

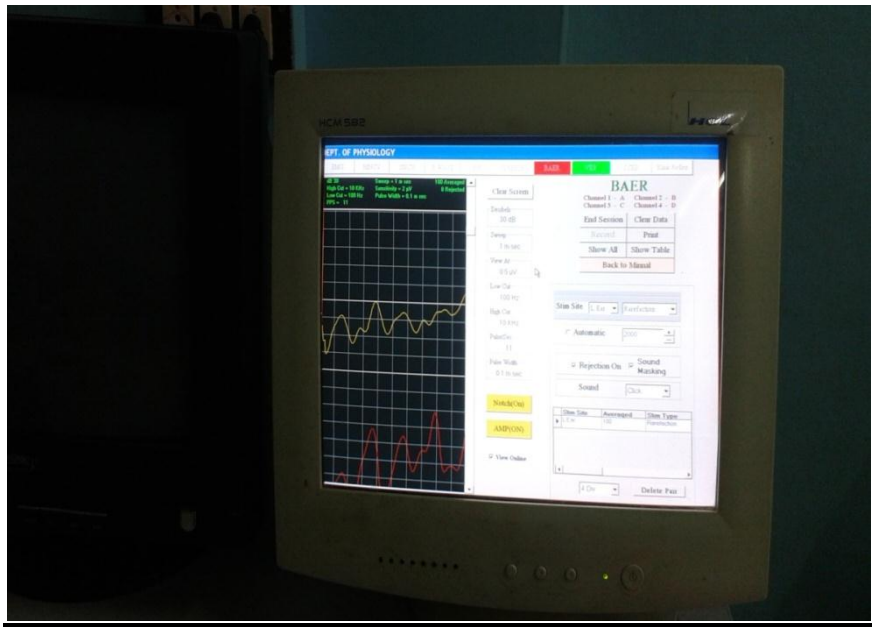


Fig 8

RESULTS

RESULTS

The study group comprises of 40 Migraine patients who are subdivided in to 16 patients – Migraine with Aura and 24 patients – Migraine without Aura , 4 males and 36 females of age group 19 to 52 yrs were selected according to International Headache Society Diagnostic Criteria for Migraine. Out of 40 controls, 6 males and 34 females of age group of 19 to 55 yrs with mean age of 35.45 ± 9.9 years with no history of any headache were included in the study.

The mean values and their standard deviation for the control group and study group - Migraine patients with aura and without aura were tabulated. Various electrophysiological parameters in VEP and BAEP are compared between the two study groups and the control group.

The results were analysed using student t test. P value less than 0.05 was considered as statistically significant.

Findings of evoked potential study in Migraine with Aura : (Table 3)

- **Visual Evoked Potential :**

  Our study results showed that there was a significant prolongation of P100 and N145 Latency with P value < 0.05 whereas P100 amplitude value was increased in Migraine with aura patients when compared with controls but it was not statistically significant with P value 0.654.

- **Brainstem Auditory Evoked Potential :**Study results showed a significant prolongation in the Latencies of wave I , III & V and the Interpeak Latencies I - III , III – V & I - V ($p < 0.05$) as compared to control group.

Visual Evoked Potential : (Table 4)

- **VEP N75 Latency:** The mean value of N75 in Migraine with Aura was found to be 71.5438± 3.41818 and in the control group it is 70.5750 ± 4.20058 with P value 0.416 and the difference was found to be insignificant.
- **P100 Latency:** P100 Latency mean value in Migraine with Aura was observed to be 102.0625 ± 5.70782 and in the control group it is 95.1625 ± 3.56512 with P value 0.000 and the difference was found to be statistically significant.
- **N145 Latency:** The mean value of N145 in Migraine with Aura was found to be 136.2188 ± 10.45302 and in the control group it is 129.9875±8.61460 with P value 0.025 and found to be statistically significant.
- **P100 Amplitude:** P100 Amplitude mean value in Migraine with Aura was observed to be 6.2344 ± 3.28791 and in the control group it is 5.7975 ± 3.27955 with P value 0.654 and the difference was found to be statistically insignificant.

Brainstem Auditory Evoked Potential : (Table 4)

Latencies of Wave I, III & V and the Interpeak latencies I-III, III – V & I-V were measured.

- **WAVE I:** The mean value of wave I latency in Migraine with Aura was observed to be 1.2725±0.29322 and in the control group 1.1222±0.22525 with P value 0.044 and found to be statistically significant.

- **WAVE III:** Wave III latency in Migraine with Aura was observed to be 3.9381±0.62159 and in the control group 3.4323±0.63872 with P value 0.009 and found to be statistically significant.
- **WAVE V:** The mean value of wave V latency in Migraine with Aura was observed to be 6.3444±1.39867 and in the control group 5.6510±0.91618 with P value 0.033 and found to be statistically significant.
- **I - III IPL:** I – III Interpeak latency in Migraine with Aura was observed to be 2.6625±0.57633 and in the control group 2.2797±0.57041 with P value 0.028 and found to be statistically significant.
- **III – V IPL:** III – V Interpeak latency in Migraine with Aura was observed to be 2.5906±0.57130 and in the control group 2.2420±0.45662 with P value 0.020 and found to be statistically significant.
- **I – V IPL:** The mean value of I-V IPL in Migraine with Aura was observed to be 5.2556±1.04950 and in the control group 4.4888±0.81594 with P value 0.005 and found to be statistically significant.

Findings of evoked potential study in Migraine without Aura: (Table 2)

- **Visual Evoked Potential :**

  Our study results showed that there was a significant prolongation of P100 and N145 Latency with P value < 0.05. P100 amplitude did not differ significantly when compared with controls with P value 0.732.

- **Brainstem Auditory Evoked Potential:** Study results showed a significant prolongation in the Latencies of wave I, III & V and the Interpeak latencies

III – V & I - V ($p < 0.05$) as compared to control group. I - III IPL was not significantly prolonged.

Visual Evoked Potential : (Table 5)

- **VEP N75 Latency:** The mean value of N75 in Migraine without Aura was found to be 71.4896± 4.62653 and in the control group it is 70.5750 ± 4.20058 with P value 0.420 and the difference was found to be insignificant.
- **P100 Latency:** P100 Latency mean value in Migraine without Aura was observed to be 99.9792 ± 5.06261 and in the control group it is 95.1625 ± 3.56512 with P value 0.000 and the difference was found to be statistically significant.
- **N145 Latency:** The mean value of N145 in Migraine without Aura was found to be 134.5833 ± 5.45369 and in the control group it is 129.9875 ± 8.61460 with P value 0.022 and found to be statistically significant.
- **P100 Amplitude:** P100 Amplitude mean value in Migraine without Aura was observed to be 5.5371 ± 2.23703 and in the control group it is 5.7975 ± 3.27955 with P value 0.732 and the difference was found to be statistically insignificant.

Brainstem Auditory Evoked Potential: (Table 5)

Latencies of Wave I ,III & V and the Interpeak latencies I-III , III – V & I-V were measured.

- **WAVE I :** The mean value of wave I latency in Migraine without Aura was observed to be 1.3900±0.35864 and in the control group

1.1222±0.22525 with P value 0.000 and found to be statistically significant.

- **WAVE III :** Wave III latency in Migraine without Aura was observed to be 3.7850 ± 0.56300 and in the control group 3.4323 ± 0.63872 with P value 0.029 and found to be statistically significant .
- **WAVE V:** The mean value of wave V latency in Migraine without Aura was observed to be 6.3321±0.81817 and in the control group 5.6510±0.91618 with P value 0.004 and found to be statistically significant.
- **I - III IPL :**

  I – III Interpeak latency in Migraine without Aura was observed to be 2.3908 ± 0.41921 and in the control group 2.2797 ± 0.57041 with P value 0.411 and found to be statistically insignificant.
- **III – V IPL:**

  III – V Interpeak latency in Migraine without Aura was observed to be 2.5567±0.52122 and in the control group 2.2420 ± 0.45662 with P value 0.014 and found to be statistically significant.
- **I – V IPL :**

  The mean value of I - V IPL in Migraine without Aura was observed to be 4.9529 ± 0.67163 and in the control group 4.4888 ± 0.81594 with P value 0.022 and found to be statistically significant.

Comparsion of Parameters Between Migraine With Aura And Without Aura: (Table 6)

When Electrophysiological parameters(VEP N75,P100 & N145 latency and P100 amplitude, BAEP Wave I,III & V and IPL I- III , III- V & I - V) were compared

between two groups Migraine with aura and without aura , Our study results did not show any significance between two groups but when the individual parameters were compared , the values of Migraine with aura are larger than Migraine without aura.

Visual Evoked Potential :

- **VEP N75 Latency:** The mean value of N75 in Migraine with Aura was found to be 71.5438± 3.41818 and in the Migraine without aura it is 71.4896± 4.62653 with P value 0.968 and the difference was found to be insignificant.
- **P100 Latency:** P100 Latency mean value in Migraine with Aura was observed to be 102.0625 ± 5.70782 and in the Migraine without aura it is 99.9792 ± 5.06261 with P value 0.233 and the difference was found to be statistically insignificant.
- **N145 Latency:** The mean value of N145 in Migraine with Aura was found to be 136.2188 ± 10.45302 and in the Migraine without aura it is134.5833 ± 5.45369 with P value 0.521 and found to be statistically insignificant.
- **P100 Amplitude:** P100 Amplitude mean value in Migraine with Aura was observed to be 6.2344 ± 3.28791 and in the Migraine without aura it is 5.5371 ± 2.23703 with P value 0.429 and the difference was found to be statistically insignificant.

Brainstem Auditory Evoked Potential:

Latencies of Wave I, III & V and the Interpeak latencies I-III, III – V & I-V were measured.

- **WAVE I:** The mean value of wave I latency in Migraine with Aura was observed to be 1.2725±0.29322 and in Migraine without aura it is 1.3900±0.35864 with P value 0.283 and found to be statistically insignificant.
- **WAVE III:** Wave III latency in Migraine with Aura was observed to be 3.9381 ± 0.62159 and in Migraine without aura 3.7850 ± 0.56300 with P value 0.424 and found to be statistically insignificant.
- **WAVE V:** The mean value of wave V latency in Migraine with Aura was observed to be 6.3444 ±1.39867 and in the Migraine without aura 6.3321±0.81817 with P value 0.972 and found to be statistically insignificant.
- **I - III IPL :**

  I – III Interpeak latency in Migraine with Aura was observed to be 2.6625 ± 0.57633 and in Migraine without aura 2.3908 ± 0.41921 with P value 0.092 and found to be statistically insignificant.
- **III – V IPL:**

  III – V Interpeak latency in Migraine with Aura was observed to be 2.5906 ± 0.57130 and in Migraine without aura 2.5567±0.52122 with P value 0.847 and found to be statistically insignificant.
- **I – V IPL :**

  The mean value of I - V IPL in Migraine with Aura was observed to be 5.2556 ± 1.04950 and in Migraine without aura 4.9529 ± 0.67163 with P value 0.272 and found to be statistically insignificant.

Table 1: **Electrophysiological findings in the Control group (n= 40)**

PARAMETER	**Control (n=40)**			
	Min.	***Max.***	***Mean***	***S.D***
N75	62.25	78.00	70.5750	4.20058
P100	86.50	101.25	95.1625	3.56512
N145	112.75	163.00	129.9875	8.61460
P100 AMPLITUDE	.55	16.29	5.7975	3.27955
WAVE I	.70	1.50	1.1223	.22525
WAVE III	2.33	5.83	3.4322	.63872
WAVE V	3.63	8.02	5.6510	.91618
I - III IPL	1.34	4.64	2.2798	.57041
III - V IPL	1.30	3.72	2.2420	.45662
I -V IPL	2.64	6.41	4.4888	.81594

Table 2 : **Electrophysiological findings in the Study group Migraine without aura (n = 24)**

Parameters	Min	Max	Mean	Std deviation
N75	63.00	83.00	71.4896	4.62653
P100	90.00	109.50	99.9792	5.06261
N145	125.50	149.25	134.5833	5.45369
P100 AMPLITUDE	1.13	9.22	5.5371	2.23703
WAVE I	.61	2.09	1.3900	.35864
WAVE III	2.76	4.93	3.7850	.56300
WAVE V	4.74	8.45	6.3321	.81817
I - III IPL	1.63	3.24	2.3908	.41921
III - V IPL	1.86	4.08	2.5567	.52122
I -V IPL	3.80	6.36	4.9529	.67163

Table 3 : Electrophysiological findings in the Study group Migraine with Aura

(n = 16)

Parameters	Min	Max	Mean	Std deviation
N75	66.50	78.25	71.5437	3.41818
P100	93.75	114.25	102.0625	5.70782
N145	121.00	153.00	136.2187	10.45302
P100 AMPLITUDE	1.07	13.08	6.2344	3.28791
WAVE I	.57	1.72	1.2725	.29322
WAVE III	3.03	5.11	3.9381	.62159
WAVE V	3.01	8.21	6.3444	1.39867
I - III IPL	1.93	3.53	2.6625	.57633
III - V IPL	1.91	3.52	2.5906	.57130
I -V IPL	4.01	6.63	5.2556	1.04950

Table 4 : Electrophysiological findings in cases(Migraine with aura) & Control group

Parameters	Migraine with Aura	Control	P value
	Mean ± SD	Mean ± SD	
VEP Latency			
N75	71.5438± 3.41818	70.5750 ± 4.20058	0.416
P100	102.0625 ± 5.70782	95.1625±3.56512	0.000
N145	136.218 ± 10.45302	129.9875±8.61	0.025
P100 Amplitude	6.2344 ± 3.28791	5.7975 ± 3.27955	0.654
BAEP Latency			
Wave I	1.2725±0.29322	1.1222±0.22525	0.044
Wave III	3.9381 ± 0.62159	3.4323±0.63873	0.009
Wave V	6.3444±1.39867	5.6510±0.91618	0.033
I – III IPL	2.6625±0.57633	2.2797±0.57041	0.028
III – V IPL	2.5906±0.57130	2.2420±0.45662	0.020
I – V IPL	5.2556±1.04950	4.4888±0.81594	0.005

P Value > 0.05 Not significant.

Table 5 : Electrophysiological findings in cases(Migraine without aura) & Control group

Parameters	Migraine without Aura	Control	P value
	Mean ± SD	Mean ± SD	
VEP Latency			
N75	71.4896± 4.62653	70.5750 ± 4.20058	0.420
P100	99.9792± 5.06261	95.1625±3.55126	0.000
N145	134.5833 ± 5.45369	129.9875±8.61	0.022
P100 Amplitude	5.5371 ± 2.23703	5.7975 ± 3.27955	0.732
BAEP Latency			
Wave I	1.3900 ± 0.35864	1.1222±0.22525	0.000
Wave III	3.7850 ± 0.56300	3.4323±0.63873	0.029
Wave V	6.3321 ± 0.81817	5.6510±0.91618	0.004
I – III IPL	2.3908 ± 0.41921	2.2797±0.57041	0.411
III – V IPL	2.5567 ± 0.52122	2.2420±0.45662	0.014
I – V IPL	4.9529 ±0.67163	4.4888±0.81594	0.022

Table 6 : Electrophysiological findings in Migraine with aura & Migraine without aura group

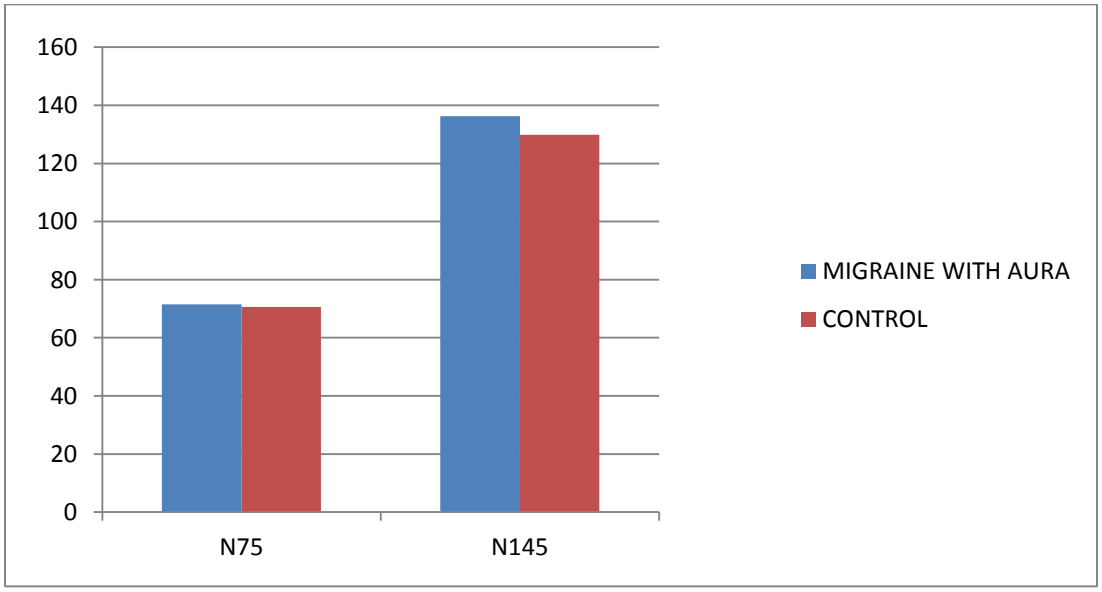
Parameters	Migraine with Aura (n= 16)	Migraine without aura (n= 24)	P value
	Mean ± SD	Mean ± SD	
VEP Latency			
N75	71.5438± 3.41818	71.4896± 4.62653	0.968
P100	102.0625 ± 5.70782	99.9792± 5.06261	0.233
N145	136.218 ± 10.45302	134.5833 ± 5.45369	0.521
P100 Amplitude	6.2344 ± 3.28791	5.5371 ± 2.23703	0.429
BAEP Latency			
Wave I	1.2725±0.29322	1.3900 ± 0.35864	0.283
Wave III	3.9381 ± 0.62159	3.7850 ± 0.56300	0.424
Wave V	6.3444±1.39867	6.3321 ± 0.81817	0.972
I – III IPL	2.6625±0.57633	2.3908 ± 0.41921	0.092
III – V IPL	2.5906±0.57130	2.5567 ± 0.52122	0.847
I – V IPL	5.2556±1.04950	4.9529 ±0.67163	0.272

MIGRAINE WITH AURA

VEP N75 Latency: The mean value of N75 in Migraine with Aura was found to be 71.5438± 3.41818 and in the control group it is 70.5750 ± 4.20058 with P value 0.416 and the difference was found to be insignificant.

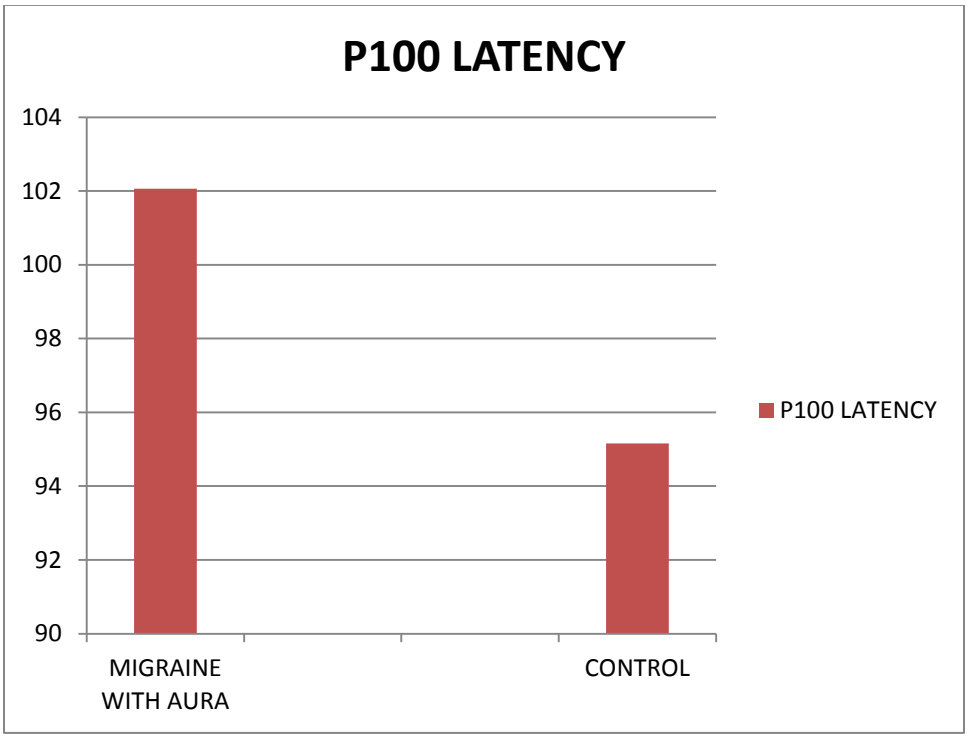
N145 Latency: The mean value of N145 in Migraine with Aura was found to be 136.2188 ± 10.45302 and in the control group it is 129.9875±8.61460 with P value 0.025 and found to be statistically significant.(Fig 9)

Fig 9: **VEP N75 & N145 Latency in Migraine with aura**



VEP P100 Latency: P100 Latency mean value in Migraine with Aura was observed to be 102.0625 ± 5.70782 and in the control group it is 95.1625 ± 3.56512 with P value 0.000 and the difference was found to be statistically significant. (Fig 10)

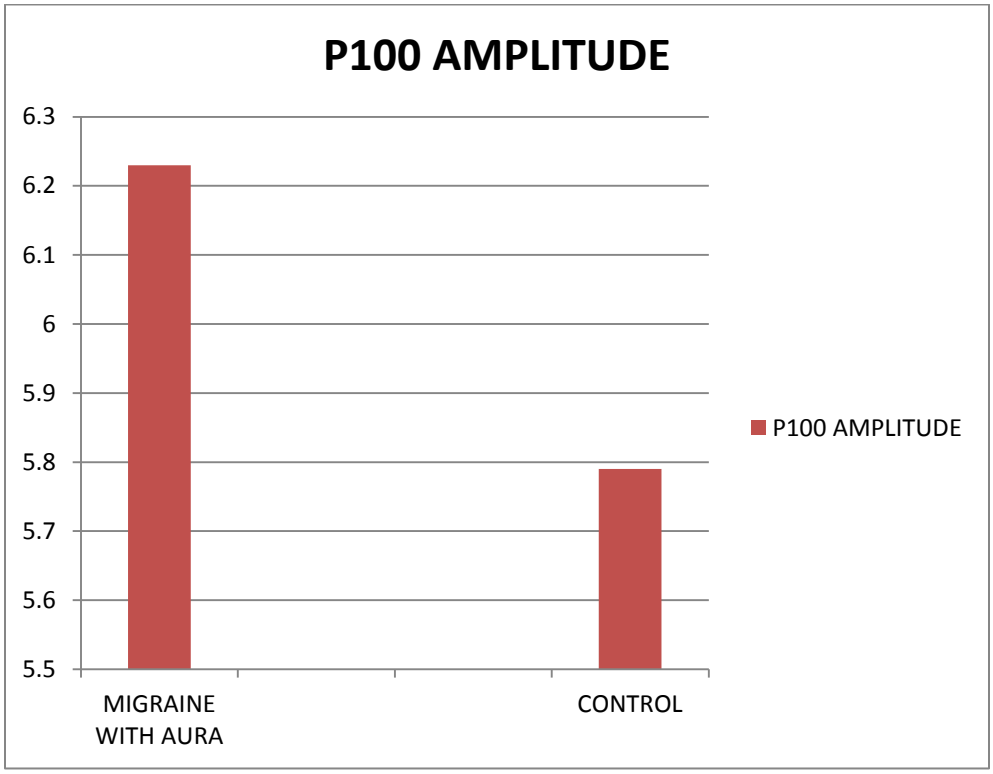
Fig 10 . **VEP P100 Latency in Migraine with aura**



P100 Amplitude:

P100 Amplitude mean value in Migraine with Aura was observed to be 6.2344 ± 3.27955 and in the control group it is 5.7975 ± 3.27955 with P value 0.654 and the difference was found to be statistically insignificant.(Fig 11)

Fig 11 P100 amplitude in Migraine with aura



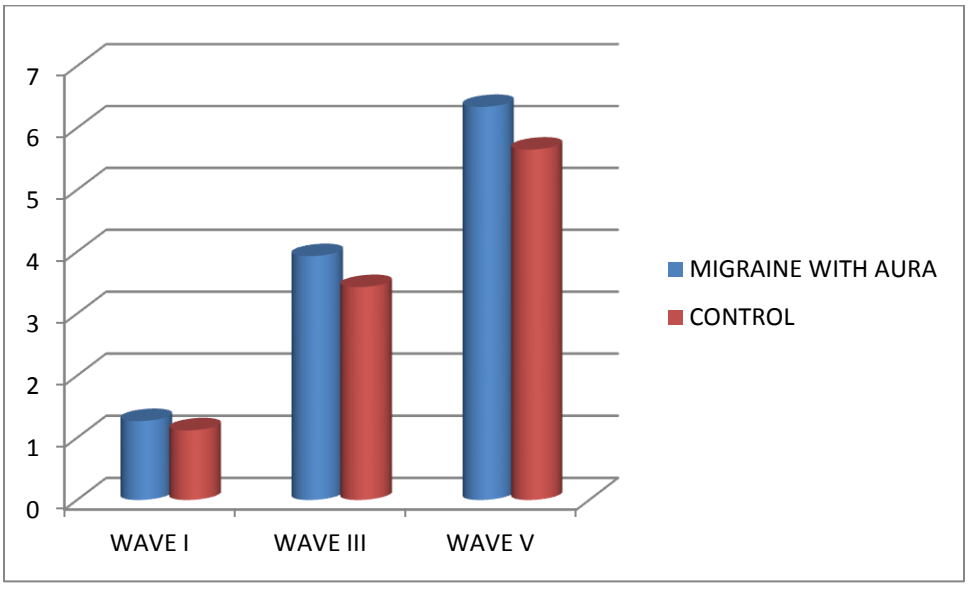
BAEP:

WAVE I: The mean value of wave I latency in Migraine with Aura was observed to be 1.2725±0.29322 and in the control group 1.1222±0.22525 with P value 0.044 and found to be statistically significant.

WAVE III: Wave III latency in Migraine with Aura was observed to be 3.9381±0.62159 and in the control group 3.4323±0.63872 with P value 0.009 and found to be statistically significant.

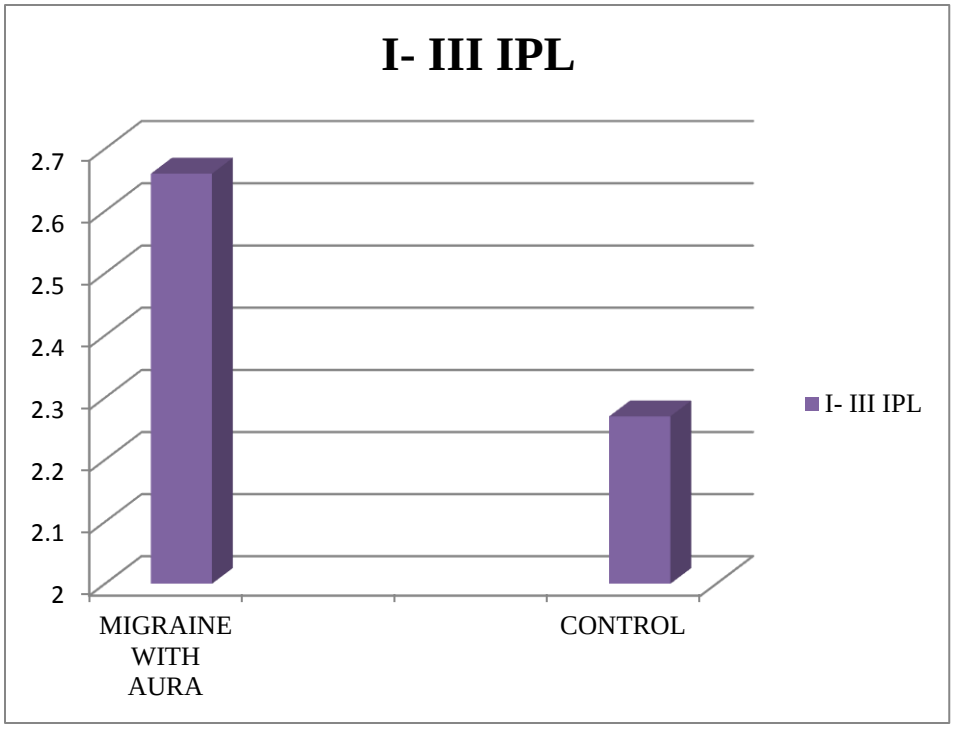
WAVE V: The mean value of wave V latency in Migraine with Aura was observed to be 6.3444±1.39867 and in the control group 5.6510±0.91618 with P value 0.033 and found to be statistically significant. (Fig 12)

Fig 12 **BAEP Wave I, III, V Latencies in Migraine with aura**



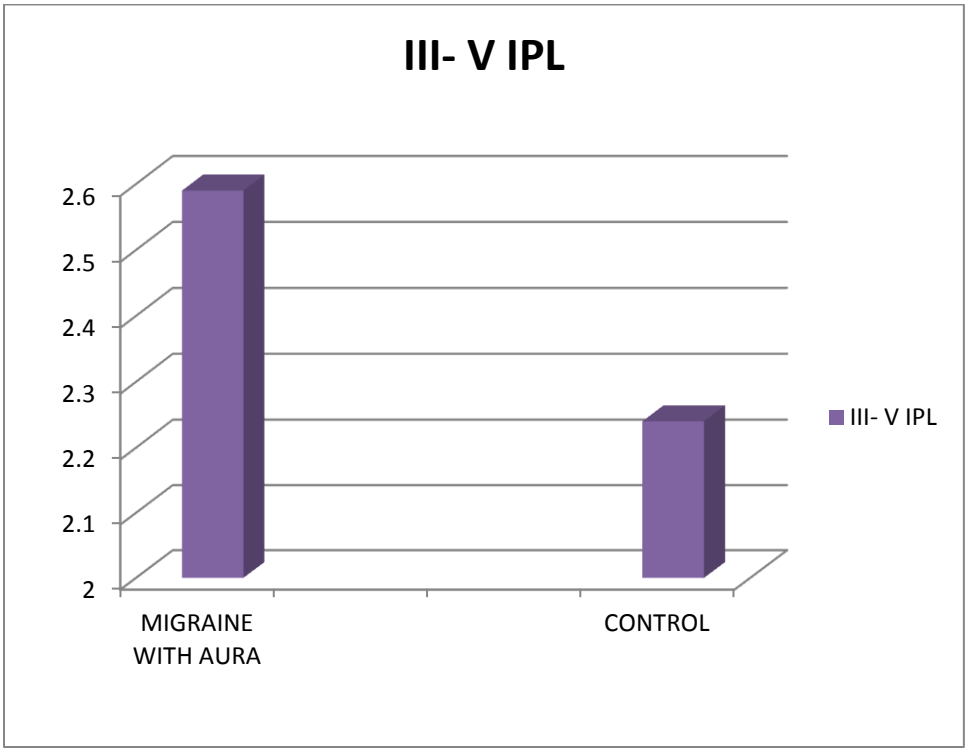
I - III IPL: I – III Interpeak latency in Migraine with Aura was observed to be 2.6625±0.57633 and in the control group 2.2797±0.57041 with P value 0.028 and found to be statistically significant. (Fig 13)

Fig 13. **BAEP Interpeak Latencies I-III in Migraine with aura**



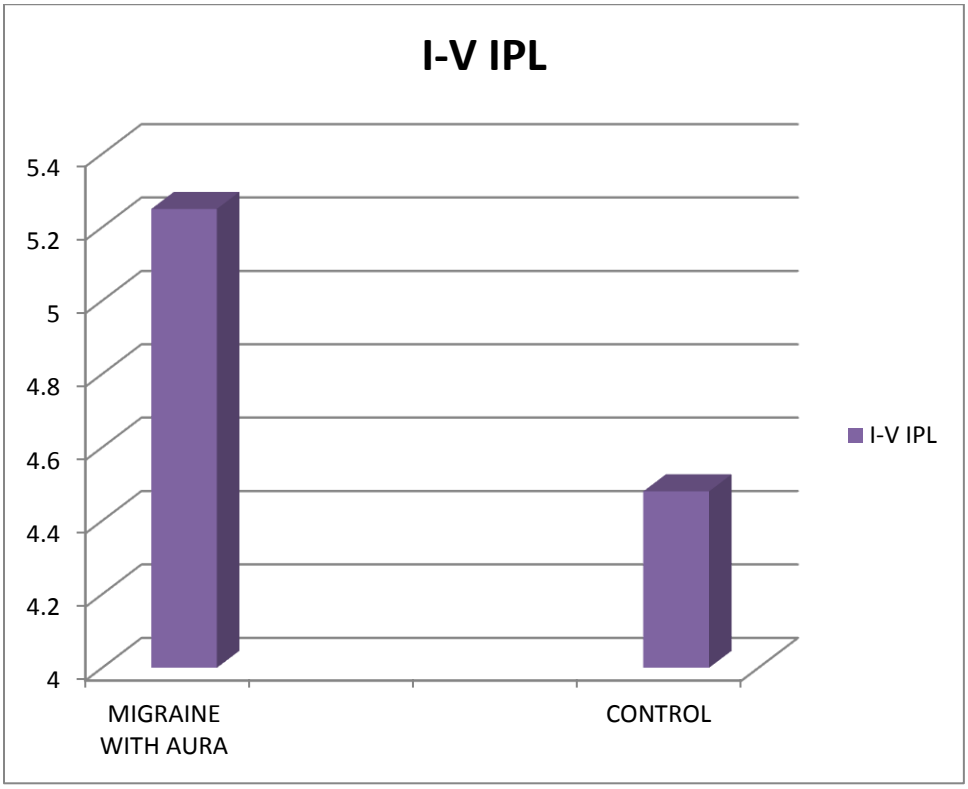
III – V IPL: III – V Interpeak latency in Migraine with Aura was observed to be 2.5906±0.57130 and in the control group 2.2420±0.45662 with P value 0.020 and found to be statistically significant. (Fig 14)

Fig 14. **BAEP Interpeak Latencies III- V in Migraine with aura**



I – V IPL: The mean value of I - V IPL in Migraine with Aura was observed to be 5.2556±1.04950 and in the control group 4.4888±0.81594 with P value 0.005 and found to be statistically significant. (Fig 15)

Fig 15. Interpeak Latency I - V in Migraine with aura

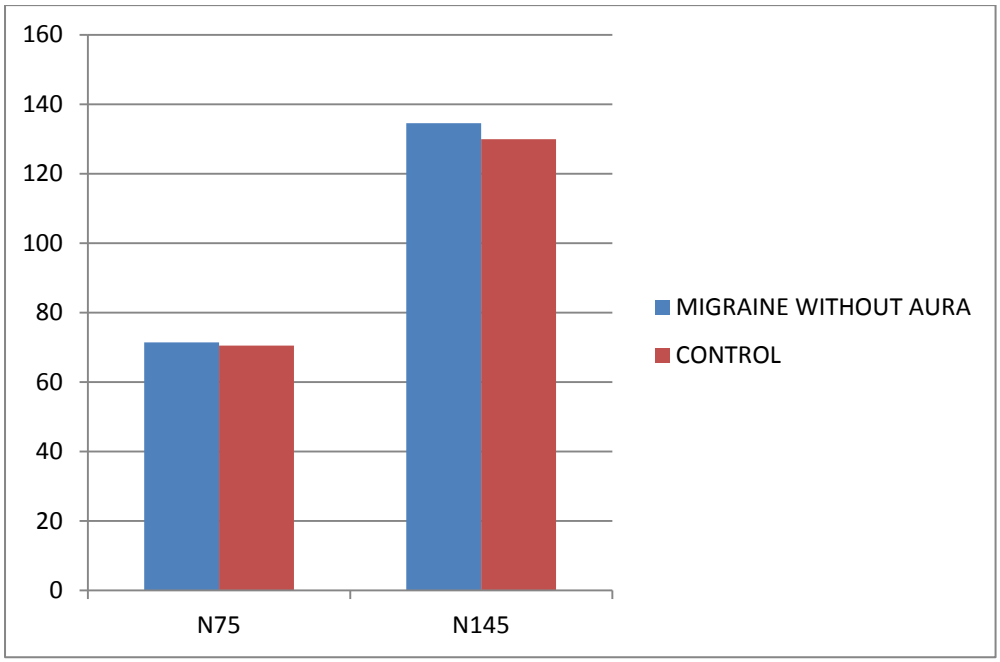


MIGRAINE WITHOUT AURA

VEP N75 Latency: The mean value of N75 in Migraine without Aura was found to be 71.4896± 4.62653 and in the control group it is 70.5750 ± 4.20058 with P value 0.420 and the difference was found to be insignificant.

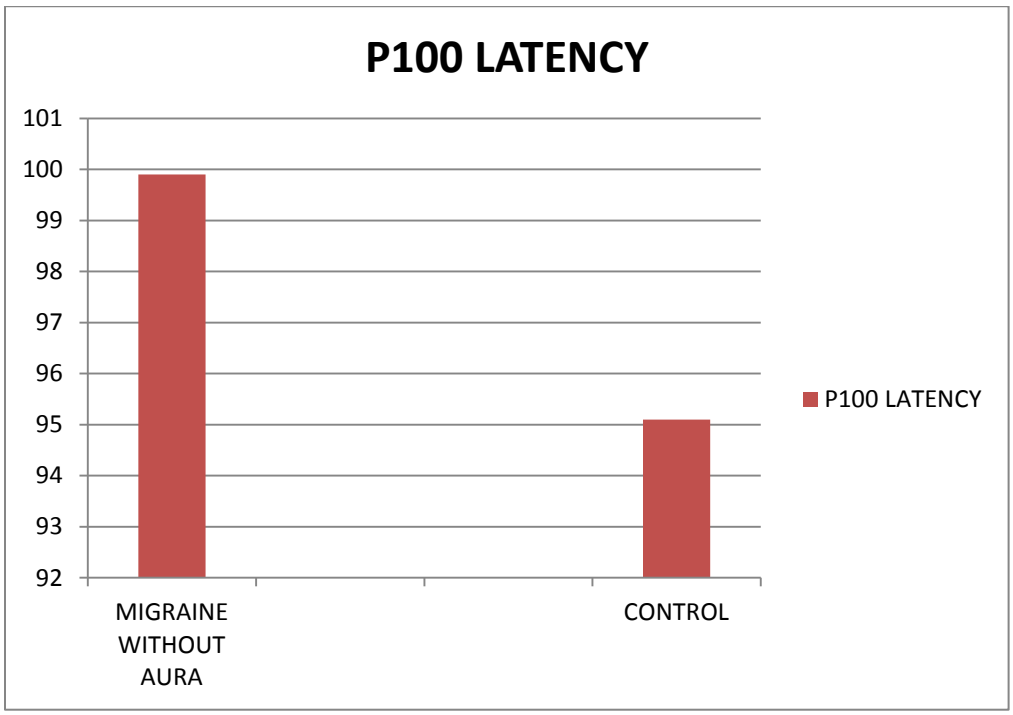
N145 Latency: The mean value of N145 in Migraine without Aura was found to be 134.5833 ± 5.45369 and in the control group it is 129.9875 ± 8.61460 with P value 0.022 and found to be statistically significant. (Fig 16)

Fig 16. **VEP N75 & N145 Latencies in Migraine without aura**



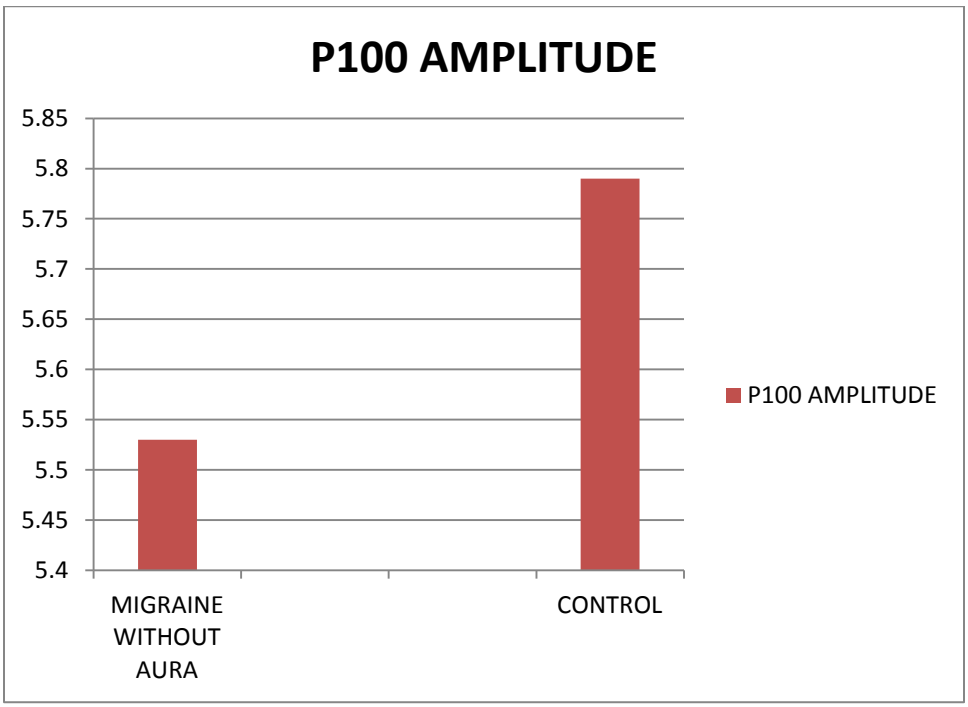
P100 Latency: P100 Latency mean value in Migraine without Aura was observed to be 99.9792 ± 5.06261 and in the control group it is 95.1625 ± 3.56512 with P value 0.000 and the difference was found to be statistically significant. (Fig 17)

Fig 17. **P100 Latency in Migraine without aura**



P100 Amplitude: P100 Amplitude mean value in Migraine without Aura was observed to be 5.5371 ± 2.23703 and in the control group it is 5.7975± 3.27955 with P value 0.732 and the difference was found to be statistically insignificant. (Fig 18)

Fig 18. **P100 Amplitude in Migraine without aura**



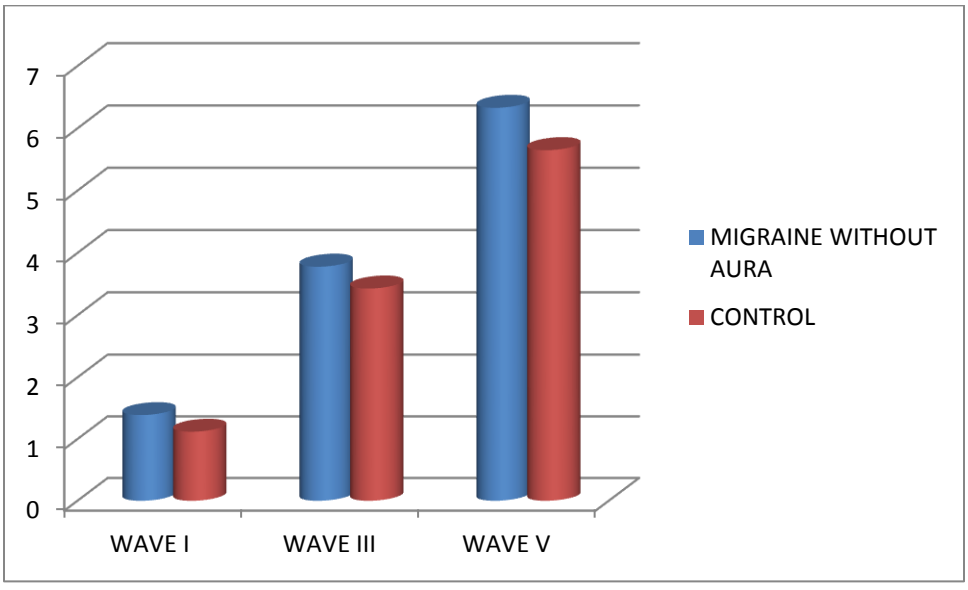
BAEP :

WAVE I: The mean value of wave I latency in Migraine without Aura was observed to be 1.3900±0.35864 and in the control group 1.1222±0.22525 with P value 0.000 and found to be statistically significant.

WAVE III : Wave III latency in Migraine without Aura was observed to be 3.7850 ± 0.56300 and in the control group 3.4323 ± 0.63872 with P value 0.029 and found to be statistically significant .

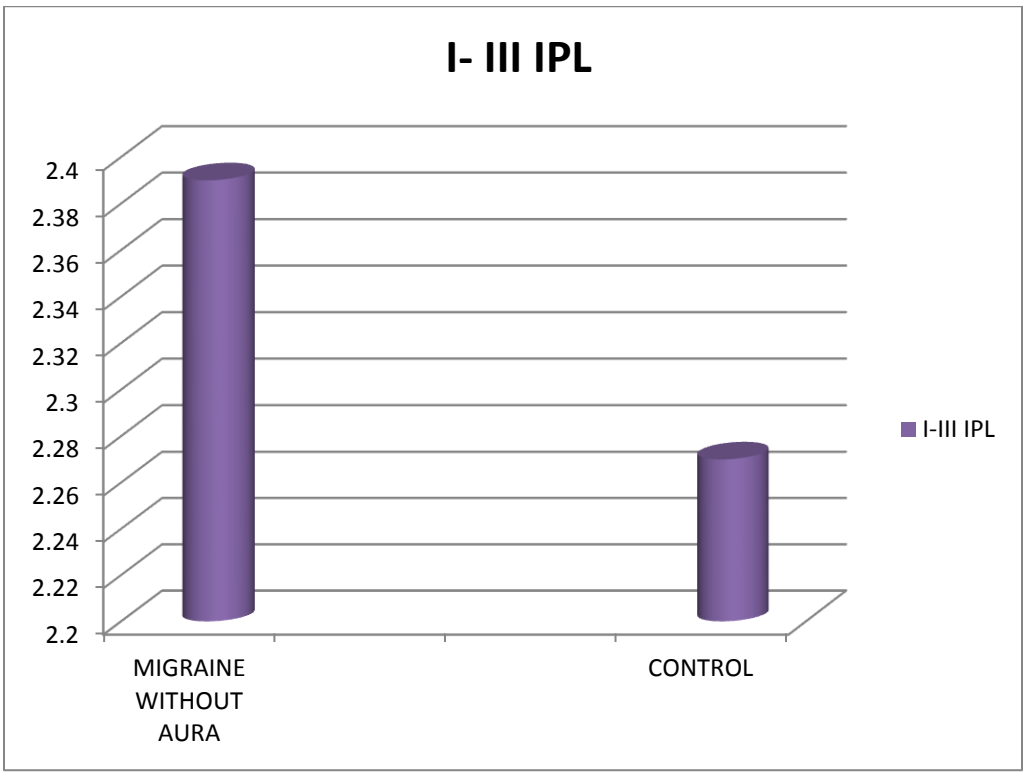
WAVE V: The mean value of wave V latency in Migraine without Aura was observed to be 6.3321±0.81817 and in the control group 5.6510±0.91618 with P value 0.004 and found to be statistically significant.(Fig 19)

Fig 19. **BAEP Waves I, III, V Latencies in Migraine without aura**



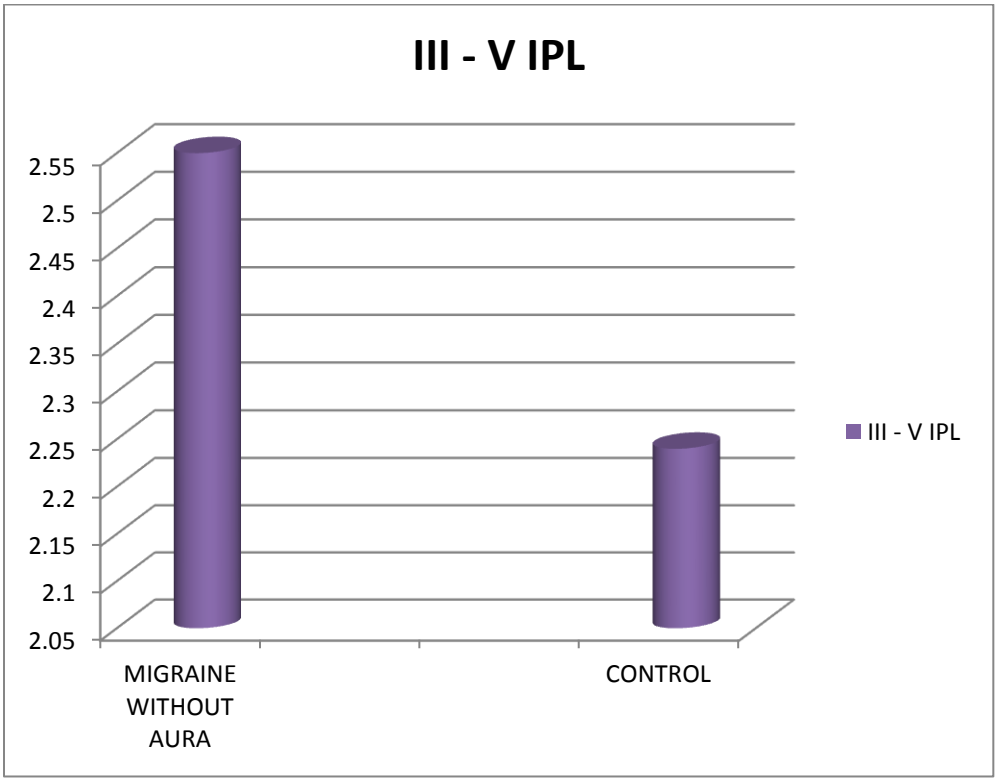
I - III IPL: I – III Interpeak latency in Migraine without Aura was observed to be 2.3908 ± 0.41921 and in the control group 2.2797 ± 0.57041 with P value 0.411 and found to be statistically insignificant. (Fig 20)

Fig 20. **BAEP Interpeak Latency I-III in Migraine without aura**



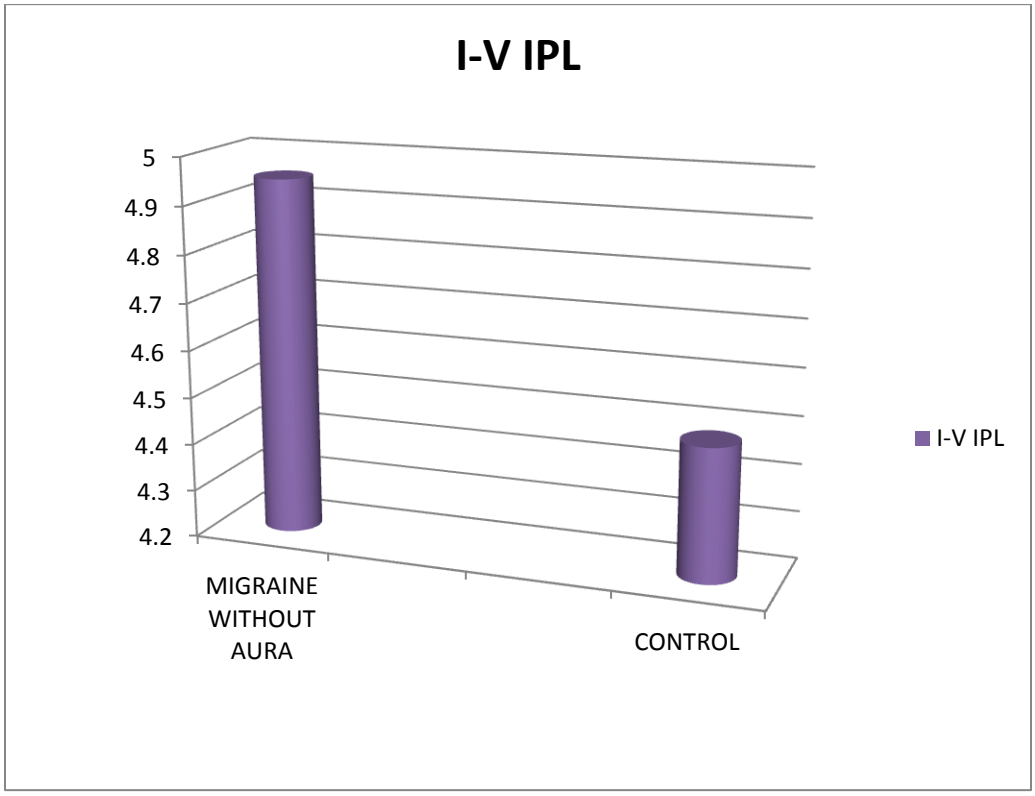
III – V IPL: III – V Interpeak latency in Migraine without Aura was observed to be 2.5567±0.52122 and in the control group 2.2420 ± 0.45662 with P value 0.014 and found to be statistically significant. (Fig 21)

Fig 21. **Interpeak Latency III – V in Migraine without aura**



I – V IPL: The mean value of I - V IPL in Migraine without Aura was observed to be 4.9529 ± 0.67163 and in the control group 4.4888 ± 0.81594 with P value 0.022 and found to be statistically significant**.** (Fig 22)

Fig 22. Interpeak Latency I – V in Migraine without aura

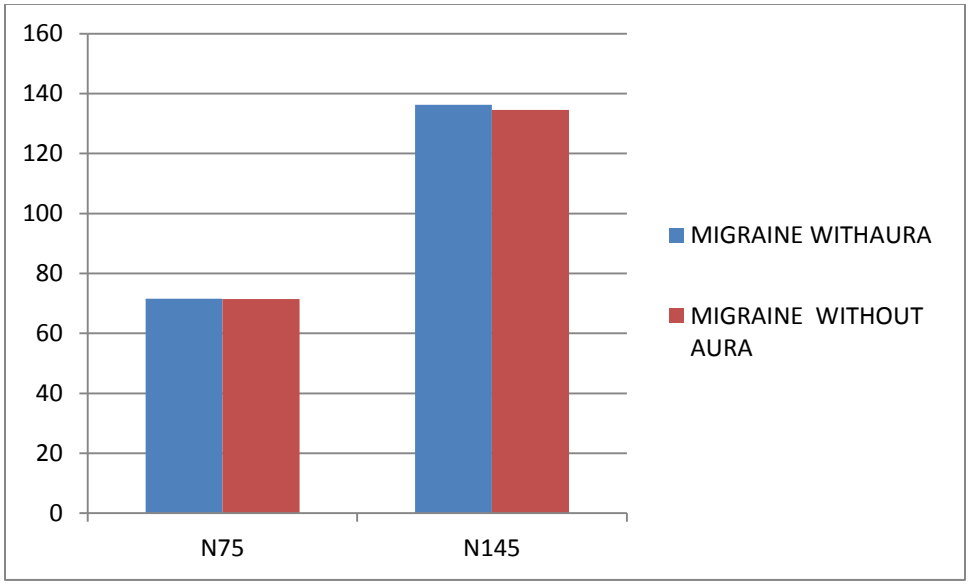


MIGRAINE WITH AURA & MIGRAINE WITHOUT AURA

VEP N75 Latency: The mean value of N75 in Migraine with Aura was found to be 71.5438± 3.41818 and in the Migraine without aura it is 71.4896 ± 4.62653 with P value 0.968 and the difference was found to be insignificant.

N145 Latency: The mean value of N145 in Migraine with Aura was found to be 136.2188 ± 10.45302 and in the Migraine without aura it is134.5833 ± 5.45369 with P value 0.521 and found to be statistically insignificant. (Fig 23)

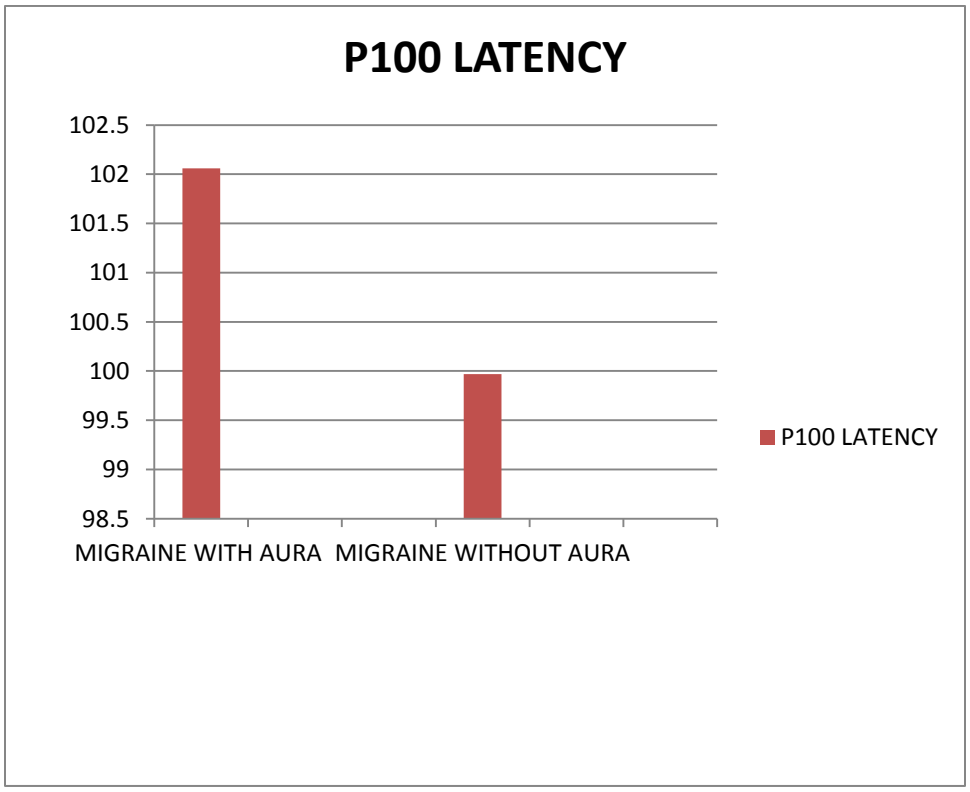
Fig 23. VEP N75 & N145 in study group



P100 Latency:

P100 Latency mean value in Migraine with Aura was observed to be 102.0625 ± 5.70782 and in the Migraine without aura it is 99.9792 ± 5.06261 with P value 0.233 and the difference was found to be statistically insignificant. (Fig 24)

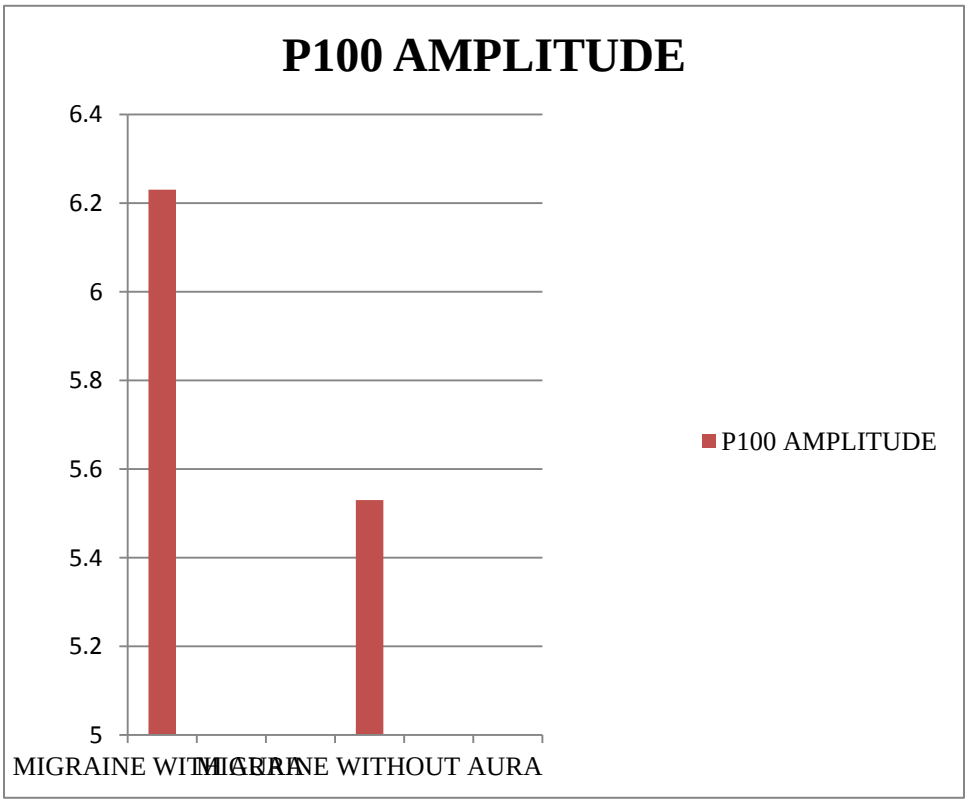
Fig 24. P100 latency in study group



P100 Amplitude:

P100 Amplitude mean value in Migraine with Aura was observed to be 6.2344 ± 3.28791 and in the Migraine without aura it is 5.5371 ± 2.23703 with P value 0.429 and the difference was found to be statistically insignificant. (Fig 25)

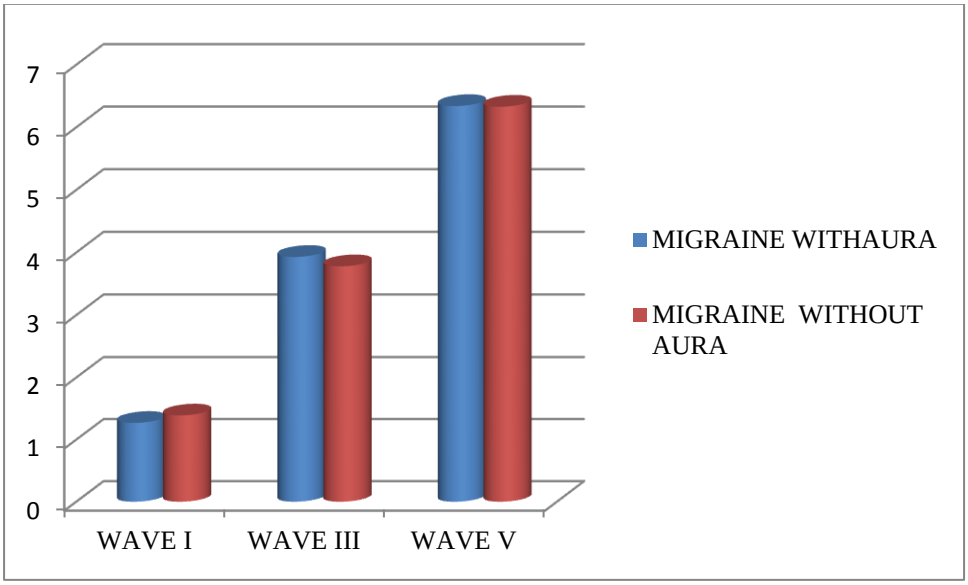
Fig 25. **P100 Amplitude in study group**



BAEP:

- **WAVE I:** The mean value of wave I latency in Migraine with Aura was observed to be 1.2725±0.29322 and in Migraine without aura it is 1.3900±0.35864 with P value 0.283 and found to be statistically insignificant.
- **WAVE III:** Wave III latency in Migraine with Aura was observed to be 3.9381 ± 0.62159 and in Migraine without aura 3.7850 ± 0.56300 with P value 0.424 and found to be statistically insignificant.
- **WAVE V:** The mean value of wave V latency in Migraine with Aura was observed to be 6.3444 ±1.39867 and in the Migraine without aura 6.3321±0.81817 with P value 0.972 and found to be statistically insignificant. (Fig 26)

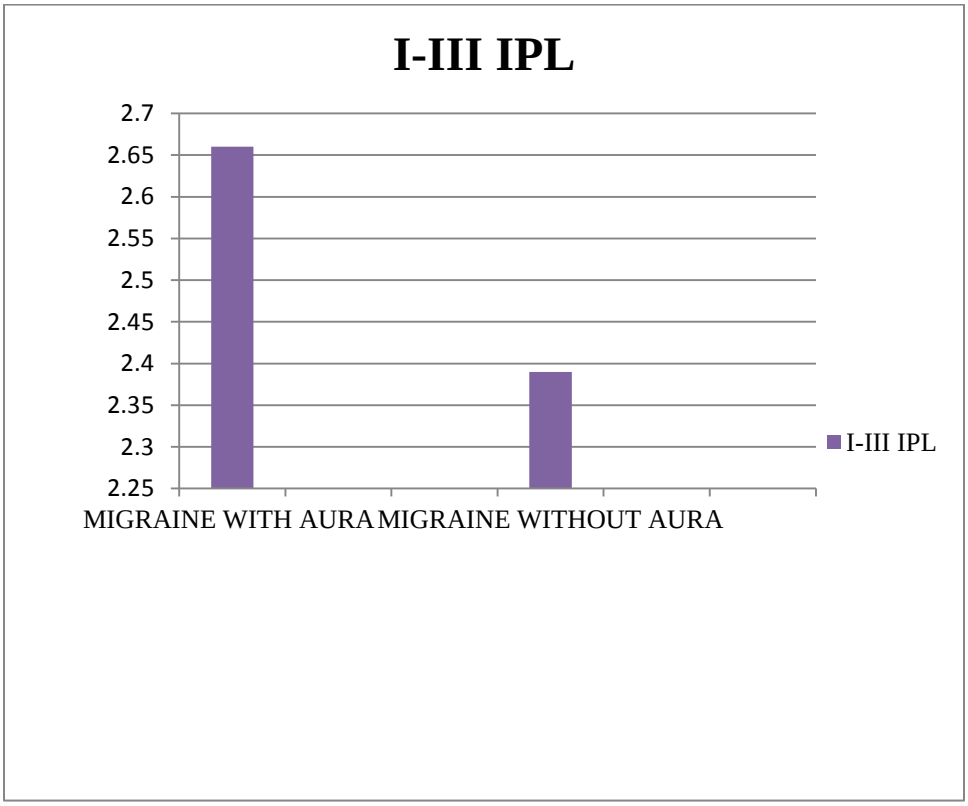
Fig 26. Wave I, III & V Latency



I - III IPL :

I – III Interpeak latency in Migraine with Aura was observed to be 2.6625 ± 0.57633 and in Migraine without aura was 2.3908 ± 0.41921 with P value 0.092 and found to be statistically insignificant .(Fig 27)

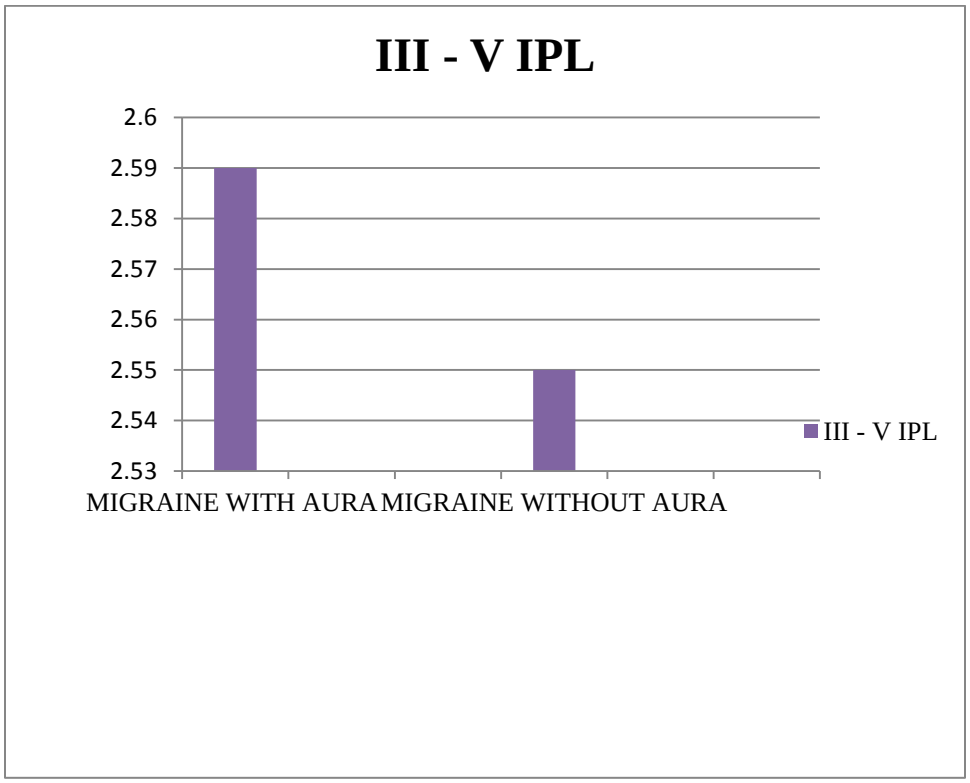
Fig 27. I-III IPL in study group



III – V IPL:

III – V Interpeak latency in Migraine with Aura was observed to be 2.5906 ± 0.57130 and in Migraine without aura was 2.5567±0.52122 with P value 0.847 and found to be statistically insignificant.(Fig 28)

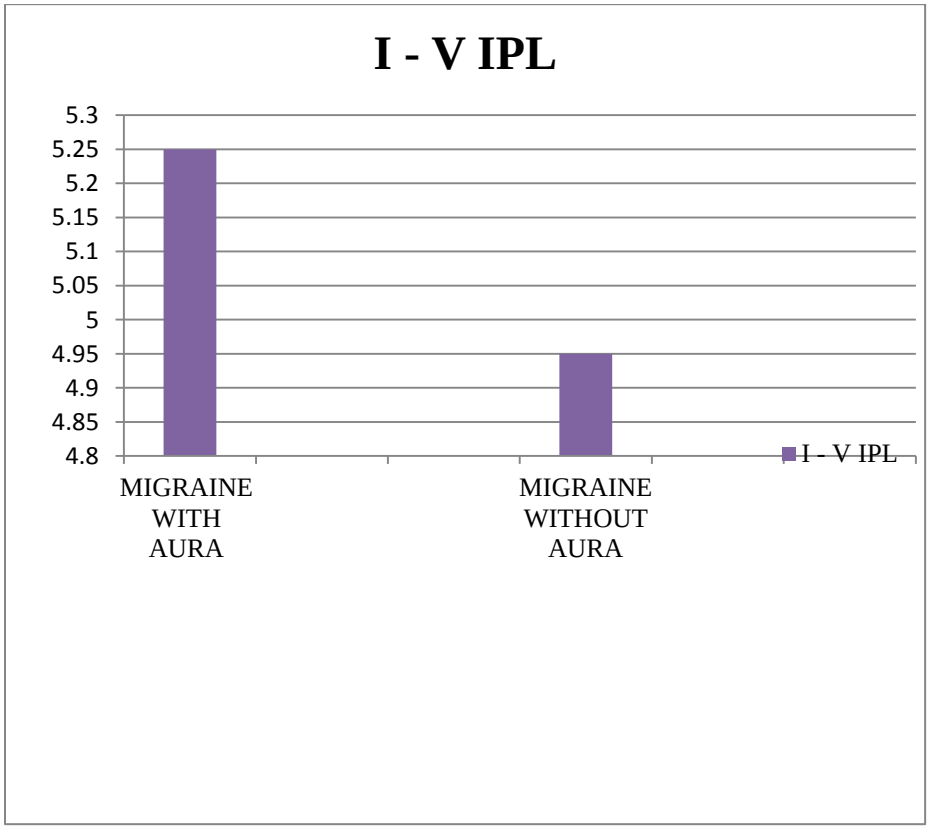
Fig 28. **III-V IPL in study group**



I – V IPL:

The mean value of I - V IPL in Migraine with Aura was observed to be 5.2556 ± 1.04950 and in Migraine without aura 4.9529 ± 0.67163 with P value 0.272 and found to be statistically insignificant**.** (Fig 29)

Fig 29. I- V IPL in study group



DISCUSSION

DISCUSSION

In the present study, the Electrophysiological parameters are evaluated in Migraine patients with and without Aura and in 40 control group healthy volunteers.

Migraine, the most common Neurological disorder is associated with substantial functional impairment, involving both physical and emotional ramifications. Migraine can best be explained as a 'Brain state ' in which the cellular and vascular functional changes occur at the same time due to dysfunction of subcortical structures, brainstem and diencephalic nuclei that modulate sensory inputs. These nuclei act as a 'Migraine Mediator' whose dysfunction will lead to abnormal perception and activation of TVS which then activate the central structures.

Thus, Migraine is mainly due to TVS activation generated within the brain without a peripheral sensory input. Migraine is the central sensory processing disorder, there is dysfunction of descending brainstem pain modulatory system. The hyperexcitability of the nociceptive circuitry downstream is responsible for the central sensitization in Migraine patients.[69]

In our present study, patients with Migraine either with aura or without aura differ significantly in various electrophysiological parameters.

Our VEP study results showed that P100 and N145 latencies were significantly prolonged with $p < 0.05$ in both Migraine with and without Aura when compared with controls whereas P100 Amplitude was increased in study group especially in cases with Aura than the control group but it was not statistically significant $P=0.654$.

The results of the present study agreed with EL Shater et al., Laila EL Mosly et al ., Kennard et al ., Khalil et al ., Mariani et al ., Drake et al ., Bockowski L et al .,

In the study conducted by **EL Shater et al.,**[35] showed significant prolongation of P100 latency only in Migraine with aura patients and there was no significant difference in P100 Amplitude between patients and controls. These changes were found to have a structural basis, due to repeated attacks resulting in ischemia and proposed that there is subtle neuronal damage in the visual system in Migraine with aura patients. These results were consistent with our present study.

Kennard et al., [40] also reported prolonged P100 latency in Migraine patients and explained it to have a structural basis. **Khalil et al.,** also found the same results but suggested the prolonged latencies are constitutional due to synaptic delay. Similar results were found in our study.

Laila EL Mosly et al .,[7] also found significant prolongation of P100 latency with no change in P100 amplitude, these changes were explained to be due to Occipital cortex dysfunction in Migraine patients. These results are in accordance with our present study.

Drake et al .,[49] found significant prolongation of P100 & N145 latencies in Migraine without aura cases due to dysfunction of brainstem centers probably related to endorphin or serotonin neurotransmission. **Mariani et al .,** [47] reported an increase in P100 latency in Migraine with & without aura whereas Amplitudes were quite dispersed among patients and controls. Suggested the alterations in the monoamine neuromediators are responsible for these changes. Similar findings were observed in our study.

Bockowski L et al ., [37] found significant prolongation of P100 latency whereas amplitudes N1-P100 & P100-N2 were prolonged in Migraine children than the children with tension type headache. They also reported that these amplitudes were lower in Migraine with aura when compared with Migraine without aura patients. These changes were due to visual dysfunction that might be secondary to a loss of inhibitory GABAergic interneurons in the visual cortex from repeated parenchymal insults. P100 latency showed similar findings in our study.

N.Ashjazadeh , B Varavipour [38] reported significant prolongation of P100 latency in classic Migraine patients with no change in the Amplitude due to subtle neuronal damage in the visual system of Migraine patients from repeated transient ischemia , probably due to constitutional change. These results were consistent with our present study.

Nofal M Khalil , Nigel J Legg , Duncan J Anderson [6]found similar results due to synaptic delay . Research work also showed positive correlation between disease duration and changes in amplitude of P100. The results of P100 latency were consistent with our present study.

Pedro.F Moreira Filho , Adalmir M. Dantas [34] found significant prolongation in P100 latency in Migraine without aura patients due to alterations in Monoamine neuromediators. Similar results were found in our study.

Thus, Migraine patients with and without aura had significant prolongation of P100 & N145 latency due to hyperexcitability of the cortex in Migraine patients even between attacks and due to synaptic delay.

Our BAEP study reports showed significant prolongation of latencies of Wave I, III & V with P <0.05 in Migraine patients when compared with controls. Also, the interpeak latencies I- III, III- V & I- V were significantly prolonged in study group, Migraine with aura than the controls. In Migraine without Aura III- V & I- V were significantly prolonged.

The results of present study were consistent with D Koushal ,S Sanjay Munjal , M Modi; N Panda , Firat Y et al., Schalke HP et al ., Anil K Dash et al ., Laila EL Mosly et al ., Drake et al ., Bayazit et al .,

D Koushal ,S Sanjay Munjal , M Modi , N Panda [(50)] studied BAEP in Migraine patients and found significant prolongation of latencies of wave I , III & V and in the IPL I - III & III- V due to involvement of brainstem structures as well as due to activation of brainstem in Migraine patients . Similar results were found in our study.

Schalke HP et al ., [(52)] found the same results and reported that there is a permanent impairment of brainstem function in Migraine patients. These findings are consistent with our present study.

Firat Y et al., [(51)] studied in paediatric Migraine patients and found prolongation of wave V latency & I- V IPL in study group due to transient impairment of brainstem function in Migraine patients.

Anil K Dash et al ., [(53)] found significant prolongation of latencies of Wave I , III, V & I-III IPL, III- V IPL & I – V IPL . The study concluded that there is brainstem involvement in Migraine and BAEP are the earliest indicator of impending auditory

involvement in patients with Migraine. These results are in accordance with our present study.

Laila EL Mosly et al ., [7] found prolongation in wave III & V and the I-III , I – V IPL due to hyperexcitability of the cerebral cortex. **Bayazit Y et al.,** [55] found prolongation of latency of wave I, III & V and the IPL III- V. Similar results were found in our study.

Sheriya A Hamed , Amal Mohammed Elatter [53] found prolongation of wave III latency and the IPL I-III , III – V & I – V. This study suggests that there is permanent vestibular damage involving either central or peripheral pathways. Similar results were observed in our study.

Thus , Migraine patients with and without aura show significant prolongation of latency in Electrophysiological studies probably due to subtle neuronal damage within the visual system especially in patients with aura due to recurrent cerebral hypoperfusion and due to cortical hyperexcitability. These findings suggest dysfunction of neuronal excitability due to defective neurotransmitter signaling and cerebral bioelectrical dysrhythmia.

CONCLUSION

CONCLUSION

The present study results show that there is involvement of the central nervous system Visual pathway and the Brainstem in Migraine patients. The Migraine patients show prolongation of latency in Electrophysiological studies.

Migraine patients with aura and without aura show significant prolongation of P100, N145 Latency with no change in P100 amplitude and in BAEP the latencies of waves I , III & V and the IPLs I-III , III- V & I-V are prolonged. These findings suggest there is defect in the central processing of visual function and BAEP alterations suggest involvement of Brainstem structures during Migraine attack.

Thus, VEP and Auditory brainstem evoked responses are considered as useful, non-invasive, reliable & diagnostic techniques for better understanding the Neurophysiological processes involved in Migraine patients which aid in the selection of adequate, effective treatment in Migraine subjects.

However, further studies are needed to compare the duration of the disease with the changes in the Electrophysiological study and to explain the role of Neuromodulatory centers in the brainstem in pathophysiology of Migraine. Then, the role of pattern reversal check size on VEP parameters in Migraine patients and lack of habituation during prolonged stimulation should be evaluated.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Nicholas A.Boon, Nicki R.Colledge, Brian R. Walker, John A.A. Hunter., Davidson ‘s Principles & Practice of Medicine . 20th edition Elsevier pg..1160-1163.
2. Andreoli and Carpenter ‘ s Cecil Essentials of Medicine., Charles C.J.Carpenter , Robert C.Griggs, Ivor J. Benjamin . 7th edition saunders Elsevier p: 1069- 1073.
3. Dan L.Longo , Antony S. Fauci , Dennis L. Kasper, J.Larry Jameson , Stephen L. Hauser, Joseph Loscalzo., Harrison ‘s Principles of Internal Medicine 18th edition vol 1., McGraw Hill Medical p.114- 120.
4. Till Sprenger and Peter J Goadsby Minireview..Migraine pathogenesis and state of pharmacological treatment options. BMC Medicine 2009, 7:71.
5. S N Chugh , Ashima chugh Textbook of Medicine for Medicine.. Delhi Arya publications pg ..596 – 599.
6. Nofal MKhalil , Nigel J Legg , Duncan J Anderson Long term decline of P100 amplitude in Migraine with Aura. J Neurol Neurosurg Psychiatry 2000;69:507 – 511.
7. Laila El Mosly , Azza Bayoumy , Hoda Massoud ,Mahmoud Abdel Moty , Manal Hafez , Taghreed Elshafie and Rasha El Bialy Impact of Migraine Headache on Quality of Life in a group of Female patients using Neurophysiological Assessment. AAMJ ,Vol.10,N.2, April,2012,suppl.
8. Akbar Hamzei Moghaddam ,Rostam Syfaldiny , Farhad Iranmanesh , Hamid Mahadavy., Visual Evoked Potentials in patientswith Classic Migraine. ZJRMS 2013; 15 (4) :25-28.
9. Merrit ‘s Textbook of Neurology 9th edition p:837-842.
10. Marschall S. Runge , M. Andrew Greganti , Frank H.Netter., Netter’s Internal Medicine 2nd edition . Elsevier p:873-881.

11. Nasim Maleki , Lino Becerra and David Borsook Migraine: Maladaptive Brain responses to stress. Headache 2012 ;52 (suppl 2) : 102-106.
12. Dr. S.N. Khosla Essentials of Medicine..CBS Publishers p .643-646.
13. . Parveen Kumar, Dr Michael Clark ‘s Clinical Medicine 8th edition .Elsevier p:1107- 1111.
14. Marten Scheffer , Albert Van den Berg , Michel D . Ferrari Migraine strikes as Neuronal Excitability reaches a Tipping point. PLoS ONE 88(8) ;e72514: march 17 , 2013.
15. Martin Lauritzen Pathophysiology of the Migraine aura, The spreading Depression Theory. Brain 1994, 117, 199- 210.
16. Andrew Prescot , Lino Becerra , Gautam Pendse , Shannon Tully,Eric Jensen , Richard Hargreaves,PerryRenshaw,Rami Burstein and David Borsook. Excitatory neurotransmitters in brain regions in Interictal Migraine patients. BiolMed central Molecular pain 2009,5 : 34.
17. Rieke Oelkers , Konard Grosser , Eberhard Lang, Gerd Geisslinger, Gerd Kobal, Kay Brune and Jorn Lotsch. Visual evoked potentials in Migraine patients: alterations depend on pattern spatial frequency. Brain 1999,122, 1147-1155.
18. Judit Afra,Alberto Proietti Cocchini , Victor De Pasqua , Adelin Albert and Jean Schoenen Visual evoked potentials during long periods of pattern reversal stimulation in Migraine. Brain 1998, 121, 233-241.
19. Karen E. Waldie , Markus Hausmann , Barry J Milne, Richie Poulton Migraine and cognitive function .Neurology 2002 ;59 :904- 908.
20. Michael Donaghy Brain‘s diseases of the Nervous system. Oxford university. 12th edition.

21. Randolph W. Evans Diagnostic Testing in Neurology p: 249-284.
22. Walter G. Bradley , Robert B. Daroff, Gerald M. Fenichel , Joseph Jankovic Neurology in Clinical Practice Vol 1. Principles of Diagnosis and Management . 5th edition Elsevier p.471- 476.
23. Michael J. Aminoff , Electrodiagnosis in Clinical Neurology, Visual evoked potentials 5th edition Elsevier p:453-468.
24. U K Misra , J Kalita Clinical Neurophysiology Visual evoked potentials. 3rd edition p:310-324.
25. J. Vernon Odom Michael Bach Mitchell Brigell Graham E. HolderDaphne L. Mc culloch ISCEV standard for clinical Visual evoked potentials. Doc Ophthal 2010,120 :111- 119.
26. Eileen E. Birchand Rain G. Bosworth Electrodiagnosis in Clinical Neurology, Visual evoked potentials in Infants and children. 5th edition Elsevier p:473-483
27. Neil R.Miller , Nancy J. Newman , Valerie Biousse , John B. Kerrison Walsh and Hoyt ‘s Clinical Neuro- Ophthalmology.. Lippincott Williams & Wilkins 6th edition p:140-144.
28. Dr.A K Jain Manual of Practical Physiology., p: 301-309.
29. Samuel R. Atcherson , Tina M. Stoody Auditory Electrophysiology A Clinical Guide. P.67- 81.al Application.
30. Alan D. Legatt Electrodiagnosis in Clinical Neurology, Brainstem Auditory Evoked Potantials :Methology, Interpretation and Clinic al Application. P : 490-519.
31. U K Misra , J Kalita Clinical Neurophysiology Brainstem Auditory Evoked Potential .3rd edition p : 330- 344.
32. G K Pal , Pravati Pal Textbook of Practical Physiology.3rd edition p: 298 – 303.

33. Jack Katz , Larry Medwetsky , Robert Burkard , Linda J . Hood Handbook of Clinical Audiology. 6th edition Lippincott Williams & Wilkins p: 222 – 240.
34. Michael Donaghy Brain‘s diseases of the Nervous system. Oxford university . 12th edition .
35. M.F.EL Snater, Y.Abo El Naga , A. Gaber, A.Hazzo , A.Nassif Migraine with and without aura : Clinical and Electrophysiological changes.. Egyptian Journal of Neurology, Psychiatry and Neurosurgery July 2006 Vol .43 Issue :2.
36. Pedro.F Moreira Filho , Adalmir M. Dantas Pattern Reversal Visual evoked potentials in Migraine subjects without aura. ArqNeuropsiquiatr 1994, 52 (4) : 484- 488.
37. Bockowski L , Sobaniec W , Smigielska Kuzia , Kulak W, Solowiej E The pattern reversal visual evoked potentials in children with Migraine with aura and without aura. Roczniki Akademii Medycznej w Bialymstoku vol 48, 2003.
38. N. Ashjazadeh , B Varavipour Abnormalities of Visual evoked potentials in Migraine patients. IJMS Vol 28, No.2, June 2003.
39. Professor Peter J. Goadsby serotonin 5 HT 1B/1D Receptor agonists in Migraine .
40. Kennard C , Gawel M and Rudolf Nde M. Visual evoked potentials in Migraine subjects. Res Clin Study Headache 1987; 6 : 73-80.
41. American academy of Neurology the Electroencephalogram in the evauation of headache. Neurology 1995;45 :1411-13.
42. Bramanti P , Grugno R, Vitetta A , Di Bella P , Muscara N and Nappi G Migraine with and without aura:electrophysiological and functional neuroimaging evidence . Functional Neurology 2005 ;20 (1) :29- 32.

43. Polich J Ehlers Cl and Dalassio DJ. Pattern shift visual evoked responses and EEG in Migrane. Headache 1986 ; 26 (9) : 451-6.
44. Golla FL, Winter AL. Analysis of cerebral responses to flicker in patients complaining of episodic headache . Electroencephalogr Clin Neurophysiol 1959, 11:539- 549.
45. Richey ET , Kooi KA , Waggoner RW. Visually evoked responses in Migraine. Electroencephalogr Clin Neurophysiol 1966, 21:23- 27.
46. Lehtonen JB. visual evoked cortical potentials in man. Studies on recording and stimulation technique and findings in Migraine patients. Thesis . University of Turku, 1972.
47. Mariani E , Moschini V , Pastorino G , Rizzi F , Severgnini A , Tiengo M . Pattern shift visual evoked potentials in Migraine subjects with visual aura. Headache 1990 ; 30 :435- 438.
48. Bena P, Bianco C , Costa P , Piazza D , Bergamasco B Visual evoked potentials and Brainstem Auditory Evoked Potential in Migraine and Transient ischemic attacks. Cephalalgia 1985 May ; 5 suppl 2 : 53 – 8.
49. Drake ME, Pakalnis A , Hietter SA , Padamadan H. Visual and Auditory evoked potentials in Migraine . Electromyogr Clin Neurophysiol 1990 Feb – Mar ; 30 (2) :77 – 81
50. D Koushal ,S Sanjay Munjal , M Modi , N Panda Auditory brainstem evoked responses in Migraine patients. The Internet Journal of Neurology 2008 Vol.12 number 1.
51. Firat Y , Ozturan O , Bicak U , Yakinci C, Akarcay M Auditory brainstem response in pediatric Migraine : during the attack and asymptomatic period. International journal of Pediatric Otorhinolaryngology 2006, 70 (8) : 1431-1438.

52. Bayazit Y ,Yilmaz M , Mumbuc S , Kanlikama M. (2001) .Assessment of Migraine -related cochleovestibular symptoms. Rev Laryngol Otol Rhinol (Bord) ; 122 (2) :85-8.

53. Anil K. Dash , Naresh Panda , Gaurav Khandelwal , Vivek Lal , Sherbaj S.Mann.Migraine and audiovestibular dysfunction : is there a correlation? American Journal of Otolaryngology – head and Neck Medicine and surgery 29 (2008) 295 – 299.

54. Boylu E , Domac FM , KocerA , Unal Z , Tanridaq , Us O . visual evoked potentials abnormalities in Migraine patients. Electroencephalogr Clin Neurophysiol 2010 sep – oct; 50 (6) :303-8.

55. Yang Y , Li P , Ye HC Brainstem auditory evoked potentials and assessment of personality test in patients with Migraine. Hunan medical university 2000, 25 (1) : 63 – 64.

56. Zgorzalewicz M The study of Early auditory evoked potentials in primary headaches in children and adolescents and their pathogenetic implications. Neurologia 2005, 39 (4suppl 1):s17 – 25.

57. Sherifa A. Hamed , Amal Mohamad Elattar Peripheral and central vestibular function in patients with Migraine . Jurnal ofNeurology and NeuroscienceVol 3, No.1 2012.

58. Leslie J. Dorfman, M.D., William H. Marshall, M.D. and Dieter R. Enzmann, M.D. Cerebral infarction and migraine. *Neurology* March 1979 vol. 29 no. 3 ,317

59. Shaheen E. Lakhan, MD, PhD, MEd, MS, Mihaela Avramut, MD, PhD, Stewart J. Tepper, MD Structural and Functional Neuroimaging in Migraine . Headache. 2013; 53(1):46-66.

60. Y.L.Lo , S.Hamed, H.Rumpel , L.L.Chan Auditory hallucinations and Migraine of possible Brainstem origin. J Headache pain 2011, 12:573-575.

61. Tedeschi G, Russo A, Tessitore A Relevance of functional neuroimaging studies for understanding migraine mechanisms**.** Expert Rev Neurother. 2013 Mar;13(3):275-85. doi: 10.1586/ern.13.20.

62. Regional Cerebral Blood Flow During Migraine Attacks By Xenon-133 Inhalation And Emission Tomography ,Martin Lauritzen And Jes Olesen

63. Schalke HP, Hoffeberth B , Grotemeyer KH ,Husstedt IW Electronystagmographic investigations in migraine and cluster headache during the pain-free interval. Cephalalgia. 1989 Dec;9(4):271-5.

64. F. Sicuteri , A.Testi and B. Anselmi Biochemical investigations in Headache .General Medical clinic of Forensic University. Int Arch Allergy 19 ; 55- 58 (1961)

65. Katalin Kovacs et al , Laszlo Bors , Laszlo Tothfausi , Jl na Jelensik , Gyorgy B ozsik , Loszlo , Kerenyi and Samuel Komoly . Cephalalgia Vol 9 ,, Issue 1 , p:53-57 , mar 1989.

66. Curtrer FM , O' Donnell A , Sanchez del Rio M Functional neuroimaging :enhanced understanding of Migraine pathophysiology. Neurology 2000;55 (9 suppl 2) :S36-45.

67. Baburhan Guldiken Triptans in the treatment of Migraine Clinical Medicine : Therapeutics 2009 :1711- 713.

68. Dalia A .Biswas , Meghana A. Gaikwad A study of Visual evoked potentials and effect of relaxation technique in patients with Migraine. Int J Adv Med 2014 may ;1 (1) : 24-33.

69. Eric A.Moulten , Rami Burstein , Shannon Tully , Richard Hargreaves ,Lino Becerra, David Borsook Interictal dysfunction of a brainstem descending modulatory center in Migraine patients. PLoS ONE 3(11):e3799.

ANNEXURES

ABBREVIATIONS

- VEP : Visual evoked potential
- BAEP : Brainstem auditory evoked potential
- OCD : Obsessive compulsive disorder
- IHS : International headache society
- MIDAS : Migraine disability assessment score
- MMSE : Mini mental state examination
- CSD : Cortical spreading depression
- TVS: Trigeminal Vascular system
- TCC : Trigeminal cervical component
- ERP : Event related potential
- EP : Evoked potential
- IPL : Interpeak latency
- ABR : Auditory brainstem response

INFORMED CONSENT

Dr. R.Sowmiya, Post graduate student in the Department of Physiology, Thanjavur Medical College, Thanjavur is doing the study entitled **'Evaluation of Visual evoked potential and Auditory evoked potential in Migraine'**. The procedure of the study has been explained to me in my own language. I understand that there is no risk involved in the above procedure and it is purely non- invasive. I hereby give my consent to participate in this study. The data obtained here may be used for research and publication.

Station: Signature of the subject

Date:

Signature of the Investigator

PROFORMA

EVALUATION OF VISUAL EVOKED POTENTIAL & BRAINSTEM

AUDITORY EVOKED POTENTIAL IN MIGRAINE

NAME: AGE: SEX:

ADDRESS: OCCUPATION:

PRESENT HISTORY:

H/O Headache :

Duration :

Frequency:

HISTORY SUGGESTIVE OF AURA:

H/O Numbness / Tingling

H/O Double vision

H/O Flash of light

H/O Tinnitus

H/O Speech disturbances

H/O Floaters

H/O Nausea / Vomiting / Giddiness

H/O Ear discharge

H/O Visual disturbances

PAST HISTORY:

H/O Hypertension / Diabetes / Thyrotoxicosis

PERSONAL HISTORY:

FAMILY HISTORY:

MENSTRUAL HISTORY:

DRUG HISTORY:

GENERAL EXAMINATION:

Pallor: Icteric: Cyanosis: Clubbing: Lymphadenopathy:

VITAL SIGNS:

Pulse: Respiratory rate:

BP: Vision:

Examination of CVS:

Examination of RS:

Examination of Abdomen:

Examination of CNS:

Examination of Eye: Right: Left:

Examination of Ear: Right: Left:

Examination of Nose& Paranasal sinuses:

Examination of Teeth & Oropharynx:

DIAGNOSIS: Migraine with aura / Migraine without aura

ROUTINE INVESTIGATIONS:

Blood sugar :

Urea :

VEP :

	N75 Latency	P100 Latency	N145 Latency	P100 Amplitude
LEFT EYE				
RIGHT EYE				

BAER:

	Wave I	Wave III	Wave V	I – III IPL	III – V IPL	I – V IPL
LEFT EAR						
RIGHT EAR						

MASTER CHART

Visual Evoked Potential and Brainstem Auditory Evoked Potential in Migraine with Aura Cases

S.No	Age/ Sex	VEP N75 Latency(ms)		VEP P100 Latency (ms)		VEP N145 Latency (ms)		VEP P100 Amplitude(µv)		BAEP LT						BAEP RT					
		LT	RT	LT	RT	LT	RT	LT	RT	I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
1	31/F	73.5	64.5	110	111	154	152	8.62	8.93	1.75	3.82	6.12	2.07	2.3	4.37	0.98	3.2	5.48	2.22	2.28	4.5
2	44/F	64.5	70	115.5	113	144.5	134	6.15	6.96	1.2	3.25	5.2	2.05	1.95	4	0.85	2.82	4.88	1.97	2.06	4.03
3	30/M	77	70.5	103.5	100.5	136	132.5	5.71	7.88	1.4	3.82	8.07	2.42	4.25	6.67	1.32	3.82	6.62	2.5	2.8	5.3
4	43/F	70.5	75.5	105	96	148	133.5	1.8	0.34	1.4	4.4	6.18	3	1.78	4.78	1.05	2.42	4.92	1.37	2.5	3.87
5	19/F	66	71	98	101	145.5	152	2.51	1.53	0.8	4.05	6.42	3.25	2.37	5.62	0.85	4.65	8.43	3.8	3.78	7.58
6	19/F	70.5	76	110.5	111	139.5	141	12	14.17	1.72	5.7	.78	3.98	3.08	7.06	1.42	4.53	7.65	3.08	3.12	6.2
7	27/F	79	68	93	104.5	139	136	6.98	6.17	0.35	4.55	6.4	4.2	1.85	6.05	0.8	3.58	7.4	2.78	3.82	6.6
8	45/F	75.5	70.5	105.5	103	128	124	6.44	7.11	0.78	2.58	4.85	1.8	2.27	4.07	1.5	4.53	7.2	3.03	2.67	5.7
9	42/M	71	72.5	96	99	125	134	6.14	3	1.3	3.25	5.1	1.95	1.85	3.8	1.23	3.15	5.5	1.92	2.35	4.27
10	47/F	77.5	79	100.5	100.5	121	121	6.23	2.38	1.65	3.75	5.78	2.1	2.03	4.13	1.23	3.35	5.2	2.12	1.85	3.97
11	29/F	66	67	98.5	96.5	126	126.5	7.06	10.87	1.2	3.88	5.88	2.68	2	4.68	1.45	2.98	4.8	1.53	1.82	3.35
12	49/F	73.5	74	100	101.5	126	121.5	8.64	3.12	1.1	4.62	6.32	3.52	1.7	5.22	1.82	4.15	6.42	2.33	2.27	4.6
13	42/M	75	78.5	91.5	96	116.5	135.5	4.6	1.33	1.4	3.78	7.02	2.38	3.24	5.62	2.05	5.85	9.2	3.8	3.35	7.15
14	49/F	66	70.5	100.5	97	133	133	12.53	11.61	1.38	3.32	5.7	1.94	2.38	4.32	1.1	4.85	9.2	3.75	4.35	8.1
15	19/F	60	77	103.5	109.5	150	145.5	5.07	4.03	1.05	4.42	6.85	3.37	2.43	5.8	1.4	3.3	5.68	1.9	2.38	4.28
16	30/F	72.5	63.5	97.5	94.5	156.5	124.5	9.68	14.9	0.88	4.32	7.5	3.44	3.18	6.62	2.38	5.42	8.35	3.04	2.93	5.97

Visual Evoked Potential and Brainstem Auditory Evoked Potential in Migraine without Aura Cases

S.No	Age/ Sex	VEP N75 Latency(ms)		VEP P100 Latency (ms)		VEP N145 Latency (ms)		VEP P100 Amplitude(μv)		BAEP LT						BAEP RT					
		LT	RT	LT	RT	LT	RT	LT	RT	I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
1	36/F	60	69.5	90.5	102	121	131	3.57	2.33	0.82	3.35	6	2.53	2.65	5.18	1.45	3.65	5.22	2.2	1.57	3.77
2	38/M	76	70	92	92	129	132	1.68	2.01	1.65	3.12	4.68	1.47	1.56	3.03	1.85	3.98	6.45	2,15	2.47	4.6
3	33/F	73	67	103.5	93	133.5	132.5	3.53	6.3	1.8	4.85	7.58	3.05	2.73	5.78	0.9	2.82	4.58	1.92	1.76	3.68
4	33/F	68.5	70	95	95	125.5	137	6.37	8.57	0.75	3.32	9.15	2.57	5.83	8.4	2.33	3.82	6.15	1.49	2.33	3.82
5	30/F	66.5	65.5	104	100.5	131	131	7.51	7.26	1.05	3.88	6.75	2.83	2.87	5.7	1.32	4.78	8.25	3.46	3.47	6.93
6	34/F	74.5	70	103.5	98	141.5	145	8.53	9.92	1.35	3.68	7.95	2.33	4.27	6.6	0.9	3.5	5.03	2.6	1.53	4.13
7	19/F	73	71	101.5	101	128.5	142.5	9.74	8.59	0.85	3.02	5	2.17	1.98	4.15	1.42	3.8	5.8	2.38	2	4.38
8	52/M	82	74.5	107	102.5	134.5	137.5	6.1	4.86	0.6	2.75	4.68	2.15	1.93	4.08	0.62	3	4.8	2.38	1.8	4.18
9	19/F	74	70	87.5	92.5	137	139.5	5.81	4.42	0.65	2.8	5.05	2.15	2.25	4.4	1.5	3.7	5.9	2.2	2.2	4.4
10	19/F	70.5	69.5	105	99.5	146	131.5	4.53	5.08	1.15	2.72	5.18	1.57	2.46	4.03	1.15	3.35	5.68	2.2	2.33	4.53
11	33/F	75	73.5	98.5	94	136.5	132.5	5.5	5.77	1	3.72	6.02	2.72	2.3	5.02	1.27	4.15	6.62	2.88	2.47	5.35
12	23/F	76	73.5	109	103	137	135	10.92	2.56	1.7	5.25	7.55	3.55	2.3	5.85	1.85	4.58	6.22	2.73	1.64	4.37
13	28/F	74.5	65.5	97	97	136.5	149.5	0.27	8.66	1.52	3.65	5.98	2.13	2.33	4.46	1.92	4	6.95	2.08	2.95	5.03
14	32/F	65	76	99	106	129	137	7.29	9.57	0.78	2.95	5.22	2.17	2.27	4.44	1.4	5.72	8.02	4.32	2.3	6.62
15	33/F	59.5	66.5	95.5	95.5	123	128	3.85	6.05	1.58	3.82	7.08	2.24	3.26	5.5	1.68	4.1	6.42	2.42	2.32	4.74
16	44/F	68.5	69	96	95	130.5	130.5	9.57	8.28	1.98	3.98	7.72	2	3.74	5.74	2.2	5.88	9.18	3.68	3.3	6.98
17	33/M	72	68	100.5	102.5	137.5	141.5	10.82	3.46	0.92	2.98	5.1	2.06	2.12	4.18	1.3	3.5	7	2.2	3.5	5.7
18	36/F	77.5	85.5	102	105.5	136	129	3.56	4.85	1.08	2.7	5.68	1.62	2.98	4.6	1.18	2.82	5.48	1.64	2.66	4.3
19	26/F	76	65	91	93.5	139	123	4.99	2.47	1.55	4.58	7.52	3.03	2.94	5.97	0.95	3.25	5.95	2.3	2.7	5
20	36/F	83	83	105.5	103	125.5	137	1.06	1.21	1.58	3.68	6.1	2.1	2.42	4.52	1.9	3.95	6.48	2.05	2.53	4.58
21	29/F	66	68	94	111.5	147.5	151	6.53	3.43	1.82	3.62	6.08	1.8	2.46	4.26	1.5	4.62	7.82	3.12	3.2	6.32
22	42/F	75.5	67	101.5	107.5	134	134	2.29	3.09	1.88	4.05	6.35	2.17	2.3	4.47	1.02	3.3	5.52	2.28	2.22	4.5
23	39/F	80	65	110	109	132.5	139	8.23	6.3	2.6	4.92	7.35	2.32	2.43	4.75	1.52	3.92	6.52	2.4	2.6	5
24	33/F	76	66.5	105.5	105.5	135	126.5	11.09	0.12	1.2	4.08	5.92	2.88	1.84	4.72	1.8	4.18	6.92	2.38	2.74	5.12

Visual Evoked Potential and Brainstem Auditory Evoked Potential in Controls

S.No	Age/ Sex	VEP N75 Latency(ms)		VEP P100 Latency (ms)		VEP N145 Latency (ms)		VEP P100 Amplitude(µv)		BAEP LT						BAEP RT					
		LT	RT	LT	RT	LT	RT	LT	RT	I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
1	40/F	64.5	64.5	90.5	89.5	143.5	126	10.2	11.87	1.35	3.4	5.42	2.05	2.02	4.07	1.7	3.95	5.75	2.25	1.8	4.05
2	40/F	71	73	91.5	91	132.5	130.5	9.77	9.55	1.65	3.85	7.88	2.2	4.03	6.23	1	5.08	7.05	4.08	1.97	6.05
3	31/M	66	68.5	89	90.5	112.5	113	6.51	5.63	1.82	6.15	8.05	4.33	1.9	6.23	0.57	5.52	8	4.95	2.48	7.43
4	21/F	68.5	67.5	98	92	128	124	5.47	0.97	1	2.58	5.82	1.58	3.24	4.82	0.85	2.45	4.05	1.6	1.6	3.2
5	44/F	79	60.5	98.5	92	131.5	134.5	3.56	6.63	0.8	2.7	4.28	1.9	1.58	3.48	0.8	2.65	4.5	1.85	1.85	3.7
6	40/F	76.5	77	98	98.5	136.5	137	0.26	1.89	0.6	2.6	4.6	2	2	4	1.4	3.3	5.42	1.9	2.12	4.02
7	40/F	74	77	98	102.5	137	138.5	6.29	6.28	0.85	2.98	5.98	2.13	3	5.13	1.05	3.38	5.05	2.33	1.67	4
8	54/M	76	80	89	92.5	119	122.5	0.75	1.3	0.78	2.08	3.38	1.3	1.3	2.6	1.2	2.58	3.88	1.38	1.3	2.68
9	42/F	68.5	66	99.5	96	129	123.5	3.24	7.09	1.2	2.6	3.92	1.4	1.32	2.72	0.82	3	6.4	2.18	3.4	5.58
10	55/F	65	68.5	98	97	128	124	6.37	9.05	1.05	3.6	5.62	2.55	2.02	4.57	0.95	3.6	7.4	2.73	3.72	6.45
11	23/F	70.5	70.5	97	93.5	127.5	123	8.57	6.36	1.48	5.48	8.65	4	3.17	7.17	1.02	3.9	6	2.88	2.1	4.98
12	19/F	84	64	95	102	126	143	14.09	2.24	0.68	3.18	6.25	2.5	3.07	5.57	0.72	3.72	6.92	3	3.2	6.2
13	27/F	71.5	68	97.5	103.5	146	141.5	7.42	10.88	0.9	3.18	5.55	2.28	2.37	4.65	1	5.82	9.02	4.82	3.2	8.02
14	35/F	66.5	68.5	97	98.5	143.5	130.5	16.11	16.47	1.02	3.12	4.9	2.1	1.78	3.88	1.23	3.2	5.2	1.97	2	3.97
15	32/F	72.5	70.5	96	95	129.5	121.5	5.8	3.5	1.3	3.45	5.88	2.15	2.43	4.58	0.6	3.25	6.02	2.65	2.77	5.42
16	27/M	79	73.5	102	97.5	133	125.5	3.13	7.03	1.18	3.38	5.7	2.2	2.32	4.52	0.62	2.5	4.62	1.88	2.12	4
17	20/M	76	77.5	100	102.5	117	143	1.76	3.87	0.57	3.62	6.7	3.05	3.08	6.13	1.25	3.58	7.95	2.33	4.37	6.7
18	47/F	70.5	73.5	100.5	98.5	130.5	135	6.93	1.51	1.25	3.88	6.5	2.63	2.62	5.25	1.7	3.12	4.47	1.42	1.35	2.77
19	39/F	70	74	95	93.5	136	132	8.44	4.52	1.55	4.5	7.42	2.95	2.92	5.87	1.12	3.18	5.12	2.06	1.94	4
20	37/F	67.5	73.5	92.5	95.5	133	123.5	3.94	0.4	1.35	3.9	5.72	2.55	1.82	4.37	1.1	3.1	5.88	2	2.78	4.78

Visual Evoked Potential And Brainstem Auditory Evoked Potential in Controls

S.N0	Age/ Sex	VEP N75 Latency(ms)		VEP P100 Latency (ms)		VEP N145 Latency (ms)		VEP P100 Amplitude(µv)		BAEP LT						BAEP RT					
		LT	RT	LT	RT	LT	RT	LT	RT	I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
21	38/F	63	63.5	92	93	131.5	130.5	6.83	3.9	0.78	2.98	5.22	2.2	2.24	4.44	0.9	2.98	4.95	2.08	1.97	4.05
22	44/F	79	64	101	96	121.5	126	1.66	9.39	1.05	2.78	5.03	1.73	2.25	3.98	1.92	4.08	5.5	2.16	1.42	3.58
23	25/F	72.5	75	92.5	97	132	134.5	1.03	4.57	1.52	3.75	6	2.23	2.25	4.48	1.05	3.9	5.52	2.85	1.62	4.47
24	31/F	66.5	75.5	93.5	96.5	129.5	128.5	0.34	0.76	1.68	3.2	4.75	1.52	1.55	3.07	1.42	3.75	5.25	2.53	1.5	3.83
25	39/F	67	64	93.5	92	120.5	123.5	9.68	1.89	1.62	3.48	5.22	1.86	1.74	3.6	0.98	3.85	5.78	2.87	1.93	4.8
26	27/F	74	78	100	92	144.5	141	4.02	10.33	1.75	3.82	6.2	2.07	2.38	4.45	0.95	3.12	5.35	2.17	2.23	4.4
27	29/F	69	74	96.5	104	167.5	158.5	1.77	1.57	1.4	3.3	5.42	1.9	2.12	4.02	1.23	3.52	6.02	2.29	2.5	4.79
28	40/M	65.5	69	83	90	131	136	1.95	2.99	1.82	3.8	6.08	1.98	2.28	4.26	0.98	3.05	5.35	2.07	2.3	4.37
29	45/F	71.5	73.5	92.5	92	127	121	2.41	5.06	0.9	2.65	4.72	1.75	2.07	3.82	1.05	3.55	3.85	2.5	2.3	4.8
30	26/F	75.5	73.5	99.5	98	146.5	136	6.84	5.17	1.23	2.58	3.8	1.35	1.22	2.57	0.88	3.45	5.98	2.57	2.53	5.1
31	25/F	65.5	69	95	100	126.5	132	14.29	6.08	0.78	2.48	4.95	1.7	2.47	4.17	1.45	3.68	5.75	2.23	2.07	4.3
32	25/F	70	77	91	91	136.5	120.5	8.59	6.18	1.82	4.32	6.65	2.5	2.33	4.83	0.7	3.18	4.85	2.48	1.67	4.15
33	50/M	65	59.5	99	96	134.5	123	4.65	6.39	1.52	3.85	5.78	2.33	1.93	4.26	1.35	2.55	4.4	1.2	1.85	3.05
34	43/F	68.5	68.5	92.5	98	123	127	5.8	5.07	0.78	1.92	5.45	1.14	3.53	4.67	0.8	3.45	5.25	2.65	1.8	4.45
35	29/F	75.5	77.5	93	97.5	120	118.5	3.09	4.58	1.05	3.15	5.55	2.1	2.4	4.5	0.95	4.7	7.72	3.75	3.02	6.77
36	44/F	63.5	70.5	93.5	91	125.5	117.5	10.17	3.25	1.58	3.78	5.98	2.2	2.2	4.4	0.98	3.38	5.6	2.4	2.22	4.62
37	19/F	80	63	91	83.5	122	112.5	5.17	5.81	0.82	2.52	5.1	1.7	2.58	4.28	1.32	2.95	4.65	1.63	1.7	3.33
38	34/F	72	77	95	89	126	120	3.28	2.17	1.82	4.03	6.35	2.21	2.32	4.53	0.45	3.12	4.9	2.67	1.78	4.45
39	39/F	64	61.5	96.5	104	127	126	8.59	0.12	1.92	3.7	5.22	1.86	1.44	3.3	0.72	2.42	4.8	1.7	2.38	4.08
40	53/F	65	67	97	96	126	133.5	4.35	1.35	1.3	3.75	5.28	2.45	1.53	3.98	0.75	3.02	5.2	2.27	2.18	4.45