EVALUATION OF OTOACOUSTIC EMISSIONS, BRAINSTEM EVOKED RESPONSE AUDIOMETRY AND SERUM LEVELS OF ANTICYCLIC CITRULLINATED PROTEIN ANTIBODIES IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that the dissertation entitled **"Evaluation of Otoacoustic Emissions and Bainstem Evoked Response Audiometry and serum levels of Anti Cyclic citrullinated Protein Antibodies in patients with active Rheumatoid arthritis"** by the candidate Dr. R.. Bhuvaneswari for M.D Physiology is a bonafide record of the research done by her during the period of study (2014-2017) in the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai-600003.

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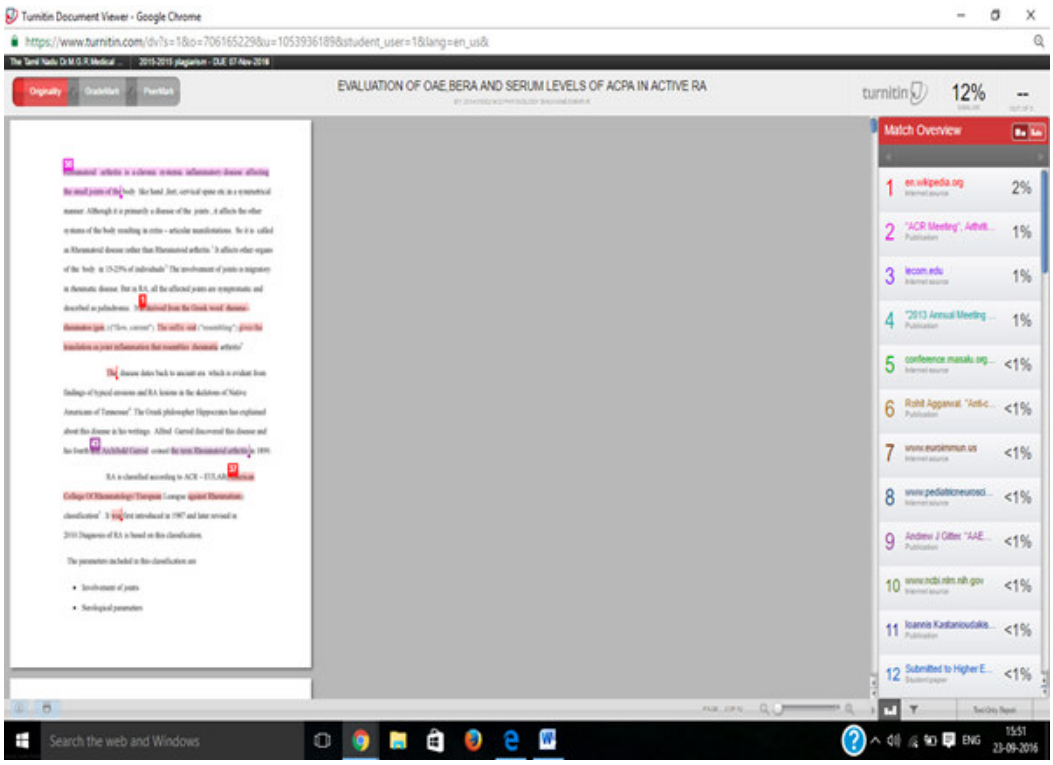
GLOSSARY OF ABBREVIATIONS

BERA	BRAINSTEM EVOKED RESPONSE AUDIOMETRY
RA	RHEUMATOID ARTHRITIS
SNHL	SENSORINEURAL HEARING LOSS
AVCN	ANTERIOR VENTRAL COCHLEAR NUCLEUS
PVCN	POSTERIOR VENTRAL COCHLEAR NUCLEUS
CNS	CENTRAL NERVOUS SYSTEM
Ms	MILLISECONDS
dB	DECIBELS
ACPA	ANTICYCLIC CITRULLINATED PROTEIN ANTIBODIES
RF	RHEUMATOID FACTOR
APR	ACUTE PHASE REACTANTS
PTPN22	PROTEIN TYROSINE PHOSPHATASE
PAD 14	PROTEIN ASSOCIATED WITH DIFFERENTIATION
DMARD	DISEASE MODIFYING ANTIRHEUMATIC DRUGS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INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory disease affecting the small joints of the body like hand ,feet, cervical spine etc.in a symmetrical manner. Although it is primarily a disease of the joints , it affects the other systems of the body resulting in extra – articular manifestations. So it is called as Rheumatoid disease rather than Rheumatoid arthritis.[1] It affects other organs of the body in 15-25% of individuals.[2] The involvement of joints is migratory in rheumatic disease. But in RA, all the affected joints are symptomatic and described as palindromic. It is derived from the Greek word rheuma -rheumatos (gen.) ("flow, current"). The suffix -oid ("resembling") gives the translation as joint inflammation that resembles rheumatic arthritis

The disease dates back to ancient era which is evident from findings of typical erosions and RA lesions in the skeletons of Native Americans of Tennessee[4]. The Greek philosopher Hippocrates has explained about this disease in his writings. Alfred Garrod discovered this disease and his fourth son Archibald Garrod coined the term Rheumatoid arthritis in 1890.

RA is classified according to ACR – EULAR(American College Of Rheumatology/ European Leaugue against Rheumatism) classification[5] . It was first introduced in 1987 and later revised in 2010.Diagnosis of RA is based on this classification. The parameters included in this classification are

- Involvement of joints
- Serological parameters
- Acute phase reactants and Duration of the disease

It affects 0.5-1% of the population worldwide[6].The prevalence in India is 0.75% . The female to male ratio of the disease is 3:1 It is more common in females because Estrogen stimulates Tumor necrosis factor – alpha which remains a contributory factor in the disease.

Etiology : It is multifactorial. The following factors are responsible for the expression of the disease.

Genetic factors : There is genetically determined breach in immunological tolerance few years before the onset of the disease. They belong to class II Major Histocompatibility antigen type (HLA) like TPTPN 22 & PAD14.The shared epitope on HLA DR 4 &1 plays an important role in susceptibility to the disease.

Epigenetic factors :

- Lifestyle practices such as Smoking ,Environmental stress
- Infections etc.

Stress accelerates the formation of autoantibodies like Rheumatoid Factor and Anti cyclic Citrullinated Protein Antibodies.They are targeted against modified proteins ,the citrullinated proteins in the synovium which are Fibrinogen and Vimentin.

Pathogenesis

The immune system is made up of array of cells and antibodies to attack the foreign invaders of our body .But in autoimmune diseases they target the normal own tissues of the body resulting in inflammation of various tissues and organs. The immune cells attack and destroys the healthy cells and tissues in autoimmune disease .In RA, The immune cells start attacking the normal synovium of the joints resulting in

- synovitis
- Release of inflammatory cytokines
- Increased expression of autoantibodies and
- Deposition of immune complexes which triggers the disease process.

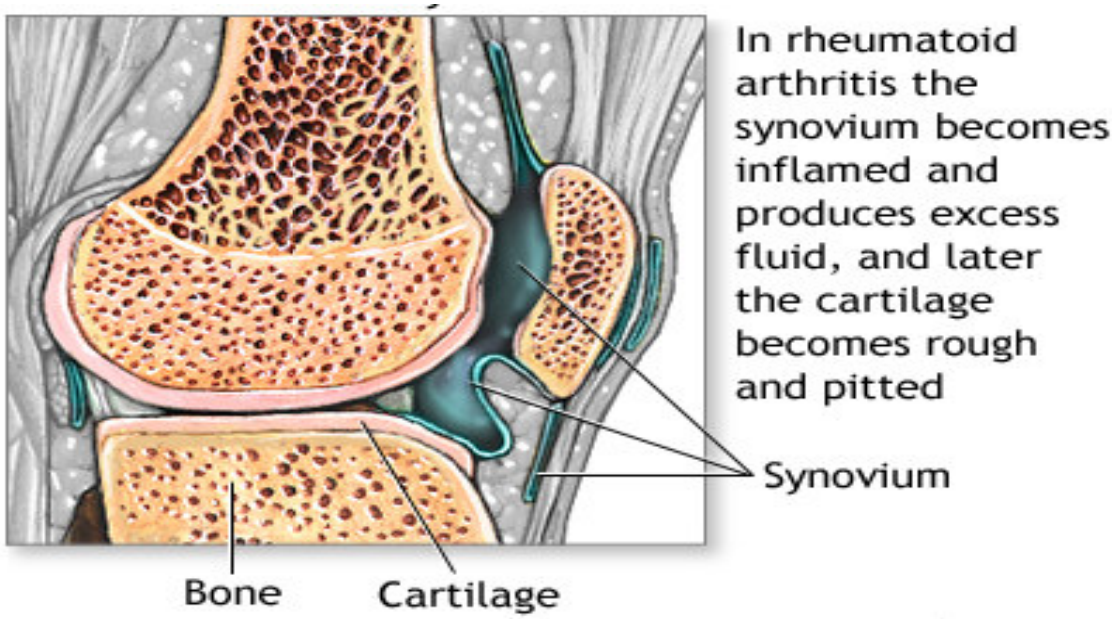
The immune cells attack the synovium of the joints resulting in tethering of tissue , damage to the cartilage and erosion of the bone. The destruction of the joint is due to fibroblasts and synoviocytes. Osteoclasts causes bony erosions. Destruction of cartilage is brought about by proteolytic enzymes in pannus .

The disease is characterised by

- Pain and swollen,tender joints
- Early morning stiffness
- Muscle atrophy around the joints
- Decrease in strength and efficiency of the muscles

- Muscle weakness
- Limitation of movement
- Loss of function & disability

Figure 1:Synovium in RA



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The active disease is defined according to DAS 28 score >5.1 which is characterised by synovitis with four of the seven warning signs for a period of six weeks or more .Early morning stiffness remains the hallmark of active disease which lasts for 30-45 minutes associated with pain and swelling of the joints.Increased acute phase reactants & autoantibodies (RF,ACPA) are evident. Treatment aims at reduction of the symptoms. The various modalities of treatment are

- Disease Modifying Antirheumatic Drugs
- Anti malarial drugs
- Non steroidal anti – inflammatory drugs
- Glucocorticoids
- Biological agents

The mortality in the disease is due to extra – articular manifestations especially the cardiovascular abnormalities. The disease is characterised by remissions and remains progressive for life.The disease activity is assessed by DAS 28 scoring system The serum of these patients show positivity for Rheumatoid factor and ACPA's along with rise in Acute phase reactants.

ACPA's in the serum is the powerful biomarker in the diagnosis of RA at an early active stage.[7] It is highly specific with minimal clinical symptoms and even in the preclinical period. These are autoantibodies against citrullinated proteins in the synovium like fibrinogen,vimentin etc. The process of citrullination in inflammation is normal and self limiting.In RA the altered shape of these proteins are recognised as antigens .The autoantibodies are formed against these antigens elicits an abnormal immune response and results in the disease. ACPA's are included as a criteria for the early diagnosis of RA in 2010 ACR-EULAR classification.

The extra- articular manifestations develop due to the

- Deposition of Immune complexes

- Release of inflammatory mediators
- Vasculitis
- Rheumatoid nodules etc.

RA affects the auditory system in various ways[8].The small joints of the middle ear and the cochlea of the inner ear are affected in the inflammatory process. The hair cells of the inner ear which are ,the receptors of hearing are affected causing Sensorineural hearing loss .The sound waves produce mechanical vibrations of the hair cells of the inner ear .The hair cells generate receptor and action potential and transmits the signals in the form of electrical energy to the brainstem and higher centres. They also act as amplifiers.

The hair cells of the inner ear express antigens and become the target of immune attack.The deposition of immune complexes and proinflammatory cytokines like Interleukin- 6 (IL-6) destroys the hair cells in the active stage of the disease.The hearing impairment due to SNHL in RA ranges from 25-72%

Sensorineural hearing loss is classified according to the levels of involvement of the central auditory apparatus.The involvement of sensory receptors is termed as sensory (cochlear) and the vestibulocochlear nerve extending to the higher centres as Neural (Retrocochlear) hearing loss. In RA, the cochlear hair cells are affected and results in sensory type of SNHL. Pure Tone Audiometry is done to identify the hearing loss, and

subjected to Brain stem Evoked Response Audiometry. The screening test to identify the early involvement of hair cells is the Otoacoustic Emissions test.

Otoacoustic emissions are sounds produced by healthy hair cells of the cochlea. They were predicted by Thomas Gold in 1948 and later it was proved by David Kemp in 1978. They are measured with sensitive microphones placed in the external auditory canal. Transient Evoked Oto Acoustic Emissions are used for the evaluation of function of cochlear hair cells. In RA ,the hair cells which are affected leads to the decrease or disappearance of OAE which is a biomarker of cochlear type of hearing impairment at an early stage .[9] Those with abnormal OAE may be subjected to diagnostic OAE & the severity is determined.

Brainstem Evoked Response Audiometry is a non- invasive objective test of hearing .The cochlear potentials recorded in humans was first reported by Sohmer and Feinmesser in 1967. Jewett and Williston described the wave patterns and explained their origin from the brain stem in 1971.BERA gives information about the function of auditory pathways. It can be done in awake and restless patients. It is the electrophysiological response evoked in the auditory pathway in response to click stimuli.It is recorded by placing electrodes in the ear and vertex and used to detect lesions and conduction abnormalities of the auditory pathway upto the midbrain.The evoked response are recorded within 500ms of the application of the stimulus. The evoked potentials recorded within the first 10 milliseconds after the application of brief stimuli is a short latency response(SLR) is described as

BERA.It comprises of five or more waves with 3 inter peak latencies.The latencies and inter peak latencies provide information regarding the site of lesion in the auditory pathway extending from the cochlea to inferior colliculi.

. The hair cells of the inner ear are affected in active RA. So the evoked potentials generated from the hair cells are affected which is reflected in the auditory nerve and contributes to the prolonged latency of wave 1. The latencies of wave Il, III & V and the inter peak latencies are found to be normal,indicating peripheral involvement of the auditory pathway.

The hair cells of the inner ear are affected by immune complex deposition resulting in sensorineural hearing loss in the active stage of RA (**Magaro M et al1990)**[10]

Amir emamifar et al. in his study has explained that patients suffering from active RA are more prone to develop sensorineural hearing loss .The more specific and sensitive biomarker of the active stage of the disease is the ACPA's detected by ELISA**(Rohit Agarwal et al 2009)**[11] . The site of lesion in RA is diagnosed by BERA and the functional integrity of hair cells are screened by Oto acoustic emissions test.

Taking into consideration the above explained factors,my study focusses on the involvement of hair cells of the inner ear in active stage of rheumatoid arthritis which is confirmed by the increased titre of serum ACPA's. The involvement of hair cells is screened by OAE test & the waveforms are studied by BERA.The serum ACPA levels and values of

wave I latency of BERA are compared between active RA patients and correlated to prove the involvement of hair cells in active rheumatoid arthritis. The hair cell involvement without any evidence of hearing loss , if identified earlier can be intervened and measures may be taken to preserve them which will prevent the hearing disability & make the patients to lead a better lifestyle in the society.

REVIEW OF LITERATURE

Rheumatoid arthritis is a chronic systemic inflammatory disease whose aetiology is not clearly known .It favours an autoimmune origin.It is characterised by symmetrical peripheral polyarthritis affecting the small joints of the hand ,feet,cervical spine etc. resulting in joint damage and physical disability . It is characterised by systemic extra-articular manifestations affecting other organs like lungs , heart & blood vessels, eyes,ears in 15-25 % of individuals.[12] .So it is appropriately called as Rheumatoid disease. The disease results in Pulmonary diseases,Cardiovascular disorders , Peripheral Neuropathy ,Vasculitis and Haematological abnormalities[13]. It is a disease dating back to ancient times and continuing in the modern era.

Rheumatoid arthritis is derived from the Greek word Rheumatos &oid ("resembling") gives the translation as joint inflammation that resembles rheumatic fever. Rhuma which means watery discharge that might refer to the fact that the joints are swollen or that the disease may be made worse by wet weather

Epidemiology

Disease incidence

The annual incidence of the disease is higher in Northern Europe and Northern America (Marc et al[14]) based on 1987 ACR criteria[15.] It increases between 25-55 years of age , reaches a plateau till 75 years and then decreases. 41 out of every 100,000 population are diagnosed with the disease every year worldwide. It affects women between 30-60 years and a little later in men. The life time risk of developing the disease is 4% in

women and 3% in men. The rate of RA is higher (42-15%) in monozygotic than dizygotic twins (3%) .There is increased frequency of the disease in first degree relatives of patients.Lower incidence is reported every year in East Asia.The prevalence in India is 1.5-2%. Female to male ratio is estimated to be 2:1. This is due to estrogen which stimulates Tumor necrosis factor alpha ,a contributory factor in the disease.

Prevalence

Worldwide prevalence of the disease is estimated to be 0.4 -1%. which is age specific & the rate increases with age .In Asia the range is 0.2-0.3% with an increase in urban areas . Decline in prevalence of the disease is found in subsequent generations among the Indian population[16].In India it is 1.5-2% .& in first degree relatives it is 2-3%[17.]

History

History of the disease dates back to ancient times. Evidence regarding the existence of the disorder affecting the ears is found in ancient texts, Renaissance artwork etc. to post-mortem remains of exhumed skeletons in Modern era.[18] It is an ancient disease having its journey to the Modern era.

Rheumatoid means resembling Rheumatism. It was recognised in texts dating back to 4500 BC . First reference to the disease was around 1500 BC by Ebel Papyrus who described a similar condition. Egyptian Mummies also stand evidence to this disease . This condition is explained in Indian literature Charak Samhita (300-200 BC)

The Greek Philosopher Hippocrates quotes about the disease as

" In the arthritis which generally shows itself about the age of thirty-five there is frequently no great interval between the affection of the hands and feet; both these becoming similar in nature, slender, with little flesh…For the most part their arthritis passeth from the feet to the hands, next the elbows and knees, after these the hip joint. It is incredible how fast the mischief spreads."[19.]

It is also supported by various writings and paintings in the 16th century by Greek Physician Arataeus, Caesar's Physician Scribonius, the Byzantine Physician Soranus, Emperor Constantine IX's adviser Michael Psellus, and various other ancient physicians[20] and in Peter Paul Rubens paintings respectively.

Figure 2: Painting by Paul Rubens showing the deformed fingers

In 123 AD symptoms similar to rheumatoid arthritis were described . Bruce Rothschild found bony changes in the skeletal remains of Native Americans in Tennessee. Even today the Native Americans are more susceptible than other ethnic groups. Some celebrities affected with this

disease were Lucille Bell (Comedian) ,James Coburn (Actor) ,Camoyn Maheim (Actress)[21]

Augustine Jacob Landre Beauvais ,a 28 year old resident Physician at Saltpetriere Asylum in France noticed severe joint pains in many patients and. pioneered the discovery of the disease in 1800 . The symptoms and signs shown by these patients were different from Rheumatic arthritis and Osteoarthritis .Alfred Garrod , an English physician was the first person to distinguish this form of arthritis from Gout in which there was an increase in the Serum Uric acid levels and named it as Rheumatic gout in his Treatise on "Nature of Gout and Rheumatic Gout". Archibald Garrod ,the fourth son of Alfred Garrod did a lot of research & Finally in 1890 he coined the term Rheumatoid arthritis in his book "Treatise on Rheumatism and Rheumatoid arthritis".

Nomenclature of the disease

Rheumatoid means resembling rheumatism. Galen (129-216 AD) introduced the term Rheumatism. Camroe defined the term Rheumatologist in 1940 and Rheumatology by Hollander in 1949. International Conference in Rheumatism was started in 1932 . Later it was renamed as American Rheumatism Association and then to American College of Rheumatism.

Classification

2010 American College of Rheumatism/European League Against Rheumatism (ACR/EULAR) criteria is the standard for classifying and diagnosing the disease .[22] replacing the 1987 criteria[23] .Its sensitivity

ranges from 77% - 95% and specificity from 85%- 98%[24].It aims at identifying the disease at an earlier stage thus reducing the duration of the disease and complications by effective treatment

2010 ACR/EULAR classification

JOINT DISTRIBUTION (0-5)

1 large joint 0

2-10 large joints 1

1-3 small joints (large joints not counted) 2

4-10 small joints (large joints not counted) 3

>10 joints (at least one small joint) 5

SEROLOGY (0-3)

Negative RF AND negative ACPA 0

Low positive RF OR low positive ACPA 2

High positive RF OR high positive ACPA 3

SYMPTOM DURATION (0-1)

< 6 weeks 0

>= 6 weeks 1

Acute phase reactants (0-1)

Normal CRP and normal ESR 0

Abnormal CRP and abnormal ESR 1

>/= 6 suggests definite Rheumatoid arthritis

Etiology

The causes of the disease are complex and multifaceted. They are

Genetic factors : Half the risk is associated with genetic susceptibility[25]. These are predetermined years before the onset of symptoms.`The genes which are highly susceptibile in developing the disease is contributed by Major Histocompatibility Antigen class II , PTNP 22 etc. The shared epitope present on HLA –DR4 & 1 increases the susceptibility to the disease and determines the severity. Inheritance of HLA-DRB1 is commonly seen among Indians .So family history serves an important risk factor[26.] PTNP 22 gene doubles the risk of inheriting the disease. PAD 14 is a remarkable risk in Asians but not in Europeans.

Non genetic factors behave as triggers for the onset of disease .They are

- Repeated activation of innate immunity which is self limiting .
- Infections byEpstein-Barr virus, Cytomegalovirus and Human Herpes virus 6
- Bacterial infections triggers the onset of the disease[27]

Lifestyle practices

Cigarette smoking increases the expression of HLA –DR4 genes. It also increases the severity of the disease and decreases its response to DMARD's. Vitamin D defeciency is more common among these patients than general population[28.]

Hormonal

There is increased susceptibility in Postpartum and Breast feeding women. This shows that humoral - immune interactions play an important role.[29] Stress activates the post transcriptional modification of

proteins and citrullination of Arginine residues in the synovium. This process accelerates the formation of Autoantibodies like RF, ACPA's against these target proteins and initiates the disease .

International coding of rheumatoid arthritis(ICD)

According to ICD -10 2016, the code for Rheumatoid arthritis is M 05

Pathology

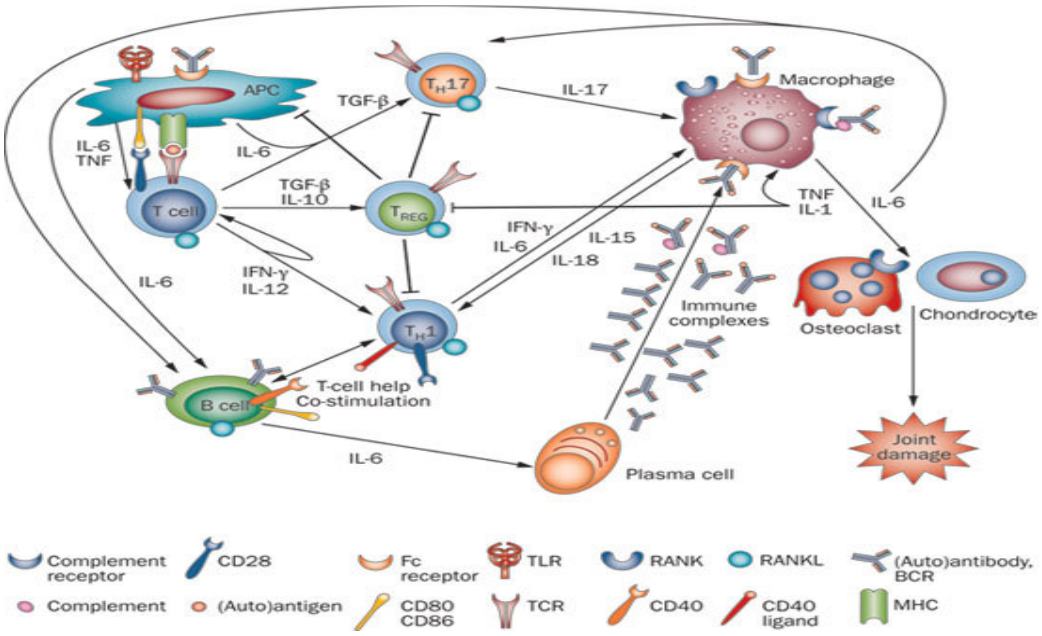
Immunological tolerance is broken down in Rheumatoid arthritis which contributes to the pathology of the disease .Immunity confers protection to the body against foreign invaders like bacteria,viruses etc.In RA the immunity starts working against the normal own tissues (synovium of the joints) and the immune response is elicited in normal tissues. This leads to the deposition of antigen antibody complexes and contributes to the pathogenesis of the disease.

The triggers of the disease explained above elicit abnormal autoimmune responses enhanced by genetic susceptibility is responsible for the vicious cycle of the disease.The altered shapes of the citrullinated proteins – Synoviocytes resemling fibroblasts ,Fibrinogen and Vimentin expressed by the synovium behave as antigens against which autoantibodies are formed.

The normal self limiting immune attacks behaves differently in the disease . In RA there is abnormal T cell activation and formation of pathogenic antibodies by B cells .The synovium is targeted by the antibodies causing inflammation. This results in leakage from the vessels which attracts more immune cells to the joints. Simultaneously the dendritic cells process the

antigen and present it to the immune cells. There is increased formation of autoantibodies by B cells resulting in the inflammation & production of IL-6 & MMP3 (Matrix Metalloproteinases) which in turn increase the expression of autoantibodies thus creating a vicious cycle resulting in the disease.

Figure 3: Pathogenesis in RA



There is T-B cell interaction in the lymphoid follicles which stimulates B cells to produce Cytokines and autoantibodies like Rheumatoid factor and antibodies to Citrullinated proteins . The activated synovial macrophages and the products of local tissue damage acts via Toll like receptors to produce inflammatory cytokines like Tumor necrosis factor , Interleukins 1,6,& 15. These act on synovial fibroblasts and causes swelling of membrane , damage to soft tissues and cartilage.

These fibroblasts are a source of Chemokines ,Leukotrienes and Metalloproteinases which in turn causes local tissue damage and

remodelling. Activation of osteoclasts by Receptor Activator of Nuclear Factor k –Ligand (RANKL) and chondrocytes by cytokines (IL 1 & TNF) results in destruction of bone and cartilage. The affected joint becomes hypoxic and goes for neovascularisation. Endothelial activation with recruitment of more leukocytes and a vicious cycle of inflammation results. Tumor necrosis factor activates endothelium and production of cytokines. IL 6 and other proinflammatory cytokines produces systemic effects , increases acute phase reactants, autoantibodies, anemia of chronic disease , fatigue and decreased cognition.

Pannus

The inflammatory granulation tissue erodes and destroys the underlying articular cartilage along with osteoclasts. This ends up in fibrous or bony ankylosis, atrophy of adjoining muscles and progressive biomechanical dysfunction.

Clinical features

The disease has an acute and florid onset .It is palindromic with relapses and remissions for some hours to days. It is characterised by

- Swollen tender and warm joints
- Stiffness of the involved joints early in the morning or after prolonged inactivity, hallmark of active phase of the disease . This is due to the accumulation of edema in inflamed tissues on sleeping . During movement the fluid is drained by lymphatics .It lasts for 30-45 minutes.

- Limitation of movement due to synovitis
- Loss of movement due to bony erosions & deformities

The commonly involved joints are the small joints of hands, feet and wrists in upper limbs . Larger shoulder and knee joints are also affected

Extra-articular manifestations

Skin :

- **Rheumatoid nodules** [30] occur in various organs in 30% of patients. It is a central area of fibrinoid necrosis sorrounded by macrophages and fibroblasts with connective tissue containing lymphocytes and plasma cells. It measures few millimetres to few centimetres in size. It is seen over bony prominences and areas of mechanical stress. These patients are RF positive with signs of erosive arthritis.
- **Vasculitis** ranging from microinfarcts around nailfolds to Livedo reticularis which is a network of erythematous to purplish discolouration of skin.

Lungs:Fibrosis , pleural effusions,Caplan's syndrome

Kidneys :Renal amyloidosis due to chronic inflammation[31]

Heart and blood vessels :Atherosclerosis , Myocardial infarction and Stroke[32]

Eyes : Episcleritis, Keratoconjunctivitis sicca **,**Keratitis with loss of vision

Liver : Primary biliary cirrhosis **,**Autoimmune hepatitis

Blood

- Poor absorption of iron and its sequestration in the macrophages resulting in Anemia of chronic disease & **thrombocytosis** increasing the viscosity of blood and depriving the organs of its nutrition.

Neurological : Peripheral neuropathy**,**Carpal tunnel syndrome**,**Atlanto- axial subluxation due to erosion of odontoid process and transverse ligaments in cervical spine during the course of the disease

Constitutional symptoms

- Fatigue
- Low grade fever
- Malaise
- Loss of appetite and weight suggests active disease.

Bones : Osteoporosis of inflamed joints

Cancer : Lymphomas[33]

Complications

Deformities results from longstanding uncontrolled disease.

- **Upper limb deformities :** Swan neck deformity, Trigger finger etc.
- **Lower limb deformities:** Flat foot , Cock up deformity etc.

Other Complications

- Iron deficiency anemia
- Amyloidosis
- Felty's syndrome

Diagnosis

- Clinical history
- Physical examination of the patient
- Investigations

Lab investigations

- Complete blood count
- Acute phase reactants like

  Erythrocyte sedimentation rate

  C Reactive Protein.

  Increased acute phase reactants is the hallmark of active arthritis.

Rheumatoid factor

Rheumatoid factor is a nonspecific antibody[34] RF is detected in 60-80% of patients. It precedes the disease onset by several years. The prevalence in early disease ranges from 50-60%[35.] They are autoantibodies directed against the antigenic determinants on the Fc portion of IgG. They belong to IgM isotype. There is a low transient increase in IgM RF ,a part of normal immune response in infections present in10%- 15% of normal people. (Due to citrullination of arginine residues of proteins)

In Rheumatoid disease,this process is enhanced by the immune complexes containing microbial antigens. There is a chronic increase in titre of these antibodies with the appearance of IgG and IgA subtypes.Further the genes encoding RF is somatically mutated in the disease. It is germline coded and polyreactive.[36,37] In a normal immune response, RF increases the size of

immune complexes and helps in its removal. In RA,it causes complement fixation of IgG containing immune complexes which is enhanced byIgM –RF binding in the joints. The chronicity of the disease is via Complement mediated pathways. RF producing B cells act as antigen presenting cells and self antigens are presented to T cells via uptake of immune complexes.RF in serum and RF producing B cells present in the synovium plays an important role in the causation of the disease[38] 15% have seronegative rheumatoid arthritis[39] It is positive in other diseases like systemic lupus erythematosis and also in 10% of healthy population .Hence it is a non specific test

Increased titre plays a role in prognosis of the disease and in assessing the severity of the disease such as erosiveness, progression of the disease, outcome and extra-articular manifestations[40]. RF remains as a widely used serum marker of RA according to 2010 ACR/EULAR criteria for classification of RA.The normal levels of RF in serum is estimated to be <15 IU/ml. A titre more than 15 IU/ml is significant of RA.[41]

Anti citrullinated protein antibodies(ACPA's or anti-CCP)

This is a disease specific diagnostic test for RA and has a specificity of 95%. It remains positive in the preclinical and active period of the disease.[42]

- Antiperinuclear factor, an autoantibody was discovered using Indirect Immunofluorescence test by Nienhuis and his colleagues in 1964. This recognised the antigen present in Keratohyalin granules around the nucleus.

- Young and colleagues later discovered anti-keratin antibodies in RA patients. These tests showed high sensitivity and specificity (88%-99%).standardisation and interpretation difficulties are encountered in carrying out these tests. These tests showed high sensitivity and specificity (88%-99%).Standardisation and interpretation difficulties are encountered in carrying out these tests and not practised nowadays.
- In the year 1995, Sebbag and his colleagues demonstrated that these autoantibodies are targeted against citrullinated Fillagrin ,an epithelial cell protein.
- In 1998, Schellekens and colleagues created synthetic linear citrullinated peptides from human Fillagrin which is easily detected by ELISA with enhanced sensitivity and specificity. A cyclic citrullinated peptide (CCP) was developed to improve antigen composition and antibody recognition.

ACPA's has the ability to recognise early active arthritis in RA patients.

Citrullination is post translational conversion of Peptidylarginine to Peptidylcitrulline and this is catalysed by calcium dependent Peptidylarginine deaminases[43] . Citrullination is a physiological process that occurs during apoptosis and terminal cellular differentiation (keratinization) dependent on increased PAD and intracellular calcium levels .Increased citrullination is seen in inflammation of the tissues like lungs ,CNS and skeletal muscles. Increased citrullination is highly evident in RA due to the altered shapes of these proteins that triggers the disease . Antiperinuclear factor in 1964 and a

few years later , Antikeratin antibodies that targets citrullinated Filaggrin was found in serum of RA patients. The targets in the synovium are Fibrinogen and Fibronectin as Fillagrin is not present in the synovium. ..HLA-DRB1SE(shared epitope) gene exposes the citrullinated peptides to pathogenic T cells. Cigarette smoking ,one of the risk factors of the disease, increases the expression of PAD enzyme and thus enhances citrullination in genetically predisposed individuals. The self antigens presented to the immune system initiates loss of immunological tolerance and thus the expression of the disease.[44]

The identification of first generation and second generation cyclic citrullinated peptides are carried out by Enzyme linked immunosorbent assay . CCP2 which is based on synthetic peptides is the **gold standard** diagnostic test for Rheumatoid arthritis.It has a sensitivity of 60-70% and a specificity of 95%.[45].Increased titres of ACPA's antedate the symptoms and helps in the diagnosis of the disease at an early, active stage**.**

Demorrulle et al[46]has explained in his study that ACPA's is highly specific for the diagnosis of active disease in RA, its etiology, prediction of future risk and its prevention

Dr .shyam et al has explained in his study that ACPA's remain a specific biomarker of active RA.

Serological point of care test

It is a recent advancement in the early detection of the disease. It is a combined detection of RF and anti-MCV assay.Anti-MCV are

antibodies against Mutated Citrullinated Vimentin. This test shows a sensitivity of 72% and specificity of 99.7%.[47]

Imaging techniques

- Osteopenia seen in X – rays of the affected joints in active early disease
- Soft tissue swelling and loss of joint space.Bony erosions and subluxation of the joints are made out in advanced cases.
- Magnetic resonance imaging reveals early erosion of affected joints
- Doppler ultrasound reveals synovial inflammation which is a predictive marker of future joint damage[48]

Treatment

Treatment does not provide a cure but decrease pain and prevent deformities enabling a normal day to day life[49].

The aim of therapy is

To modulate pathogenic cells, neutralise the effect of molecules produced,alleviate pain and restore tolerance.They are

- Disease Modifying Anti Rheumatic Drugs (DMARD's - Methotrexate ,Hydroxychloroquine,Sulfasalazine)
- Analgesics
- Cox -2 inhibitors
- Leflunamide,a Pyrimidine synthesis inhibitor

Biological agents

- Tumor necrosis factor inhibitors like Etanarcept, Infiximab etc.

Biological agents are advised when the previous medications are not effective after a trial of 3 months.

- Glucocorticoids for short term flare ups

Life style modification

- Regular exercise improves physical function by increasing muscle strength.

Surgery

- Synovectomy preferred in early cases that prevents development of rapid deformities of joints. Joint replacement in severe cases[50]

Physiotherapy which improves the muscle strength

Alternative medicine

- Mind and body practises are beneficial along with conventional treatment

Remissions

It means none or only minimal residual disease activity. DAS 28 score is practised to comment on remissions.

DAS 28 score(Disease activity score of 28 joints.)

It is an indicator of disease activity and response to treatment. This score guides to start or stop treatment.It is a measure of disease activity in which 28 joints are asessed.

It focusses on

- Examination of joints if swollen and tender
- Global sore of pain and its nature
- ESR/CRP of which the latter is recommended
- Health assessment questionaire which assess the function
- X rays and imaging techniques like USG& MRI

A composite score is derived from the above said criteria . It is done by

- Counting the number of swollen joints(28)
- Counting the number of tender joints (28)
- Global assessment of health indicated by marking a 10cm line between very good and very bad by the patient

Results are fed into a mathematical formula and the score is obtained as follows

>5.1-active disease , >3.2 & <5.1 - moderate disease activity ,<3.2 – inactive

Regular DAS 28 score is carried out to recommend

- Change in treatment
- Increase or decrease therapy
- If the score is persistently high,it is indicative of progressive joint damage

The joints included bilaterally are

- Proximal interphalangeal joints (10)
- Metacarpophalangeal joints (10)
- Wrist joints (2)

- Elbow joints(2)
- Shoulder joints (2)
- Knee joints (2)

Calculation of DAS 28

Table 1: DAS SCORING SYSTEM

current DAS28		DAS28 decrease from initial value		
		≥ 1.2	> 0.6 but ≦ 1.2	≤ 0.6
≦ 3.2	Inactive	Good improvement	Moderate improvement	No improvement
≥ 3.2 but ≤ 5.1	Moderate	Moderate improvement	Moderate improvement	No improvement
> 5.1	Very active	Moderate improvement	No improvement	No improvement

Prognosis

The course of the disease is variable from mild short term illness to progression throughout life.

Morbidity

There is a two fold increase in depression due to restricted mobility. The morbidity is due to extra –articular manifestations .40% of the patients

become disabled within 3 years of treatment and 80% become moderate to severe disability within 20 years.

Mortality

Death from cardiovascular disease is common.[51] The risk of developing heart attack is 60% higher within 1 year after being diagnosed[52]The mortality ratio is about 2:3 among people with rheumatoid arthritis than general population worldwide.[53] 40% of deaths resulted from cardiovascular causes such as Ischemic heart disease. There is a decrease in the lifespan by 8-15 years

Prevention

Olive oil and fish oil seems to be protective. Vitamin D is found to be protective against the disease as it acts as an important modulator of inflammatory response.[54] Omega 3 fatty acids and Gamma Linoleic acid reduce pain and stiffness.[55]

Active disease

- Duration of the disease for a period of more than six weeks [56] to one year characterised by a DAS 28 score >5.1
- Early morning stiffness, the hallmark of active disease
- Joint inflammation (synovitis) without erosive damage to the joints
- Thrombocytosis ,Increased APR .
- Constitutional symptoms like fatigue,loss of weight & appetite,fever

Early intervention during this period maintains the integrity of the joints and minimises extra - articular involvement. There is effective

response to DMARD treatment in active disease. Hence this period of the disease is called as "**window of opportunity"** Progression of the disease is retarded and destruction is prevented in early ,active disease by intervention with Glucocorticoids,DMARD's ,Biological agents or combination of the above[57]

Active disease is defined as follows

- DAS28 score >5.1
- Elevated Acute phase reactants
- Early morning stiffness >45 minutes.[58]
- Swollen and tender joint counts ≥6 each[59] (DAS 28 score >5.1)

ACPA's in active disease

The break down of immunological tolerance aided by genetic predisposition and influenced by various trigger factors results in vicious cycle of inflammatory response.The proinflammatory cytokines released during the disease process accelerates citrullination of Arginine residues and the production of autoantibodies like RF & ACPA's. The inflammation evident by swollen & tender joints,increased acute phase reactants also increases the titre of ACPA's and it remains elevated in active disease which is very specific to the disease process.So ACPA's remain an effective marker of active rheumatoid arthritis.

Sigita et al has explained that ACPA's with RF is a valuable serological marker in the early active stages of rheumatoid arthritis[60]ACPA's helps to detect the disease at an early active stage[61]

Hearing defects in active rheumatoid arthritis

As one of the extra-articular involvement in the disease, the auditory system can be affected in many ways. Sensorineural hearing loss (sensory type) of the cochlear type is more common in active RA patients. The prevalence of this entity of hearing defect ranges from 25%-72% in RA. Hearing loss ranges from nearly undetectable degree of disability to a profound loss of hearing ability to function in the society.

Hearing defects

10% of adults suffer from hearing disorders due to various causes. They can present at any age and some present in early life. 30-35% of individuals over the age of 65 years and 40% above 75 years present with varying degrees of hearing loss. According to WHO, about 270 million people suffer from moderate to profound hearing loss. National institute of Health states that 15% of American population in the age group between 20-69 years present with high frequency hearing loss .Hearing defects are classified into conductive & sensorineural hearing loss

Sensorineural hearing loss is once again classified into sensory and neural hearing loss. Sensory hearing disorders results from lesions of inner ear comprising of hair cells .Neural type from lesions of vestibulocochlear nerve or central auditory pathway.The former is called as C**ochlear** and the latter as **Retrocochlear** hearing loss

Etiology of SNHL

Genetic : More than 100 genes are responsible for normal hearing . The loci is found to be 5 out of 24 chromosomes[62]Protein Connexin 26 when mutated disrupts the recycling of potassium ions and hence hearing loss.It may be Syndromic (eg:Pendred's syndrome) &Non syndromic (autoimmune diseases,noise trauma etc).

Etiology of sensory hearing loss in Rheumatoid arthritis

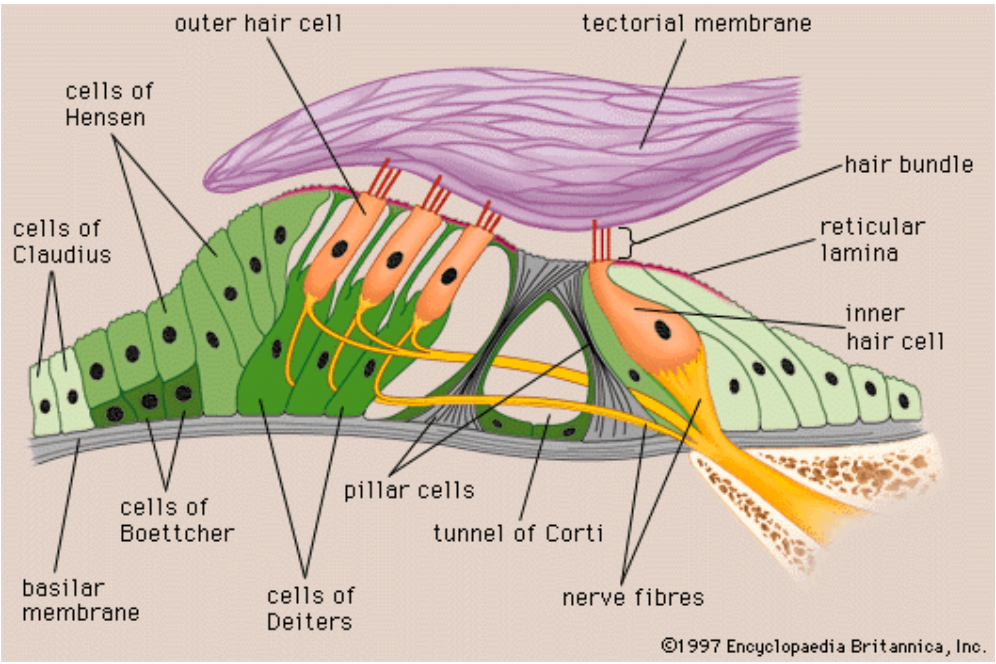
- Destrution of cochlear hair cells in active disease due to the deposition of immune complexes[63]
- The hair cells express antigens like 58Kda protein,68 Kda protein etc which initiates abnormal immune response.
- Thrombocytosis in active disease results in sluggish blood flow and compromises nutrition to the hair cells.
- Vasculitis resulting in auditory neuropathy.
- Rheumatoid nodules in the ears.
- Drugs used in the treatment of RA like Salicylates, Antimalarials,DMARD'S etc. that are ototoxic ,which affects the hair cells.
- Decrease in the neuronal and supporting structures.
- Atrophy of stria vascularis[64.]

Anatomy

The inner ear has a Bony Labyrinth in the Petrous portion of the Temporal bone filled with Perilymph containing low concentration of Potassium ions and a Membranous Labyrinth within the Bony Labyrinth filled with Endolymph rich in Potassium ions.This labyrinth has three components namely,

- Cochlea containing hearing receptors
- Semicircular canals with receptors responding to head rotation
- Otolith organs containing receptors responding to gravity and head tilt.

Figure 4: Structure of the inner ear



The cochlea is divided into three chambers by the Basilar and Reissner's membrane .They are upper Scala Vestibuli , lower Scala Tympani containing Perilymph & Scala Media containing Endolymph.The Organ of Corti extends from the base to the apex of the Cochlea which lodges the hair

cells .These hair cells are the sensory receptors of auditory system. These mechanoreceptors of the cochlea of the inner ear carries the function of hearing and it is responsible for **Mechanotransduction** – a process that detects movement in the environment and converts them into electrical potentials.[65] There are two types of **hair cells** namely three rows of outer hair cells and one row of inner hair cells.There are 20,000 outer hair cells and 3500 inner hair cells in the cochlea The afferents to the hair cells arborise at their bases and their cell bodies are located in the spiral ganglion . Their axons ,the efferents from the hair cells form the cochlear division of the vestibulocochlear nerve. The tight junctions between the hair cells prevent the endolymph reaching their bases. But the basilar membrane is permeable to perilymph,formed from plasma and hence the bases are bathed in it. So the hair cell processes project into the endolymph formed by the stria vascularis of the scala media with a high concentration of potassium ions.

Hair cells are present within the supporting cells whose basal end is in contact with afferent neurons . 30-150 rod shaped hairs project from the apical surface into the fluid of cochlear duct called as stereocilia. They are made up of cores of parallel filaments of actin coated with myosin. These increase in their heights in a progressive manner. Tiplinks are fine processes which extends from the tip of the Stereocilium to the adjacent higher stereocilia.Mechanically sensitive cation channels are present at this junction in the taller Stereocilia.

Function of the hair cells

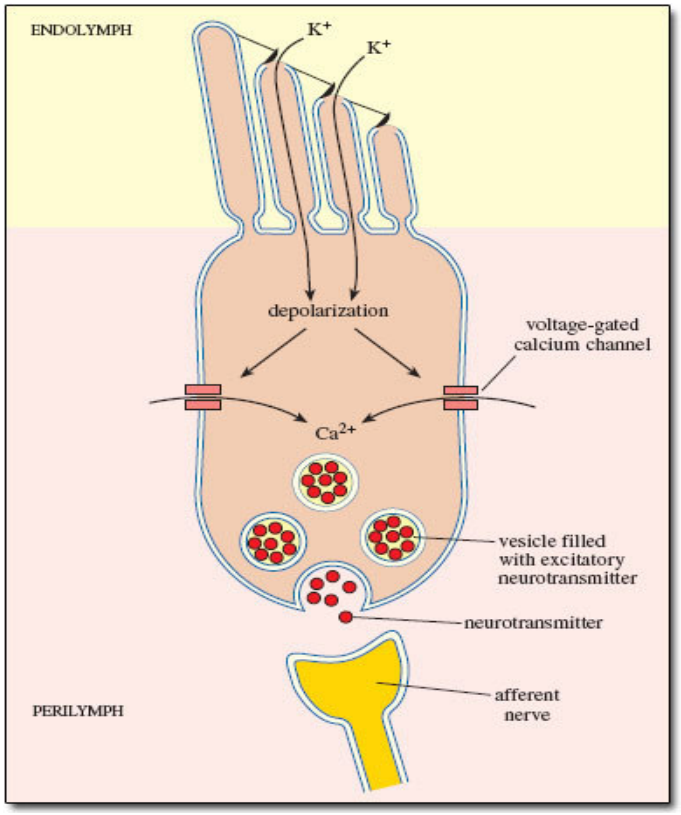
The inner hair cells function as sensory receptors of hearing .when stimulated by the sound vibration, there occurs movement of the fluids in the inner ear.As a result ,action potentials are generated in the hair cells transmitted through their synaptic connections with the auditory nerve and then to the brainstem. Although outer hair cells are receptors of hearing, they play an important role in the sound amplification, they take part in increasing the amplitude of the sounds received by them from the middle ear and sound clarity. The outer hair cells are responsible for Otoacoustic emissions . The inner hair cells by their synaptic connections with the auditory nerve initiates action potentials that are transmitted to the brain stem. Prestin ,a membrane motor protein is responsible for these variations that takes place in the outer hair cells

Mechanism of action

The deflection of the shorter stereocilium towards the taller one created by the vibration of sound opens voltage gated ion channels.There is an influx of Potassium and Calcium ions abundant in the endolymph[66] resulting in the depolarisation of the cell. The resting membrane potential of the hair cell is -60 mV. During depolarisation it decreases to -50 mV . This generates a receptor potentials called as Endocochlear potential which opens more voltage gated calcium channels and results in the release of neurotransmitters at the basal portion of the cell which is Glutamate. These neurotransmitters escape between the hair cell and the nerve terminal and binds with the receptors, initiating depolarisation of adjacent neurons and triggers the action potentials in the

auditory nerve. These neurotransmitters escape between the hair cell and the nerve terminal and binds with the receptors, initiating depolarisation of adjacent neurons and triggers the action potentials in the auditory nerve.

Figure 5: Receptor potential in the hair cell



As the processes move in the opposite direction ,it causes hyperpolarisation.The molecular motor probably myosin in the taller stereocilium moves the channel towards the base .The tension in the tiplink is released and the channels close bringing it to the resting state.

Clinical significance

Damage to the hair cells decreases the sensitivity to hearing. The hair cells cannot regenerate. Once damaged,it results in permanent hearing loss.[67] Damage to the hair cells results in the abnormalities in mechanotrasduction and hence the receptor potential and action potential.There occurs delayed transmission of these action potentials through the auditory pathway to the higher centres.

Research is aimed at gene therapy and stem cell therapy in regeneration of the hair cells. Deletion of Retinoblastoma 1(Rb1) gene promotes regeneration of the hair cells[68]

Pathology of sensory hearing loss in rheumatoid arthritis

There is damage to the hair cells in the active phase of the disease by

- Deposition of immune complexes.
- Compromised nutrition due to sluggish blood flow etc.
- Proinflammatory cytokines released during active disease damages the hair cells by an oxidative process.
- Expression of antigens by the inner ear etc.

This results in abnormalities related to the development of receptor potential in the hair cells and thus action potential in the auditory nerve resulting in abnormalities of OAE &BERA .

Investigations

General examination of the patient

ENT examination

Otoscopy

The instrument provides good magnification and lighting that helps to view the External auditory meatus, Tympanic membrane and Middle ear.

Tuning fork tests

Tuning forks with 512 frequency is used to examine hearing acuity through air and bone conduction

Rinne's test : Positive AC>BC , Negative where BC>AC

Negative in CHL & Positive in SNHL , but the intensity of sound is decreased

Weber's test

The vibrating tuning fork is placed at the Glabella .Normally Sound is equally heard in both ears

Sound is lateralised to the affected ear & normal ear in CHL &SNHL respectively

Audiological tests

The audible sound frequency ranges from 20-20000 Hz . Decibel is the logarthmic unit and roughly the least perceptive difference in sound intensity that can be detected by the human ear.The normal threshold of hearing is zero decibel

Pure tone audiometry (PTA)

Measurement of hearing levels by electronic devices like Audiometer.

It is a subjective test which needs the co-operation of the patient. The test is used to find out the hearing threshold and type of hearing loss

CHL – Bone conduction is normal

Threshold for Air conduction increase

Presence of Air –Bone gap

SNHL – Thresholds for both Air and Bone conduction increase

No Air – Bone gap

Evoked potentials

The electrical potentials generated from the nervous system of animal or human beings on application of a stimulus are called as Evoked potentials. It is very different from Spontaneous potentials recorded by Electroencephalography, Electromyography etc. These potentials recorded from Cerebral cortex, Brainstem, Spinal cord and Peripheral nerves are of low amplitude which ranges from less than a microvolt to several microvolts. The ambient noise and biological signals are averaged without averaging of responses[69].

Classification of evoked potentials

They are divided into sensory,motor & event related potentials **.** The recording from the central nervous system on stimulation of sense organs are called Sensory Evoked potentials. They are

- Auditory Evoked potentials recorded from the scalp originating at the brainstem level by click stimulus

- Visual Evoked potentials by flash of light
- Somatosensory Evoked potentials by tactile stimuli

Significance of Evoked potentials

- To assess abnormal function of sensory system
- Evaluation of clinically unsuspected abnormality of the sensory system
- Anatomic basis of disease
- Follow up of patient's clinical status over time

Evoked potentials were discovered in 1950 & its clinical utility was described in 1970. It remains as an investigatory tool for the evaluation of integrity of auditory pathway spanning from external ear to the brain stem. It is an important diagnostic method in the evaluation of SNHL in various disorders like ENT diseases , RA etc.The origin of evoked potentials dates back to the discovery of electricity.

1929- First recording of Human EEG with electrodes on scalp by Hans Berger

1939 - Short latency type of potential recorded in response to auditory stimuli by Davis

Middle and long latency responses are the rewards of the modern computers.

The recording of BERA started in 1930 with the advent of Electronic Amplifiers .BERA was Recorded as raw EEG in 1939.

Uses of BERA

- Evaluation of hearing function
- To assess Nerve conduction irregularities
- Determine the hearing thresholds in Audiology, Neurology etc

Brain stem evoked response audiometry(BERA)

BERA is an non invasive objective test . It is an electrophysiological method carried out to assess the function of auditory pathways extending from the auditory nerve to brainstem . It is a short latency potential . It records the auditory evoked potential from the ongoing electrical ativity in the brain by placing electrodes on the scalp

- 1967 -Sohmer and Feinmesser published BERA for the first time and explained that cochlear potentials could be recorded with electrodes placed on the scalp in a non invasive manner.
- 1971 - A clear description of the Human BERA and the waves obtained from the brainstem were interpreted by Jewett and Williston.
- 1977-Selters and Brackmann published about the interpeak latencies.
- 1974-The use of BERA in estimating the threshold was postulated by Hecox and Galambos
- 1975- Star and Achor demonstrated the BERA findings of CNS pathology in the brainstem.

It is the recording of the activity initiated at the base of cochlea which moves towards the apex within 4ms period of time.The parameters interpreted are

- Amplitude- Number of firing neurons
- Latency – Transmission speed
- Interpeak latency – Time between peaks

- Interaural latency – Difference in wave latency between ears

The peaks reflect activity from the basal regions of the cochlea .

Principle of auditory evoked potential

It is postulated that the electric response evoked by a sound stimulus occur after the same time interval . The auditory pathway extends from the middle ear structures through the eighth cranial nerve, the brain stem, and finally to the auditory cortex. Auditory stimuli either in the form of clicks or pure tones can be used to assess the integrity of the auditory pathway. Thus the auditory evoked potential is obtained by presenting auditory stimuli to each ear resulting in a sequence of waveforms which bear a close relationship to the structures in the auditory pathway and enables relatively specific localisation in the auditory pathway, particularly in the eighth cranial nerve and the brainstem. From the time of onset of the sound stimulus, the auditory evoked transient response can be recorded up to 500 milliseconds.

Classification of Brainstem auditory evoked potentials

This mode of investigation was first described by Jewett and Williston in 1971 and it is classified into short, middle and long latency responses.

Short latency response

The normal Brainstem auditory evoked potentials generated within first 10 ms give precise information about the brainstem functions is called the

early phase of transient response or short latency response recorded as Brainstem Evoked Response Audiometry (BERA) and this has been utilised extensively by the clinicians.

Advantages of BAEP include

- Detecting hearing loss in uncooperative patients like infants, mentally retarded or malingering individuals .The test can be done in patients under sedation and anaesthesia .
- To classify the type of deafness (i.e. sensory or neural)
- The site of lesion can be determined in Retro cochlear pathologies (eg: Acoustic neuroma)
- To distinguish between lesions of central auditory apparatus and peripheral organs
- Assessment of the maturity of the central nervous system more so in new born
- To assess the prognosis in comatosed patients,
- Diagnosing brain death etc.

Middle latency response (MLR)

Auditory evoked potentials recorded within 10-50 ms are called MLR. It is due to the activation of subcortical structures like Thalamus and primary auditory cortex.

Long latency response (LLR)

This response is generated from multiple cortical generator sources (Neshige et al1992) with latencies greater than 50 ms distributed entirely over the scalp.

Neurophysiology of brainstem auditory evoked response audiometry

The sound waves entering the ear impinges and displaces the tympanic membrane and transmitted to the ossicles of the inner ear and the oval window. These waves produce vibrations in perilymph of the scala vestibuli and tympani which in turn vibrates the potassium rich endolymph in the ductus cochlearis .As a result the basilar membrane, spiral organ and tectorial membrane unedrgo displacement by the sound vibrations. The hair cells situated in the spiral organ by their motile stereocilia moves by the vibration of sound waves and generates auditory receptor potentials . The receptor potentials get summated to trigger action potentials in the dendrites of afferent nerve fibres of cochlear nerve facilitated by the release of neurotransmitters.The apical portion of cochlea is activated by low frequency sounds and the basal portion by high frequency sounds. The click stimulus in BERA are high frequency tones that stimulates the basal portion of cochlea.

The cochlear nerve neurons in the spiral ganglia are bipolar neurons. Their dendrites are located in the hair cells and axons reach the cochlear nucleus.

Cochlear nucleus :

1. Anterior ventral cochlear nucleus (AVCN)

2. Posterior ventral cochlear nucleus (PCVN)

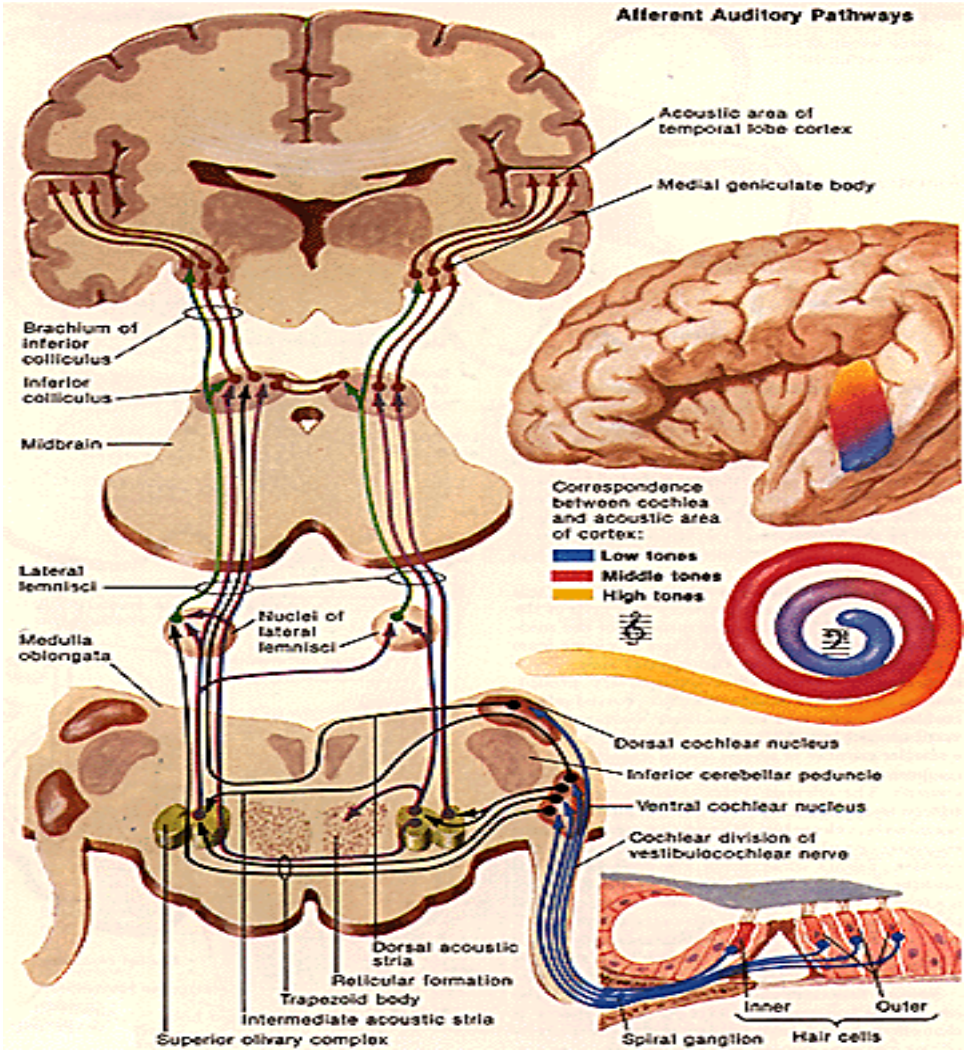
3. Dorsal cochlear nucleus (DCN)

The output from the cochlear nucleus is through the above mentioned components The outputs from AVCN via the ventral acoustic striae forms the Tapezoid body and terminates in the Superior olivary nucleus and Inferior colliculus. These discharge at short latency to auditory stimuli .

The output from PVCN through the ventral and middle acoustic striae and the dorsal cochlear nucleus through the dorsal striae terminates in the Superior olivary nucleus and contralateral Inferior nucleus. These have long latency discharge and thus differs from AVCN. The superior olivary nuclear complex comprises of medial and lateral portions at the base of pons. The medial part receives excitatory inputs from ipsilateral and contralateral AVCN. The lateral part from ipsilateral AVCN and PVCN as well as inhibitory impulses from contralateral AVCN and PVCN (via) trapezoid body. The impulses then reach the ipsilateral and contralateral Lateral lemniscus and Inferior colliculi. Hence this remains as the first site to respond to binaural stimulation. The impulse from the Inferior colliculi reach the Medial geniculate body and forms the Acoustic radiation of internal capsule and synapse in the Heschl gyrus of the Primary auditory cortex (Superior temporal gyrus and upper bank of Sylvian fissure including the frontal and parietal opercula), the deeper mesial portion which is activated by the high frequency tones like clicks used in BERA. The orderly arrangement of the neurons in the auditory pathway is responsible for the summation of synaptic potentials to produce high amplitude electric fields.

The auditory impulses travel through this pathway and generates an electric activity and it is recorded by placing surface electrodes on the scalp. This electrical activity is represented as waveforms with discrete peaks in the BERA readings. By the various parameters discussed above the study of the characters of the wave patterns and the structural and functional integrity of the auditory pathway is evaluated.

Figure 6: Auditory pathway



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Normal Waveforms of BERA

The recordings of BERA comprises of 5 or more distinct waveforms (Jewett DL et al 1971). These waveforms are analysed regarding their latency, amplitude, wave morphology which provides neurodiagnostic information on cochlear and retrocochlear auditory function.

TABLE 2: **Generators of BERA waveforms**

WAVEFORMS	GENERATORS
I	Eighth nerve(Cochlear nerve)
II	Cochlear nucleus
III	Superior Olivary nucleus
IV	Lateral Lemniscus
V	Inferior Colliculi

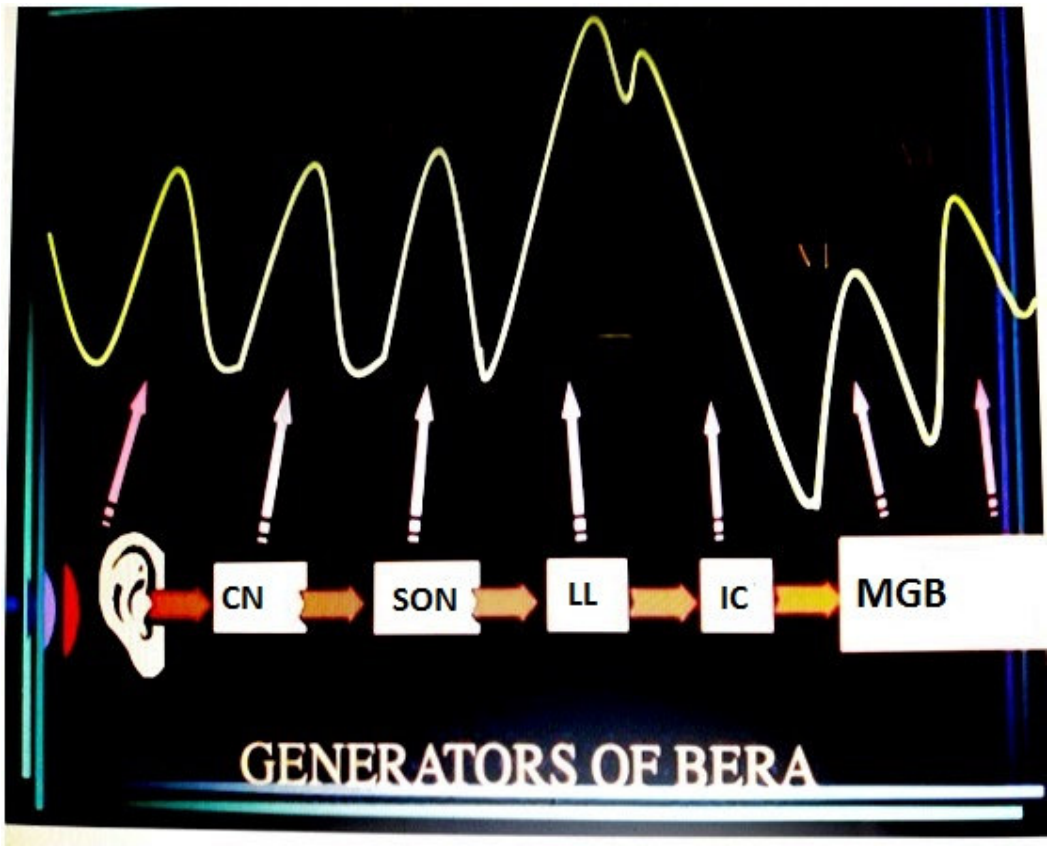
Clinical applications

It is claimed to be an important diagnostic tool in ENT diseases[70]

It is a powerful test in the diagnosis of Non organic hearing loss[71]

Neil Bhattacharyya et al [72]has shown in his studies that the latencies in BERA are longer in patients with tinnitus when compared with controls without tinnitus So ABR remains useful in monitoring and understanding tinnitus.

Photo No 1: Generators of BERA waveforms



BERA is used to evaluate prognosis in patients with coma. Patients with a Glasgow coma scale of 3 with abnormal ABR presented with a greater probability of dying than with a normal ABR.

Sköld et al in his study on 23 patients with bipolar disorder type 1, 20 patients with schizophrenia and 20 controls suggested that the amplitudes of wave 3 & 7 were higher in patients with bipolar disorder and it can be used as a Bipolar disorder biomarker. BPI may be associated with Thalamocortical circuitry abnormalities.

Cherian b1 etal [73]in his study has explained that BERA is mandatory in patients with Acute bacterial meningitis as SNHL is very common in these patients and it warrants for early intervention.**Shahai et el** [74]explains that BERA is the tool for identifying the hearing threshold .It is advantageous for infants, malingerers, eigth nerve tumors.

Mahillon v et al in his study on unilateral hearing loss due to tumors explained that 1 MRI is equivalent to 2 BERA. Although it is highly reliable technology, MRI is considered superior.

Raut vv et al[75]has explained that SNHL of cochlear type is more common. Sensory hearing loss involving hair cells is characterized by wave I falling outside the normal latency-intensity function. Wave V latency is normal at higher intensities, and prolonged when the intensity is decreased, The interwave latencies are either normal or shortened. . as described by **Amy et** al.

Oto acoustic emissions test

Otoacoustic emissions forms an essential part of the clinical examination of the auditory system.It is a specific screening test used to analyse the integrity of the cochlear function.It is an objective and non invasive test which does not require the co-operation of the subject. So it can be performed in anaesthetised & comatose patients also.OAE are spontaneous sounds emitted by the hair cells of the cochlea (OHC) in normal ears.It is used to assess the integrity of cochlea before significant functional hearing loss occurs[76]

Uses of OAE

- Screening test of hearing especially in neonates and infants with developmental disorders.
- Measure of hearing sensitivity.
- ,Differentiate cochlear and retrocochlear hearing loss.
- In feigned hearing loss .

They are low intensity sounds produced by the cochlear hair cells when they expand and contract in response to the sounds. They were hypothesized in 1940 and measured in 1970 after the invention of technical devices and use of microphones to record the low intensity responses.

Types of OAE

Transient Evoked Otoacoustic Emissions (TEOAE) – Sounds emitted in response to brief stimuli of very short duration in the form of clicks

Spontaneous Otoacoustic Emissions (SOAE) – Sounds emitted from the normal hair cells

Distortion Product Otoacoustic Emissions (DPOAE) – Sounds emitted in response to 2 simultaneous tones of different frequencies

Sustained frequency OAE –Sounds emitted in response to stimuli of continuous tones

Recording of sounds generated by the motile elements in the cochlear hair cells was first reported **by Kemp in 1978**.When the inner ear is stimulated by the sounds, the hair cells vibrate and produces an inaudible sound .It is echoed to the middle ear and measured by the probe placed in the external auditory canal.When the hearing loss is more than 25-30 decibels OAE'S are not generated.

Neurophysiology

The lateral and medial Olivocochlear bundle from Superior olive leaves the brainstem and joins the Inferior vestibular nerve which in turn joins the cochlear nerve to form Oort's vestibulocochlear nerve. Axons from lateral olivocochlear bundle synapse with afferent neurons from cochlea.The axons from medial olivocochlear bundle synapse with base of the cell bodies of outer hair cells . The medial efferents are responsible for the amplifying effects of outer hair cells.

Bolay et al 2006 explains that these amplifying effects are mediated by Acetylcholine.It is not suppressed by the inhibitory areas due to damage or during surgery **(Gunger et al 2014)**

Prerequisites

- Unobstructed outer ear canal
- Absence of middle ear pathology
- Functional cochlear hair cells
- Hearing threshold of 35 db or better

The devices are screeners and checks 5-10 frequencies with a preset limit of signal-noise ratio.The broad area of cochlea responds for a frequency range 1000-4000hz

Results

PASS –for all frequencies indicates normal hair cell function

REFER –abnormal hair cell function with increased risk of hearing impairment in future & recommended diagnostic OAE and managed accordingly.[77]

The rule of thumb is that OAE's can be detected with hearing of 35 db or better. OAE's are decreased or absent with hair cell damage.The procedure is quick and not bothersome.

Trosman et al in his study claims that OAE testing is cost effective than Audiogram. It is very useful as an objective test in occupational hearing loss like musicians and in patients with Neuropathy.

Reauis et al explains that OAE can be used to measure the cochleotoxicity of the anticancerous drug Cisplatin and also in patients with increased intracranial pressure.

Bolay et al has shown that DPOAE in migraine remains a clinical test for Phonophobia. OAE's are detected by devices with microphone and can identify

an individual without a password.This property of OAE's has biometric importance was discovered by **Stephen Beeby in 2009[78]OAE's in RA.**

The hair cells are affected in the active phase of rheumatoid arthritis as explained earlier .Early assault to the hair cells are identified by screening for OAE[79]. Further assessment with diagnostic OAE may show decreased amplitude and reproducibility of OAE's .The reproducibility of OAE in normal ears is >90% which is decreased to 70% t0 50% during which OAE's are absent on screening for the same. OAE screening is a sensitve & specific tool in the evaluation of subclinical hair cell damage in early active rheumatoid arthritis.

Treatment

Hearing loss of sensory type is more common than neural type. It should be treated immediately as neural part needs input from sensory part to grow and stay healthy.

- Early diagnosis of RA and ensuring proper compliance to treatment to minimize the degree of extra – articular manifestations and thus hearing loss
- Amplification using hearing aids
- Supportive measures like lip reading, enhanced communication etc.
- Antioxidants- vitamins A,C,E and Magnesium
- Epselen, a synthetic drug that mimics Glutathione peroxidase ,the inner ear enzyme[80]

- Direct Stimulation of cochlear nerve endings by cochlear implants

Cochlear implants are recommended for severe SNHL, according to the U.S Food and Drug administration . About 188,000 people in the world are treated with cochlear implants until the year April 2009.These devices cannot restore normal hearing, but they provide useful representation of environmental sounds. Studies are being carried out regarding hair cell regeneration by Stem cell and Gene therapy[81]

0AEs are used in early detection and monitoring of Noise-Induced Hearing Loss (NIHL) **by Giota Lalakhi Ph.D (Greece, 2003)**

Musiek et al put it succinctly: "Otoacoustic emissions must be used judiciously by the experienced clinician in conjunction with other clinical tools."

It is an important Test for the evaluation of cochlear function[82]

Active disease and ACPA

Yoshizaki et al 1998 has stated that inflammatory cytokines released during active disease induces B cell differentiation resulting in hypergammaglobulinemia and thus increases the levels of autoantibodies like RF and ACPA's in serum.He has also explained that the clinical manifestations like fatigue ,loss of weight and appetite,fever etc. encountered in active RA is due to the increased levels of these inflammatory cytokines in serum.They also increases the production of CRP from hepatocytes whose levels are increased in active RA.

Ishibaski et al. 1993:Andrews 2004 explains that increase in the levels of IL6 increase hepcidin production and is responsible for the anemia very common in active RA

The proinflammatory cytokines like IL 6 increased in active RA damages the hair cells by oxidative process.It also increases the levels of ACPA's which is increased in active RA.It also accelerates cochlear degeneration.

Hearing defects in active disease

Rheumatoid arthritis causes erosive arthropathy associated with systemic manifestations. It affects ears and results in immune-mediated mainly SNHL, which occur in 25.2% to 60% defined by **Magaro et al.**

Takasu et al. has described that the hair cells are damaged by the oxidative process in RA by the deposition of immune complexes and inflammatory cytokines like IL-6 and MMP-3 which are released during active disease and results in SNHL.

Raut VV et al in his study on 35 age and sex matched RA patients and controls found statistically significant p value <0.05 in 60% of RA patients and showed that SNHL is more common in active RA patients.

Kate Batman et al explained in his study that SNHL is seen in 42.7% of the RA patients due to the poor functioning of the hair cells in the cochlea.

Magaro M etal showed that abnormal audiometry with normal ABR findings is suggestive of cochlear involvement while abnormal audiometry and ABR is suggestive of retrocochlear involvement.

Kastanioudakis et al in his study has explained that inner ear involvement in RA is characterised by mild symmetric, bilateral sensorineural hearing loss of cochlear type in 35.5 per cent of patients.

Kemp DT has explained that OAE's play important and distinctive role in screening and diagnosis of hearing loss due to hair cell dysfunction at an earlier stage to prevent functional disability.

Role of OAE in cochlear dysfunction in RA

Amir Emamifar et al has explained that OAE's are sounds produced by healthy cochlear systems from the hair cells, So cochlear dysfunction results in decrease or disappearance of TEOAEs. The decrease in OAE's are being reported in RA patients.

Rheumatoid disease in its active stage characterised by DAS28 score >5.1 ,increased APR,RF & ACPA positivity(biomarker of active disease) affects cochlear hair cells resulting in abnormalities of cochlear hair cells ascertained by BERA and OAE . Prolonged latency of wave 1 indicates hair cell dysfunction and abnormalities on screening for OAE identifies hair cell dysfunction.

AIM AND

OBJECTIVES

The main aim of this study is to evaluate the role of Otoacoustic emissions and Brainstem Evoked Response Audiometry and serum levels of ACPA in patients with active RA in comparison with age and sex matched controls

The objectives of this study were

- To determine the functional integrity of the hair cells of the cochlea by Otoacoustic Emission test .
- To determine the functional integrity of auditory pathway & site of lesion in patients with active RA by recording Brainstem Auditory Evoked Potential.
- To assess serum ACPA levels as a biomarker of active disease in these patients.
- To find the correlation between serum ACPA levels and absolute latencies of wave I of both ears recorded by BERA in patients with active RA.

MATERIALS AND METHODS

The study was conducted during the year 2015-2016 at the Institute of Physiology and Experimental Medicine, Madras Medical College after obtaining approval from the Institutional Ethics Committee, Madras Medical College, Chennai.

Patient selection

30 Patients (cases) of both sexes in the age group between 25-45 years diagnosed as active RA according to DAS 28 score were included in the study. They were selected from the out patient department of Institute of Rheumatology , Rajiv Gandhi Government General Hospital, Chennai - 3. 30 age and sex matched apparently healthy people were selected as controls.

Inclusion criteria

- Thirty patients , both men and women in the age group of 25-45 years diagnosed as active RA were included in the study after confirming the normal hearing ability of these persons using Pure tone audiogram.

Exclusion criteria

- Children and pregnant women
- Patients with Diabetes and Hypertension
- Subjects with congenital hearing loss and Sensorineural deafness
- Tumours like Acoustic neuroma and Meningioma
- Acute brainstem stroke

- Demyelinating diseases like Multiple sclerosis
- Subjects with head injury and infections like Meningitis and Encephalitis
- Neurodegenerative diseases like Dementia
- Subjects with Neoplastic, Hepatic, Respiratory and Cardiovascular disorder or other concurrent medical illness

Control group

Thirty age and sex matched controls were selected from technicians, staffs and attenders of the patients. Informed verbal and written consent was obtained from the participants after explaining the procedure.

STUDY DESIGN: Cross sectional Case control study

PLACE OF STUDY: Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai.

All the subjects included in the study had no hearing deficit as reported after thorough ENT examination which includes Pure tone audiometry.

Specific ENT examination

Both the control and study group individuals were subjected for ENT examination which comprises of External ear examination, Tuning fork tests,Otoscopic examination of Tympanic membrane, Presence of any obstruction by wax and examination of throat and nose before proceeding for Pure tone audiometry.

Pure tone audiometry

Both the controls and cases were subjected for Pure tone audiometry at the Institute of Audiology & Speech therapy, Madras Medical College. This is done to determine the hearing threshold of the subjects , to ascertain external or middle ear pathology and to assess the integrity of conducting pathway.

Principle of Pure tone audiometry

Hearing acuity is measured by Pure tone Audiometer which delivers tones of variable frequencies and intensities to the ear by means of an earphone. The frequencies to be tested are 125,250,500,1000,2000,4000 and 8000 Hz. Intensities can be increased or decreased for each frequency which varies from 10 dB to 120dB.Audiometers used nowadays are calibrated to the international (ISO) standard level to ensure accurate results.

The test is started with an initial frequency of 1000Hz and the patient's air and bone conduction are measured . It is followed by a series of tone pips or short signals presented above their suspected threshold. Tthe patient is asked to signal every time whenever he hears a sound and the intensity is reduced in steps of 10 dB until no sound is heard. Then the intensity is increased by 5 dB until half of the tonepips are heard. In this manner the patient's threshold for a particular frequency can be determined and thresholds for the remaining frequencies are also measured.Bone conduction is measured by placing a receiver onto the mastoid bone. The emitted sound is transmitted to the cochlea through the skull bones bypassing the external and middle ear

and which gives a measure of inner ear function. The results are interpreted as Audiograms. The better ear is masked when the threshold difference between better & diseased ear is 40 db or above to avoid transmission through the skull bones.

Brainstem Auditory Evoked Potential

The patients with active RA and controls were subjected to assessment of hearing by Brainstem Evoked Response Audiometry(BERA).

Apparatus for BERA

The apparatus for eliciting Brainstem evoked response audiometry are set as per the "Recommended standards for the clinical practice of evoked potentials" which is introduced in Guideline 9A: Guidelines on evoked potential, by American society of Clinical Neurophysiology.

Pulse generator

The stimulus in the form of clicks or tone pips is conducted in to the ear through the transducer placed in the headphone or into the ear phone.

Recording electrodes

There are three electrodes, an active electrode placed on the ipsilateral mastoid process, a reference electrode placed on the vertex and a ground

electrode placed in front of the reference electrode as per the International 10-20 electrode placement system. There are two types of electrodes namely needle and surface electrodes for recording BERA .The surface electrodes are preferred as patient does not experience pain with this procedure and the chances of infection are reduced. The patient should be instructed to have a shampoo bath which makes the application of electrodes easier. 1 cm disc electrodes with conducing jelly or paste are placed at their respective sites. The electrical impedance should be kept below 5 kilo ohms for better recording .

Filters restrict selectively the frequency domain of the signal. The frequency range of a signal transmitted through the filter is called as frequency band pass.. The signal rejected in the frequency range is called stop band. Between the frequency and stop band is the transition band ,the characteristic of the filter. Neurophysiological signals needs to be filtered which is essential for noise elimination and optimizing the recording and to bring out the typical characteristics of the wave forms . Low frequency filters eliminate the low frequency components that changes slowly and allow the higher frequencies to pass through and hence they are called as high pass filters. High frequency filters remove the rapidly changing high frequency components and permit the low frequency to pass through.So they are also called as low pass filters

Amplifier

The small biological signals produced requires , a variable degree of amplification (upto 500000 times)to match the range of Analog to digital converter. The electrode impedance comprises of intrinsic impedance and the

electrode impedance of electrode-skin interface respectively Measurement of any electrical activity including action potential generated in CNS, nerve or muscle flow through the electrode to the amplifier and then return to the patient through the ground electrode. There is a drop in the amplitude of the action potential due to this electrical impedance. This attenuated action potential is amplified by the amplifiers. The impedance of the amplifiers remains greater than electrode impedance to reduce this attenuation A100:1 ratio of electrode to amplifier impedance is maintained across the range of frequencies in the waveform under study. This minimizes the distortion of waveforms and improves noise rejection. The impedance of the active, reference and ground electrode should be minimized to prevent the conversion of noise signal into neurophysiological one..

Signal averager is used to differentiate the spontaneous electrical activity in the brain like EEG and the electrical activity in response to the sound stimuli. The magnitude of the electrical activity by a sound stimulus is 1/100 of that of spontaneous electrical activity of the brain. Evoked electrical activity is time specific and occurs at specific point of time after the application of sound stimuli but the spontaneous electrical activity is not time specific there is adding up of responses in evoked potentials but not so in background potentials and so they cancel each other .This technique provides uncontaminated measure of the sound evoked electrical activity without amplification of the responses.

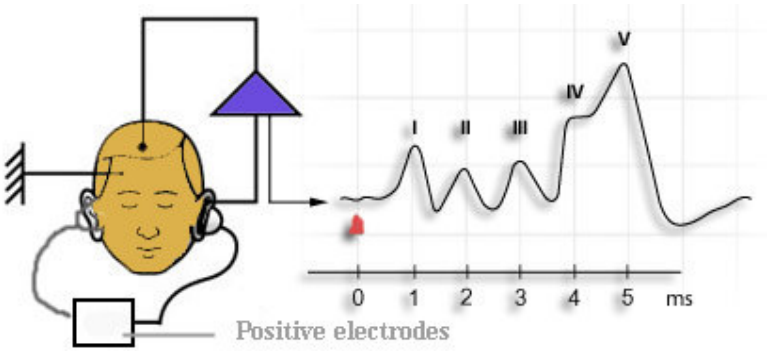
Electrical safety : Grounding and chassis leakage current of all the instruments to be checked periodically that helps in the prevention of shock during power fluctuations.

Procedure of recording BERA

Recording to be done in a quiet and semi darkened room.The patient is instructed to have a Shampoo bath The skin is cleaned with spirit and cotton and active,reference & ground electrodes are placed in their respective places.Resistance maintained below 5 kilo ohms. Monoaural auditory stimulus consisting of rarefaction clicks of 100μsec were delivered through electrically shielded ear phones at the rate of 11.1 clicks/sec. The contralateral ear is masked by pure white noise of 40dB which prevents false BAEP response. A band pass of 150-3000 Hz was used to filter out undesirable frequencies in the surroundings. Responses to 2000 clicks presentations were averaged . The result is obtained as a graph plotted with amplitude (in μvolts) on the ordinate and time (in milliseconds from the onset of stimulus) on the abcissa.with 5-7 waves or peaks within 8-10 milliseconds with Roman numerals .Analysis of these waveforms were done with regard to latency, amplitude and morphology that provides neurodiagnostic information on cochlear and retro cochlear function.

Photo No.2: Recording of Brainstem auditory evoked potential in a subject.

Figure 7: Recording of BAEP waveforms



Wave I [83]represents the potentials generated in the peripheral portion of 8th cranial nerve. This prominent initial up going peak in the ipsilateral ear appears 1.5 ms after the application of stimulus .Attenuated or absent in the contralateral ear recording channel.Absent or decreased in patients with peripheral hearing impairment

Wave II is a poorly defined wave as a small peak appears 2.8 ms after the onset of the stimulus absent in lesions of the cochlear nucleus.

Wave III is a prominent peak followed by a prominent trough appearing 3.9 ms after the click stimulus.Absent in superior olivary nucleus lesion

Wave IV appears as a distinct and identifiable wave in 50-60% of the individuals seen as a peak in the upgoing slope of after 5.1ms wave V.absent in lateral lemniscus lesion

Wave V is the most prominent peak appearing 5.5 msec after the stimulus generated in the lateral portion of lateral lemnisci or inferior colliculi

or in both. This wave component is analysed most often in clinical applications of ABR. In unilateral mesencephalic lesions, this wave is attenuated or even absent

Wave VI and VII -The origin of these waves are poorly defined and they are reasonably assumed to be generated from subcortical structures like MGB and auditory radiation with average latencies of 7.3 and 9.6 ms respectively. .

Interpretation of waveforms

The parameters taken into consideration for studying the waveforms of BAEPs are

Absolute latency : the time interval which is measured in milliseconds from the onset of stimulus to the peak of the wave.

Absolute amplitude : measured in microvolts from the peak of the wave to its trough.Amplitude of the waves is not as constant as latency and not reliable.

Inter peak latency (IPL) : The time interval between two different waves in the same ear is called inter peak latency which is otherwise called as inter wave latency. The IPLs commonly measured are

I-III IPL is represented by normal value of about 2.5 ms which reflects the conduction time between cochlea and the core of lower pons.

I-V IPL is an index of the conduction time between the cochlea and proximal part of cochlear nerve and the midbrain through pons, the normal value of which is 4.5msec.

III-V IPL The isolated prolongation of this IPL is not significant which measures the conduction from caudal pons to midbrain.

Amplitude ratio of wave V/I : As wave1 & 5 is generated outside and inside CNS respectively ,this ratio is used to compare the relationship of the expected signal amplitude. Normal ratio is 50-100%. > 300% denotes peripheral hearing impairment & < 50% indicates central hearing loss.

Inter aural latency difference : The time interval between the two ears of the same wave which should not be more than 0.5msec on application of the suprathreshold stimulus to both the ears. Factors that tend to affect BAEP are

Technical factors :.

Stimulus rate :Number of clicks presented to the ear per secondwhich is 10-40 clicks /sec. When stimulus rate becomes high, the amplitude and absolute latency of the waves behave in a opposite manner

Intensity of the sound stimulus. :At higher intensities , wave I often decreases at a faster rate with prolonged I-V IPL.At decreasing intensities all the waves except I, III, and V tend to disappear. At lower intensities(10dBSL), only peak V persist.

Stimulus phase or polarity: When the diaphragm of the transducer of the machine moves initially outward towards the eardrum, the condensation phase & when it moves inward away from the eardrum,it is termed as rarefaction phase for better resolution of the waves.

Filter : lower frequency filter of 100 or 150 Hz & high frequency 3000 Hz for the reduction of artefacts

Nature of sound: It is the click sound produced by the transducer generated as a square wave pulse of 0.1msec duration each. The sound pressure wave generated can be displayed on an oscilloscope . The sound stimuli delivered at 50-60 db above the hearing threshold.

Binaural/monaural stimulation : Monaural stimulation is recommended in clinical studies but if the sound stimulus is presented to both ears simultaneously ,then the amplitude of the waves III, IV, V are increased but not wave I.

Nontechnical factors

Age :1-5 IPL are larger in adults than young children due to slower axonal conduction.

Temperature : The latencies (7% for 1 celsius) and IPL are prolonged with decrease in temperature

Hearing status : Audiometry and hearing tests to be performed

Drugs : BAEPs are resistant to the effect of drugs, but a slight prolongation of wave V latency with barbiturates or alcohol is attributed to the lowering of body temperature

Terminologies used in evoked potential study

Decibel (dB=1/10 Bel): It is defined as '20 log (P1/P2)', where P1 is the intensity of the sound to be measured and P2 is the intensity of the reference sound.

Sound pressure level (SPL): -It is the weakest sound heard by the most sensitive ear which is the standard physical reference for sound (20 micropascals or 0.0002 dynes per cm2).

Hearing level: Zero dBHL corresponds to the average hearing threshold of normal hearing young adults in an ideal listening environment.

Sensory level: This expresses the intensity of a sound as a function of the hearing threshold for an individual ear for any given subject. Parameters studied are the latencies of waves I, III, V and IPLs of I-III, I-V and were studied from the recording of BERA for comparison among RA patients and controls.

OTOACOUSTIC EMISSIONS (OAE)

OAE's are sound vibrations produced by the cochlea. It is a specific screening test of cochlear function which is frequency specific & sensitive.It gives information about the different parts of the cochlea at the same time and assessment of cochlear function before functional and significant hearing loss occurs. OAE's are more stable and shows little error.It represents the cochlear receptor mechanism.OAE screening is a non -invasive test presenting the sound in a normal way.A fraction of sound generated by the hair cells escape from the cochlea and cause secondary vibrations in the middle ear and eardrum

within 3-15 seconds .Reduction of ambient noise is mandatory to ensure good recording.Factors affecting OAE are,

Non technical factors

Ambient acoustic noise

Physiological noise like breathing produced by the patient

Technical factors

Proper application of ear probe

Presence of wax or debris in the ear canal

Middle ear function

Procedure

After a preliminary ENT examination the device is inserted into the external auditory meatus of the subject and click stimulus given with PORTABLE LABAT machine & screened for TEOAE .The results are displayed as PASS or REFER.

Results

PASS is suggestive of normal hearing and needs no further audiological evaluation.

REFER indicates abnormalities in OAE. It indicates future risk of hearing impairment and recommended further audiological assessment .These

Photo No 3: Recording of OAE in a subject

patients are subjected to diagnostic OAE to identify the severity of hair cell damage with parameters like amplitude & reproducibility.

Anticyclic Citrullinated Protein Antibodies (ACPA's)

Estimation of Serum ACPA's is done by ELISA. Under strict aseptic precautions, blood samples were collected from the antecubital vein by venepuncture . Estimation of serum ACPA was carried outat the Institute of Rheumatology, RGGGH , Chennai.

. EUROIMMUN is a semiquantitative in vitro Enzyme Linked Immunosorbent Assay (ELISA) kit for the measurement of autoantibodies of IgG class against cyclic citrullinated peptides. The kit contains microtiter strips with individual break off reagent wells coated with synthetic CCP.

Principle

- Incubation of diluted samples of the patient in the wells given in the kit.
- Binding of IgG antibodies to the antigenic site is considered positive
- Incubation with enzyme conjugate to detect bound antibodies capable of creating a colour reaction

Storage : +2 to +8 degree Celsius

Stability : Unopened kits are stable until the expiry date

Sample: Human serum with citrate

Samples of 1:100 dilution is prepared .Coated wells,,Calibrated controls,,Enzyme conjugate, Substrate solution & Stop solution are ready for use.

Procedure

100µl of calibrated patient samples or controls are transferred into the microplate wells

Empty the wells after wash and leave the wash buffer for 30-60 seconds and empty the wells again

100µl of enzyme conjugate added into the wells and incubated for 30 mts

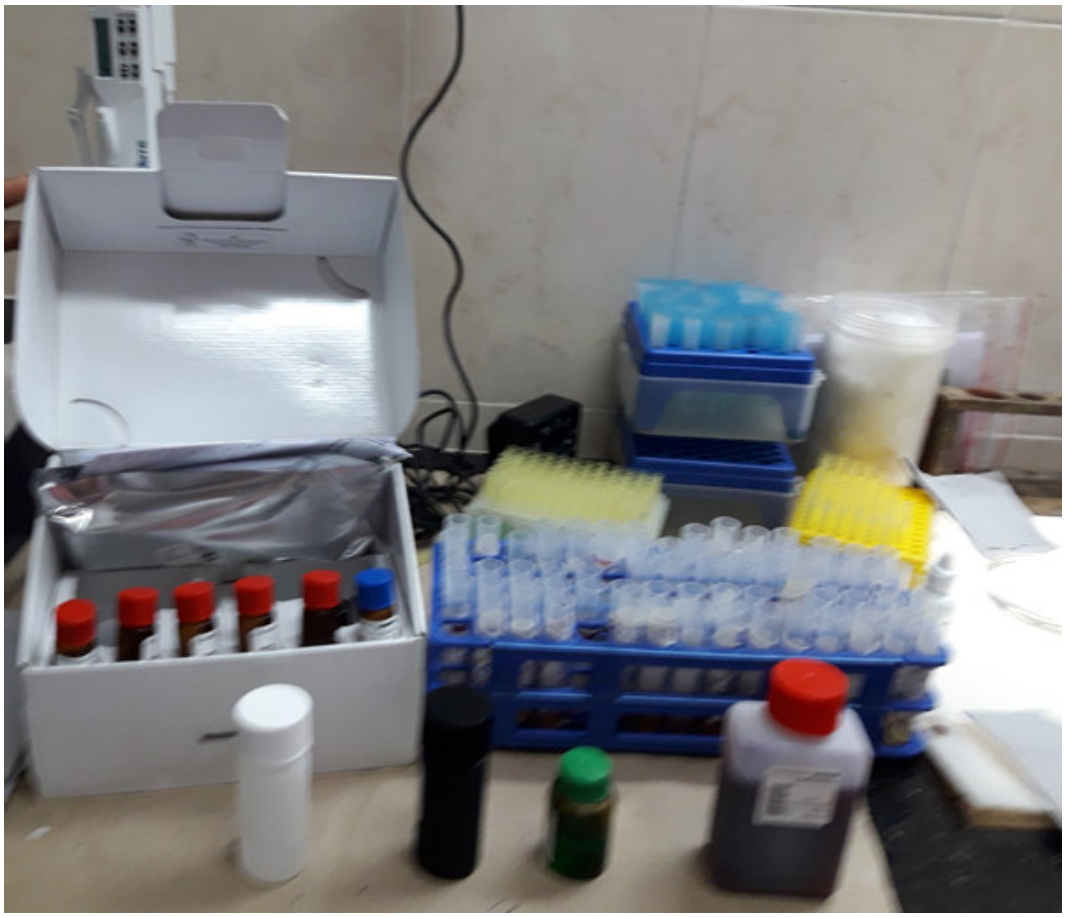
Empty & Wash . Add 100µl enzyme conjugate added to the wells and incubated for 30 mts. Empty and wash

Add 100µl of substrate solution into each microplate wells and incubate for 30mts which gives a blue colour

100µl of stop solution added to the wells which gives a yellow colour

Photometric colour measurement at a wave length of 450nm with reference wavelength within 30mts of adding the stop solution

Photo No 4: EUROIMMUN ELISA KIT



RESULTS

Read as Relative Units (RU/ML)

<5RU/ML negative

> 5RU/ML positive with increasing titres

Statistical analysis

Statistical analysis was done using the software SPSS version 21.

1. Student 't' test was carried out to compare the means of variables between RA patients and normal subjects.

2. Pearson's coefficient was done to find the correlation between serum ACPA levels and absolute latencies of wave I of both ears recorded by BERA in active RA patients.

RESULTS

Active RA patients and controls recruited for the present study had no evidence of hearing deficit.

Characteristics of study and control subjects

The study population comprises of 30 active RA patients (5 males and 25 females) in the age group 25-45 years with normal hearing status clinically. The control subjects were 30 in number with 5 males and 25 females in the age ranging from 25-45 years. The mean age was calculated to be 38.30±4.41 years in the control group and the mean age of active RA patients in cases was found to be 38.47±5.06 years.The disease duration of less than one year is taken for the study.

Brainstem auditory evoked potential & OAE parameters

Variables of BERA , OAE & ACPA between normal and active RA patients are given in the Tables 3- 19 and Graphs1- 15

TABLE 3: Comparison of mean values of absolute latencies of wave I between active RA patients and controls in the right ear

WAVE 1 RIGHT EAR	MEDIAN	SD	p VALUE
CASES	1.84	0.19	0.0001***
CONTROLS	1.607	0.07	

p value < 0.05 – significant

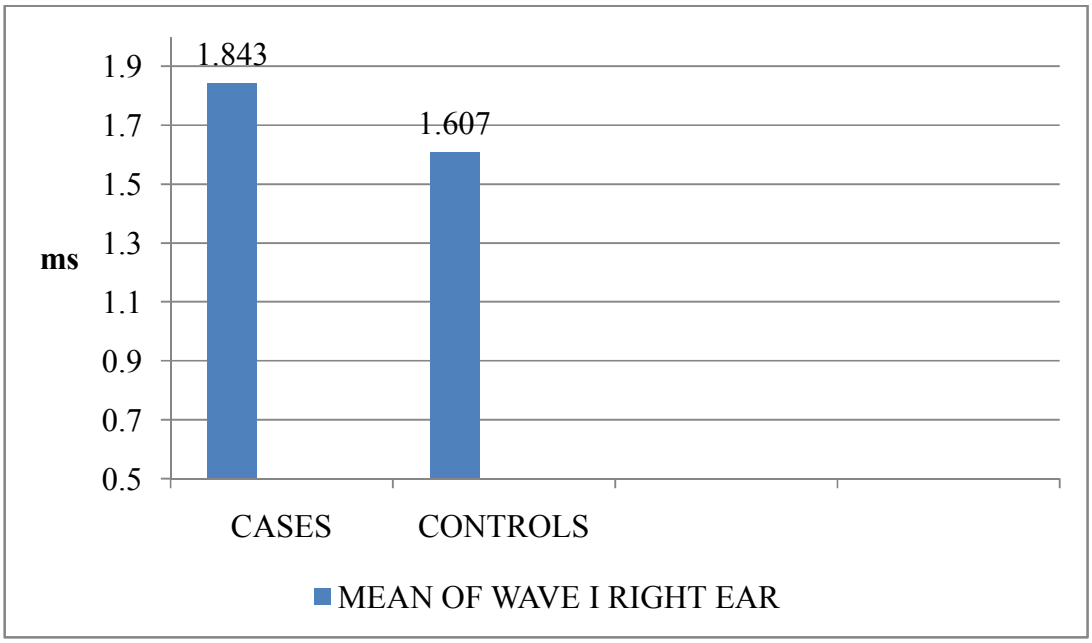
The mean values of absolute latencies of wave 1 of right ear is significantly higher in active RA patients when compared to controls

TABLE 4 : Comparison of mean values of absolute latencies of wave II between active RA patients and controls in the right ear

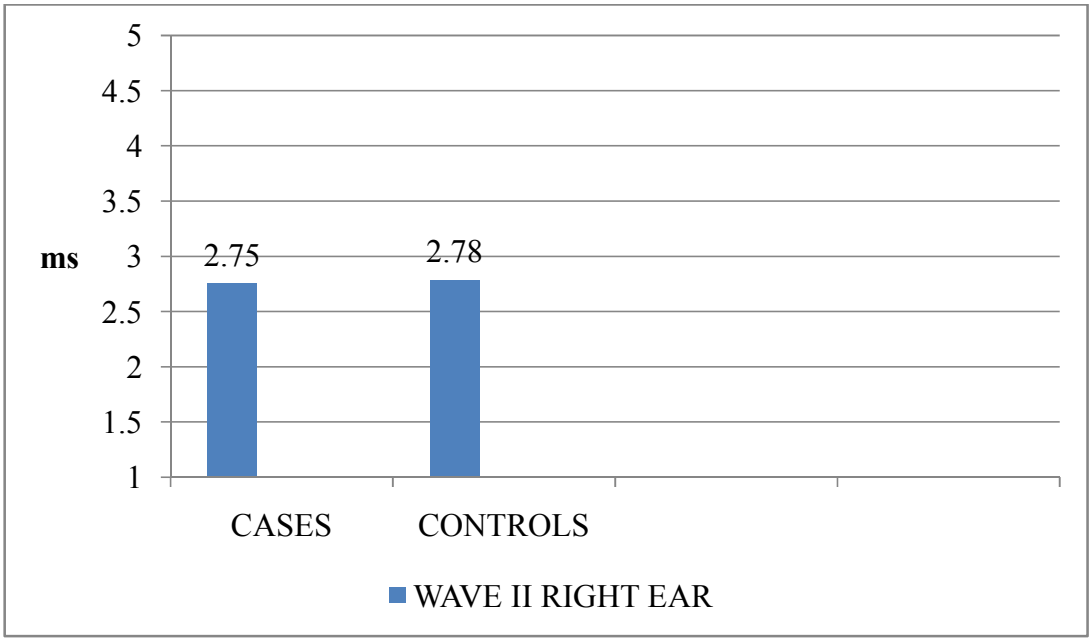
WAVE II RIGHT EAR	MEAN	SD	pVALUE
CASES	2.75	0.09	0.24
CONTROLS	2.78	0.08	

p value >0.05, not significant

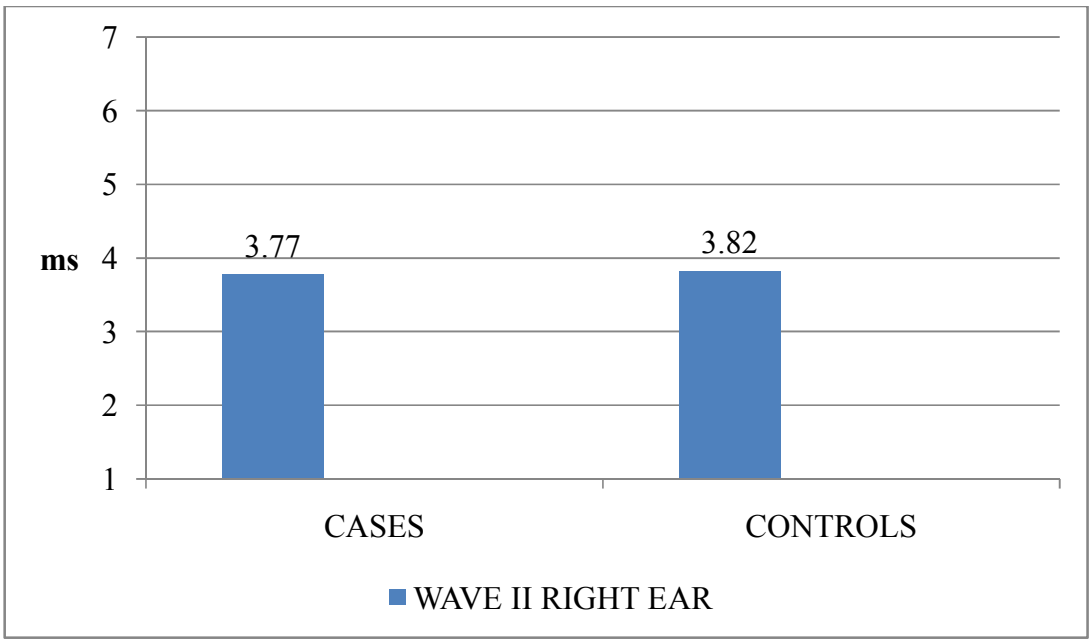
GRAPH I: Comparison of mean values of absolute latencies of wave I between active RA patients and controls in the right ear



GRAPH 2 : Comparison of mean values of absolute latencies of wave II between active RA patients and controls in the right ear



GRAPH 3 : Comparison of mean values of absolute latencies of wave III between active RA patients and controls in the right ear



GRAPH 4 : Comparison of mean values of absolute latencies of wave V between active RA patients and controls in the right ear

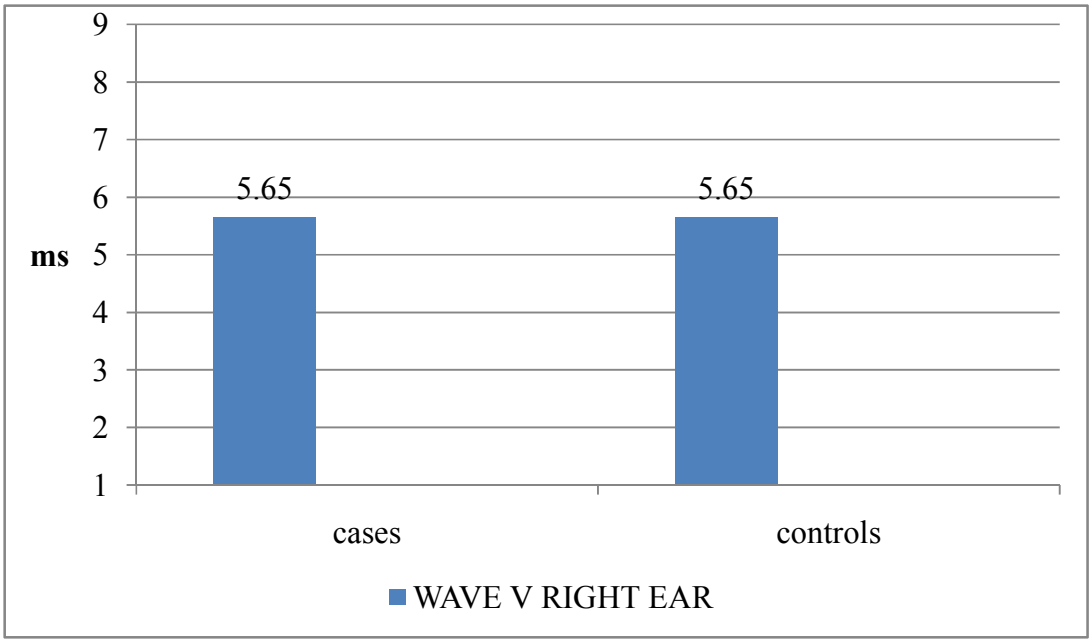


TABLE 5: Comparison of mean values of absolute latencies of wave III between active RA patients and controls in the right ear

WAVE III RIGHT EAR	MEAN	SD	pVALUE
CASES	3.77	0.18	0.28
CONTROLS	3.821	0.15	

p value >0.05 , not significant

TABLE 6: Comparison of mean values of latencies of wave V between active RA patients and controls in the right ear

WAVE V RIGHT EAR	MEDIAN	SD	pVALUE
CASES	5.65	0.12	0.99
CONTROLS	5.65	0.14	

p value >0.05 ,not significant

TABLE 7: Comparison of mean values of I-III IPL between active RA patients and controls in the right ear

IPL I-III RIGHT EAR	MEDIAN	SD	pVALUE
CASES	2.37	0.19	0.41
CONTROLS	2.42	0.20	

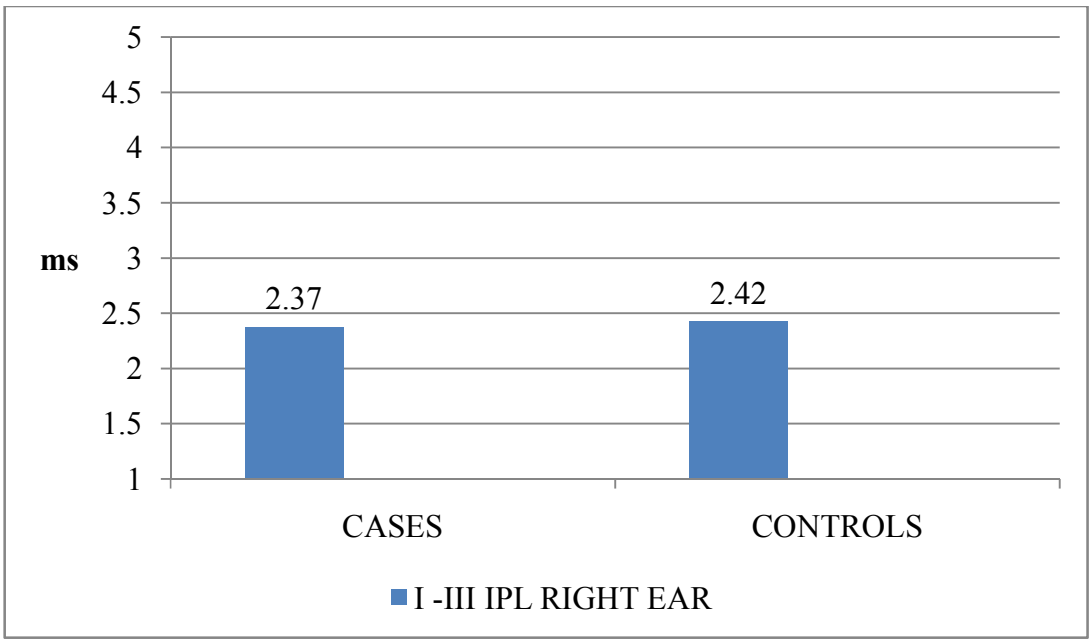
p value >0.05,not significant

TABLE 8: Comparison of mean values of I-V IPL between active RA patients and controls in the right ear

I-V IPL RIGHT EAR	MEDIAN	SD	pVALUE
CASES	4.59	4.52	0.54
CONTROLS	4.52	0.40	

p value >0.05,not significant

GRAPH 5 : Comparison of mean values of I-III IPL between active RA patients and controls in the right ear



GRAPH 6 : Comparison of mean values of I-V IPL between active RA patients and controls in the right ear

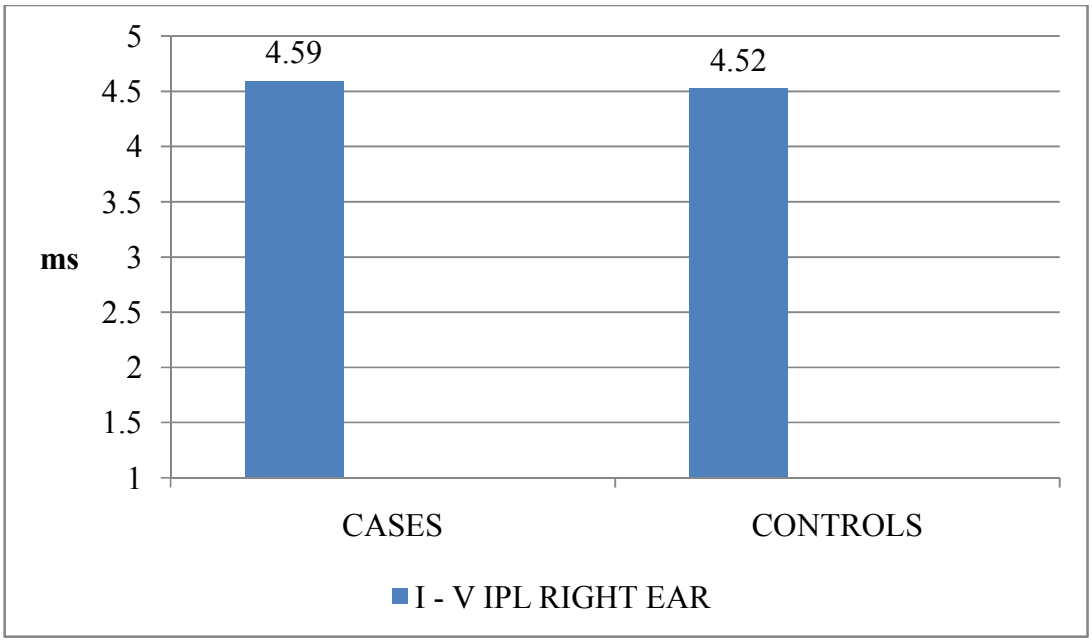


TABLE 9: Comparison of mean values of absolute latencies of wave I between active RA patients and controls in the left ear

WAVE 1 LT LEFT EAR	MEDIAN	SD	pVALUE
CASES	1.857	0.2	0.0001***
CONTROLS	1.628	0.08	

p value <0.05,significant

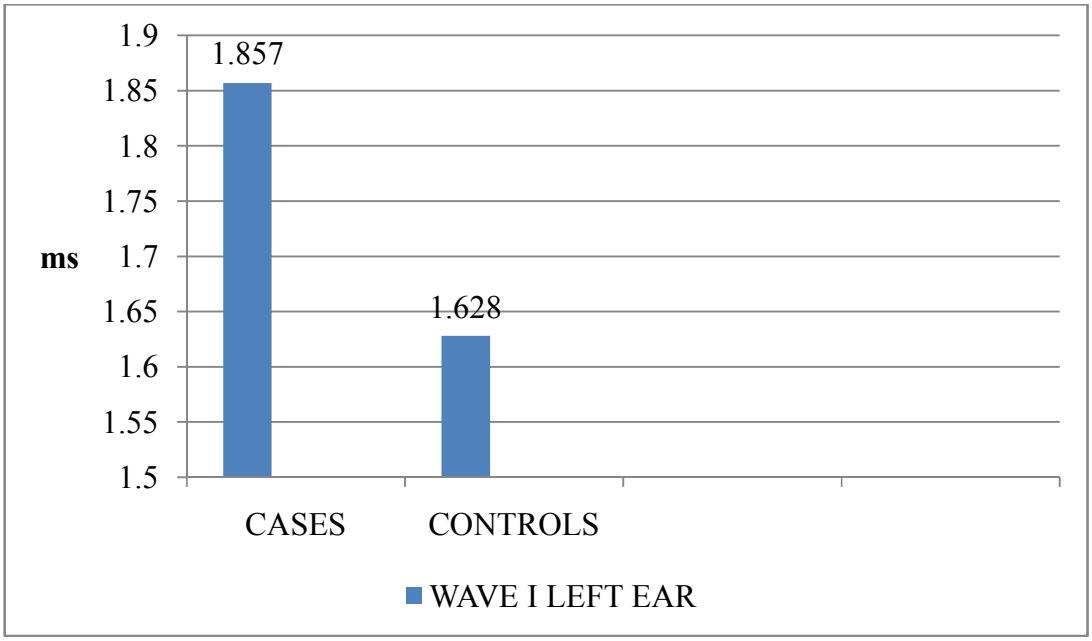
The mean value of absolute latencies of wave I of left ear is higher in active RA patients when compared to controls

TABLE 10: Comparison of mean values of absolute latencies of wave II between active RA patients and controls in the left ear

WAVE II LEFT EAR	MEDIAN	SD	pVALUE
CASES	2.804	0.04	0.9
CONTROLS	2.805	0.06	

p value >0.05,not significant

GRAPH 7 : Comparison of mean values ofabsolute latencies of wave I between active RA patients and controls in the left ear



GRAPH 8: Comparison of mean values of absolute latencies of wave II between active RA patients and controls in the left ear

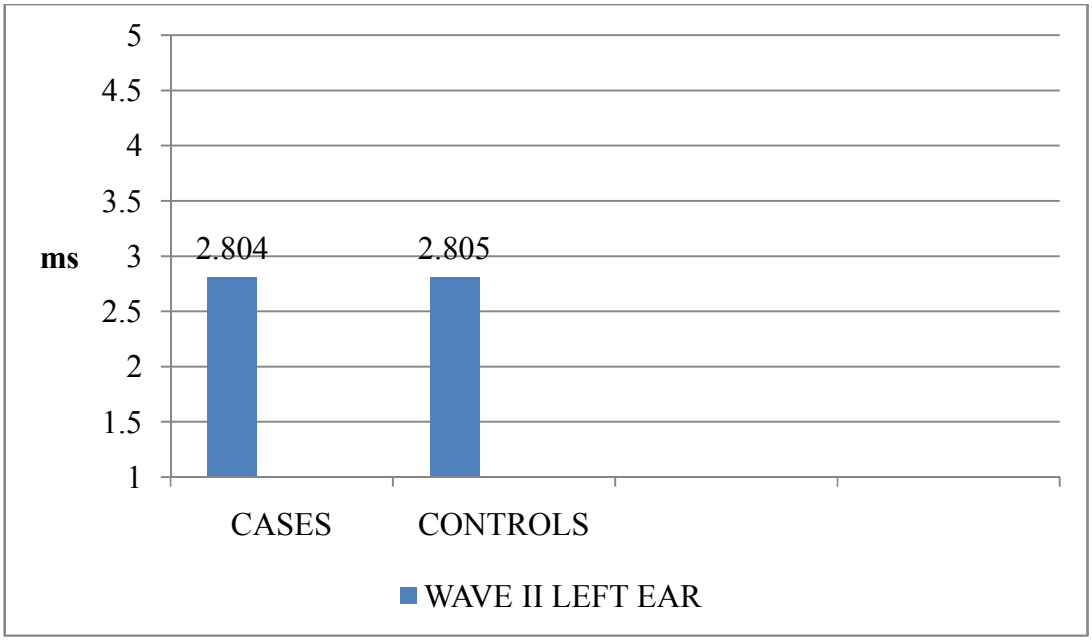


TABLE 11: Comparison of mean values of absolute latencies of wave III between active RA patients and controls in the left ear

WAVE III LEFT EAR	MEDIAN	SD	pVALUE
CASES	3.70	0.22	0.7
CONTROLS	3.72	0.22	

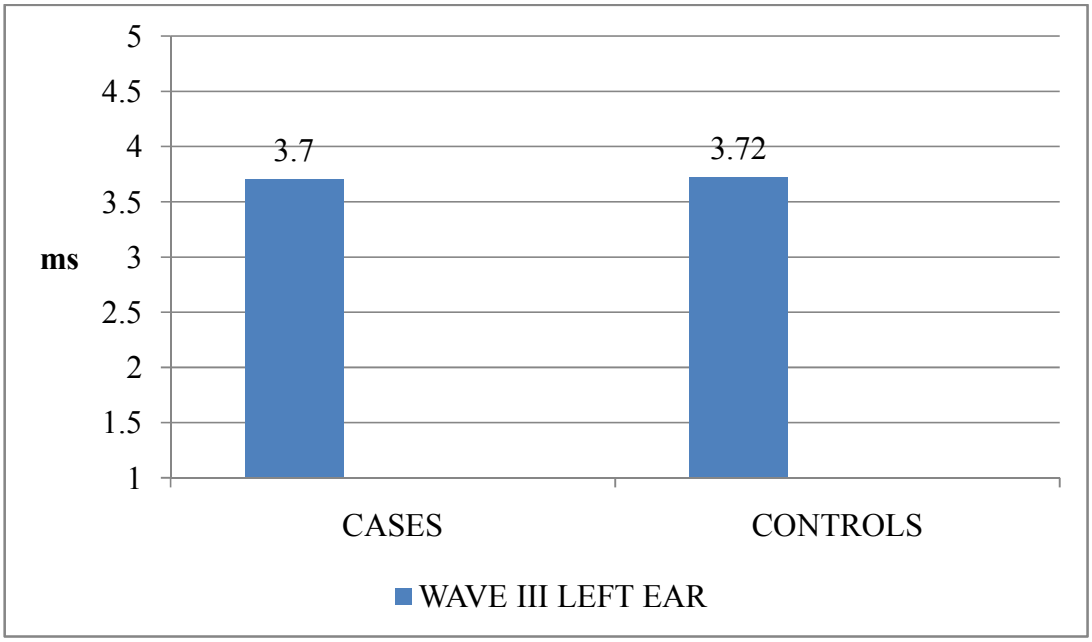
p value >0.05,not significant

TABLE 12: Comparison of mean values of absolute latencies of wave V between active RA patients and controls in the left ear

WAVE V LEFT EAR	MEDIAN	SD	pVALUE
CASES	5.57	0.20	0.5
CONTROLS	5.60	0.21	

p value >0.05,not significant

GRAPH 9: Comparison of mean values of absolute latencies of wave III between active RA patients and controls in the left ear



GRAPH 10 : Comparison of mean values of absolute latencies of wave V between active RA patients and controls in the left ear

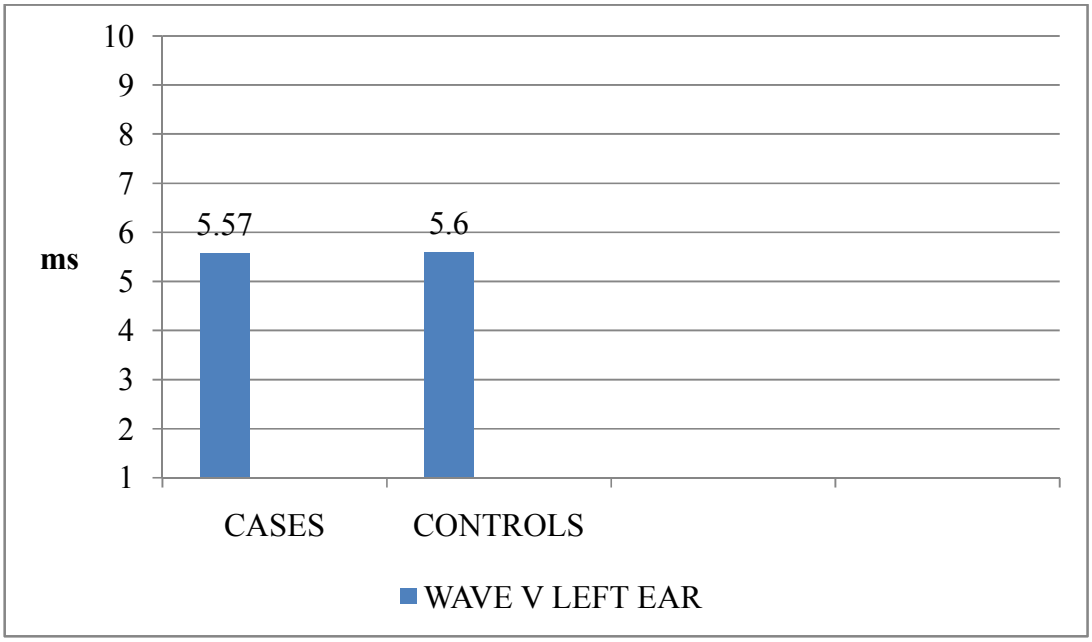


TABLE 13: Comparison of mean values of I-III IPL between active RA patients and controls in the left ear

I-III IPL LEFT EAR	MEDIAN	SD	pVALUE
CASES	2.48	0.30	0.5
CONTROLS	2.53	0.39	

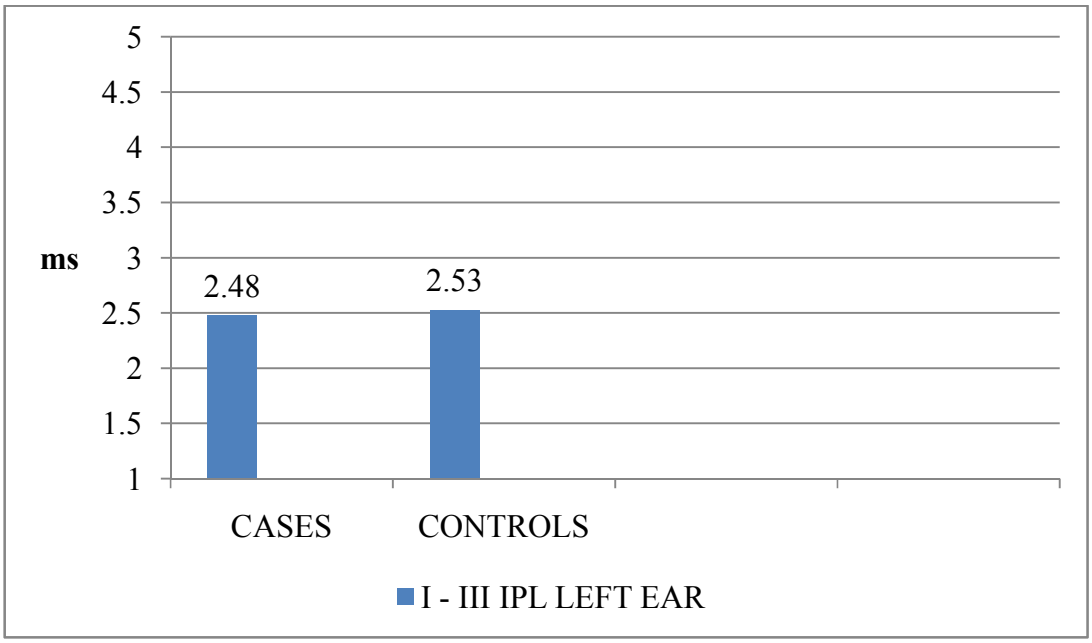
p value >0.05,not significant

TABLE 14: Comparison of mean values of I-V IPL between active RA patients and controls in the left ear

I-V IPL LEFT EAR	MEDIAN	SD	pVALUE
CASES	4.39	0.48	0.9
CONTROLS	4.38	0.54	

p value >0.05,not significant

GRAPH 11: Comparison of mean values of I-III IPL between active RA patients and controls in the left ear



GRAPH 12: Comparison of mean values of I-V IPL between active RA patients and controls in the left ear

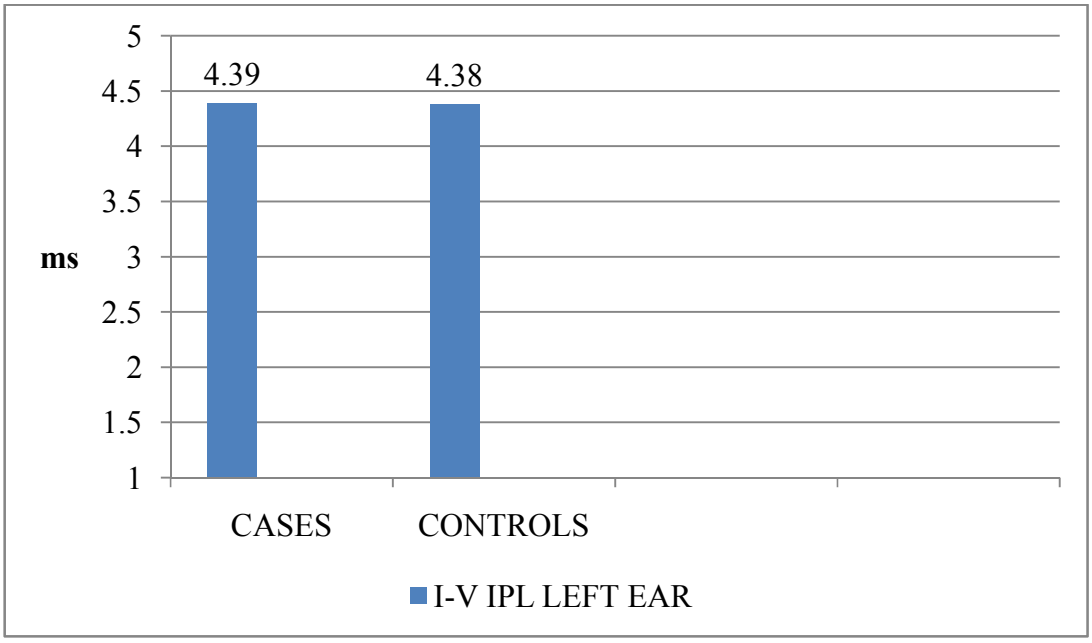


TABLE 15: Comparison of mean values of ACPA between active RA patients and controls

ACPA	MEAN	SD	pVALUE
CASES	95.060	50.3	0.0001***
CONTROLS	1.929	0.76	

p value <0.05,significant

The mean values of ACPA is significantly higher in active RA patients when compared to controls

GRAPH 13: Comparison of mean values of ACPA between active RA patients and controls

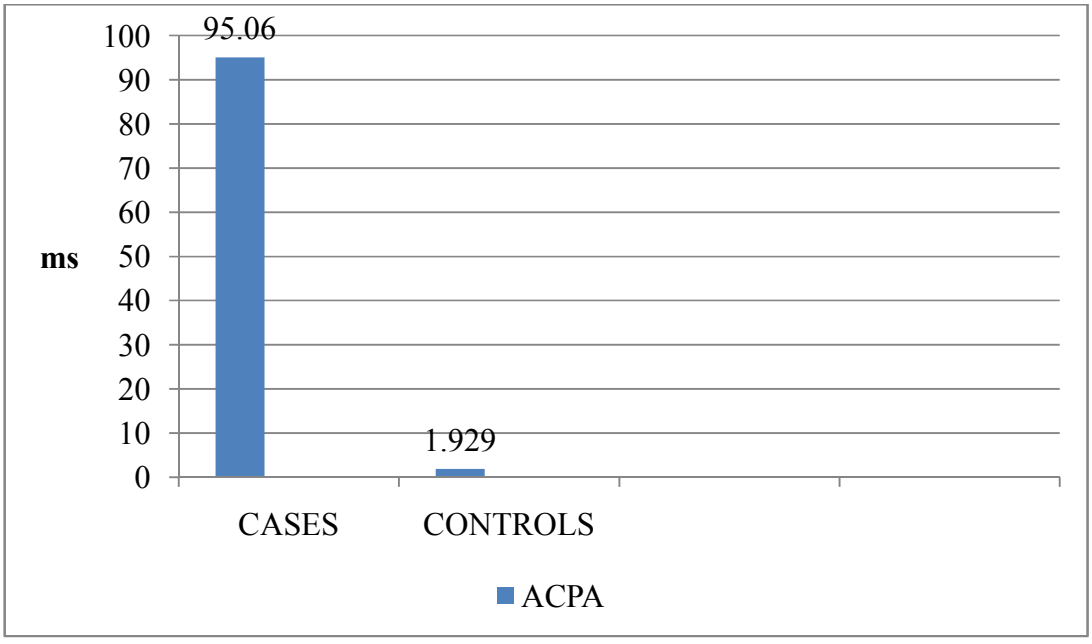


TABLE 16: Correlation between ACPA levels and the latencies of WAVE I in right ear between active RA patients and controls

CORRELATION BETWEEN ACPA LEVELS AND WAVE I LATENCY OF RIGHT EAR	CORRELATION COEFFICIENT	INTERPRETATION
	r = 0.79	Positive correlation
	p =0.00001	Significant

TABLE 17: Correlation between ACPA levels and the latencies of WAVE 1 in left ear between active RA patients and controls.

CORRELATION BETWEEN ACPA LEVELS AND WAVE I LATENCY OF LEFT EAR	CORRELATION COEFFICIENT	INTERPRETATION
	r=0.6008	Positive correlation
	p =0.0004	Significant

60 ears of controls and 60 ears of cases were subjected to OAE screening test. **Control ears passed** in the test indicating normal hair cell function. Out of 60 ears of cases ,10 right ears &9left ears passed the test .41 ears showed REFER indicating OAE abnormalities requiring detailed audiological assessment.

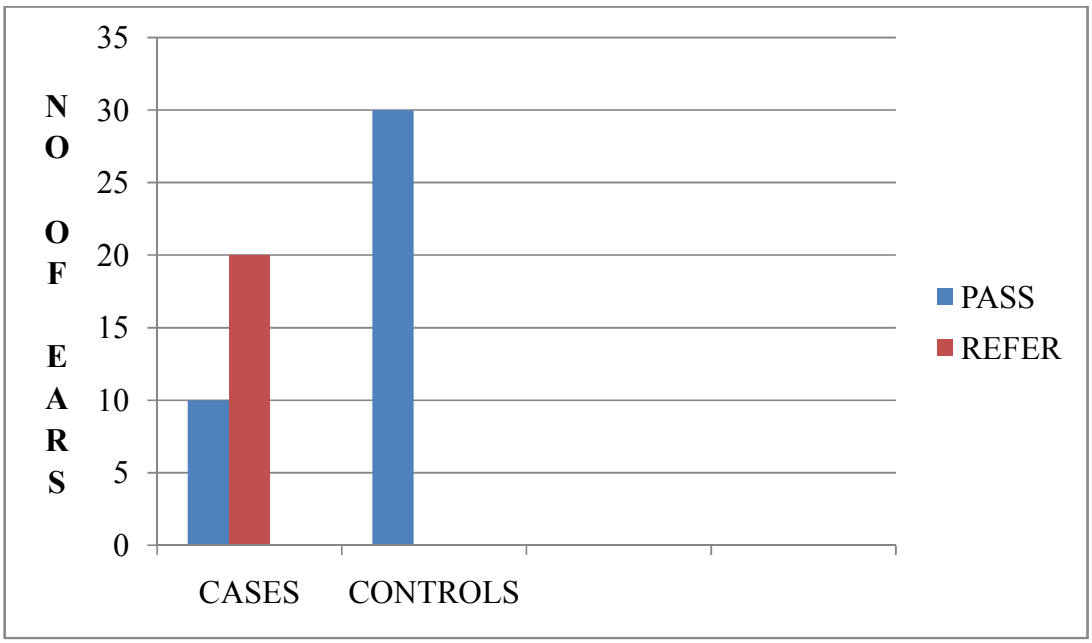
TABLE 18: Comparison of PASS & REFER in right ears of active RA patients between cases and controls

OAE IN RIGHT EAR	CASES	CONTROLS
PASS	10	30
REFER	20	0

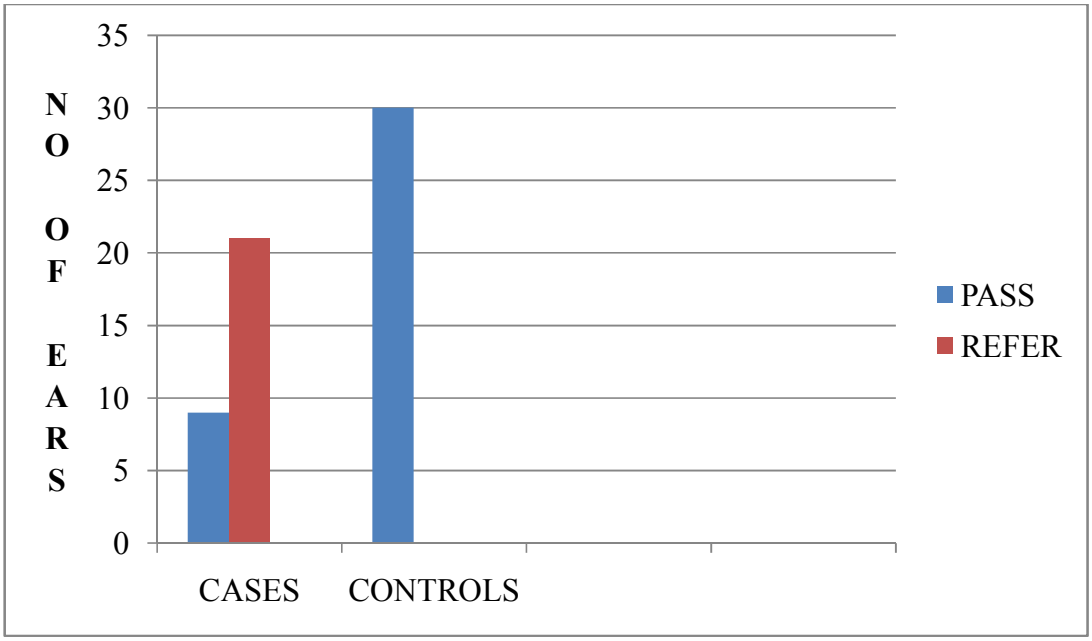
TABLE 19: Comparison of PASS & REFER in left ears of active RA patients between cases and controls

OAE IN LEFT EAR	CASES	CONTROLS
PASS	9	30
REFER	21	0

GRAPH 14: Comparison of PASS & REFER in right ears of active RA patients between cases and controls



GRAPH 15: Comparison of PASS & REFER in left ears of active RA patients between cases and controls



DISCUSSION

Patients with active RA with DAS 28>5.1 normal controls selected for the present study did not have any evidence of hearing deficit clinically& by PTA. The study population comprises of 30 patients (cases) aged between 25 and 45 years with a disease duration of less than 1 year & 30 age & sex matched controls. Their serum samples were tested for ACPA by ELISA which showed an increased titre. They were subjected to OAE test & Bainstem Evoked Response Audiometry to evaluate the integrity of the hair cell function of the inner ear & the auditory pathway.

Characteristics of study subjects

The age of RA patients included in the study was 25-45 years. The mean age in my study group is 38.47 ± 5.06 in cases & 38.30 ± 4.41 . The age of the patients included in various studies **(dikci o et al ,mar lassoed vagus et al,david et al, faisal et al)** are almost similar to that of the present study. Thus the patients in the present study are in the adult group. This is similar to many studies which included 40 (35 female and 5 males) patients with active Rheumatoid Arthritis. The mean age in those studies were 37.5 ± 9.5 years.

Beagley et al and Anias et al observed no age related effect on absolute latencies. Therefore it could be stated that any abnormalities of BERA observed in the patients can be attributed to the disease rather than age related causes.

RA patients diagnosed according to 2010 ACR/EULAR criteria participated in my study. Active disease with DAS 28 score >5.1. with a disease duration less than 1 year were recruited .They had early morning

stiffness of the affected joints for more than 45 mts.Acute phase reactants indicative of active inflammation like ESR was raised . ACPA titre was elevated .The functional integrity of cochlear hair cells was assessed by screening with OAE and BERA in these subjects ..OAE showed abnormal responses. BERA showed increased wave 1 absolute latency & normal latency of wave II , suggesting cochlear damage which may result in SNHL if not identified earlier.

Studies on active RA by **Dr.Shyam et al ,Salivenelli et al, Dikci etal, Marshal et al,** included patients with DAS 28 >5.1 criteria similar to my study. **Virginia et al,Dr.shyam et al,Yun ye et al** had recruited patients with active disease less than 1 year duration in their study and they have explained that SNHL with cochlear involvement is very common in. .Early morning stiffness is described as a marker of active disease by S**eirakowski et al** [84] in his study . **Virginia ramos et al** described in his study that SNHL develops in CRP <0.01 evidence of active disease within 1 year

Aletaha d et al in his study mentioned that patients with Das 28 >5.1 has been included in active disease according to 2010 criteria which is helpful to identify the disease at an early stage ,institute effective treatment and prevent complications[85.]

S**eth et al**[86] included patients with active disease with a DAS28 score >5.1 in his studies

Seirakowski et al, has explained that secretion of IL 6 follows the circadian rhythm and increased secretion of cortisol is not adequate to combat the active ongoing inflammation resulting in morning stiffness

ACPA in active disease

ACPA is taken as the biomarker of active disease in my study which is more specific than RF.

Gerard et al showed statistical significance of ACPA in active disease**.** **Shyam et al** emphasised on increased ACPA in active disease and claims that as a specific biomarker in active disease & explained that the release of inflammatory cytokines in active disease increase the expression of autoantibodies like ACPA .

Magaro m etal in his study shows a significant correlation with active disease and presence of RF positivity .But ACPA offers similar sensitivity, but higher specificity for RA than RF in early RA as emphasised by **Rohit et al**. SE alleles are prone to bind to citrullinated sequences more than the normal ones like vimentin, fibrinogen and cartilage in active disease and so considered a marker in active disease[87]is suggested by **pratesi et al.**

Rantappa et al[88] emphasises ACPA as a valuable diagnostic test in the course of active,early disease and explained that the breakdown of immune tolerance and complement fixation in synovitis coincides with development of joint symptoms and extraarticular manifestations

A positive correlation between DAS 28 score,ESR,Platelet count,RF,&ACPA ($p<0.05$) shows that ACPA is considered as an important indicator of disease activity in RA[89]

Dr. Shyam et al. reveals that active RA cases **of less than one year duration**, were selected with DAS-28>5.1.They had thrombocytosis , raised ESR, positive for RF, and increased titres of ACPA . ACPA positivity was associated with high disease activity ($p< 0.001$). [90]

Thrombocytosis present in active disease interferes with nutrition evidenced by **Bongartz et al[91]** in his study

Cochlear pathology in active RA

SNHL of cochlear type is common in active RA. The aim of my study is to identify the hair cell destruction at an early stage by OAE screening & BERA so that measures may be taken to protect them and prevent hearing abnormalities.

Bakr et al shows that extra-articular manifestations are common in active disease with DAS score >5.1.Extra-articular organ involvement is associated with severe ,active disease in RA patients wiyh evidence of increased mortality[92]

Dikci et al, Takatsu et al, Amir Emamifar et al ,Louisa et al ,Magaro et al claims that SNHL of cochlear pathology is common in active RA

Raut vv etal in his study on 35 cases & controls showed SNHL to be statistically significant $p<0.05$ in 60% of patients and concludes that SNHL of cochlear variety is more common in RA.

Kumar et al reported that if peripheral T lymphocytes remain activated over long periods of time,as in vicious inflammation (eg:RA) , they continue to produce high levels of proinflammatory cytokines such as interleukin IL 1,IL-6, and TNF-α that mediate cochlear degeneration resulting in SNHL

Dikci et al explains that inflammation during active disease in RA as one of the cause for SNHL and occurs early in the disease process & attributes the pathogenesis to deposition of immune complexes expression of inner antigens & inflammation.He explained that thrombocytosis present in active disease increases the viscosity of blood and causes disturbances in blood circulation and nutrition to the hair cells of the inner ear. Vasodilator and antioxidant drugs administered may protect the hair cells.

Dikci et al, Takatsu et al correlates increased ESR,IL6 &MMP3 indicative of active inflammation in the joints and occurrence of SNHL

OAE & BERA in cochlear dysfunction

I screened my patients for OAE at the Institute of Audiology & Speech therapy,Rajiv Gandhi Government General Hospital, Chennai .to determine the functional integrity of the hair cells.OAE showed abnormalities indicative of hair cell damage requiring complete audiological assessment. BERA revealed

prolonged latency of wave 1 with normal wave II indicating peripheral cochlear pathology.

TOAE provide reliable initial screening results that detect hearing dysfunction much earlier than behavioral tests, allowing for quicker intervention as evidenced by **IDevyn Lambell et al**

Jessica et al explains OAE as a screening tool for the evaluation of cochlear function & detecting its decrease in active RA patients.

Berthe et al explains that TEOAEs by their repeatability is an important tool in the identification of hair cell abnormalities[93]

Kemp DT states that BERA is a sensitive tool to diagnose cochlear & retrocochlear pathology

Liberman et al 2002,takeno et al 1994,kujawa and liberman 2009,Buchwald & Huang 1975 suggested that OAE's are generated & amplified by OHC which are biological motors.Wave 1 in BERA represents the summated activity generated in the IHC and propagated to the auditory nerve through the synapse existing between them.. So abnormalities in wave1 of BERA indicates IHC dysfunction & synaptic transmission .This is parallel to my study which showed prolonged latency of wave l in BERA indicative of hair cell involvement.

Abnormal wave 1 with normal waves II –V indicates significant peripheral hearing impairment[94]

BERA is an important tool to assess & analyse compensating central activity following cochlear damage the**(Gue et al 2012, Ruttiger et al 2013 and Singer et al 2013**). **Charles leiberman et al** has stated that synapses exist between hair cells and cochlear nerve terminals in the inner ear which is more vulnerable to damage .This produces changes in WAVE I in BERA in cochlear disorders.

Durrant et al 1998, Santarelli et al 2009 explained that Wave 1 is contributed by the IHC receptor potentials .ABRs, and OAEs, are used to identify the site of lesion (eg:hair cells).

Amy et al observed **prolonged latency of wave l with waves ll, lll,V & IPL within the normal or shortened in BERA in cochlear sensory lesions.**

Amy et al Coats, 1978; Eggermont, 1982; Elberling, 1981. ,observed a prolonged WAVE I in cochlear lesions . **Hall, 1992** shows that Wave ll, lll & V latencies are prolonged in retrocochlear hearing losses .

Prolonged latencies of wave I,III–V and I–V inter peak latencies were noticed in BERA & disappearance of TEOAEs in chronic RA that affects the auditory nerve, cochlea and auditory pathway within the brainstem[95.] This shows that central auditory pathway is involved in chronic rheumatoid arthritis.

Dikci o et al attributed prolonged latency of wave 1 to active RA. Recurrent active phases in chronic disease results in the hair cell destruction accompanied by fibrosis affecting the auditory nerve and the conduction pathway which shows prolonged latencies of ll, lll,V waves & IPLl-lll & l-V.Auditory nerve and conduction pathway is affected in chronic RA.

Salvinelli et al[96]describes increased Wave I latency in ABRs (p=0.03). Decreased reproducibility (p<0.001) and amplitude (p<0.001) of TEOAEs were found in active RA subjects in comparison to controls.

Rebecca uribe et al states that there is damage to outer and inner hair cells that is reflected in the auditory nerve which results in increased latency of wave I and decreased reproducibility of OAE in active RA with p <0.0001

Takatsu et al. Dikci o et al, Bakr et al identified impaired reproducibility of TEOAE'S depicting dysfunction in IHCs, with normal hearing in active RA similar to my study**. Dikci o et al** states that there is no statistical difference in PTA between cases & controls,.but TEOAE's showed statistically significant decrease in these patients and he concluded that hair cell dysfunction can be detected by OAE's in early active disease. Further management if initiated early with vasodilator & antioxidant drugs are useful in protecting the hair cells , when OAE's start showing a decrease.

Amir emamifar et al[97]**,Murdin et al**[98]**,Bayazit et al**[99]**,Dikci o et al**[100]**,Baradaranfar et al**[101] reported the decrease in OAE 's are seen in patients with normal hearing status in active RA indicating an early stage of hearing impairment similar to my study.

CONCLUSION

The conclusions derived from the present study are:

- Active disease in RA is characterised by DAS 28 >5.1.
- Early morning stiffness of the involved joints for more than 45 minutes suggestive of synovitis remains the hallmark of active disease.
- Increased titres of ACPA can be claimed as a biomarker in active disease .
- Rheumatoid arthritis affects the cochlear hair cells of the inner ear in active disease.

The inflammation during active disease ,expression of antigens by the hair cells ,deprived nutrition etc affects the hair cells of the inner ear in active disease. Otoacoustic emissions can be used as a screening tool to assess the functional integrity of the hair cells of the cochlea at an earlier stage. Decrease in OAE responses were evident with normal hearing at an early stage of active disease.Brainstem evoked response audiometry is characterised by prolonged latency of wave l with normal latency of wave II in these patients .The increased latency of wave I is found to be directly proportional to the increased titres of ACPA ,a measure of disease activity. Waves II, III,V and Inter peak latencies were within normal limits when compared with controls explaining the absence of central auditory pathology.

- OAE & BERA can be used to assess the cochlear functional integrity at an earlier stage and to classify peripheral and central auditory pathology.

BERA & OAE can be advocated in the detection of subtle abnormalities of the cochlear apparatus even before it is evident clinically. . Ensuring proper compliance to disease treatment may protect the hair cells from damage . Intervention at an earlier stage like,

- Intratympanic application of steroids,
- Vasodilators to improve circulation of hair cells which have high metabolic demands,
- Antioxidants like Sodium salicylate,Vitamin E etc.

These may protect the hair cells & prevent hearing impairment. Morbidity associated with the disease can be curtailed and can ensure a better quality of life for these patients to enable them to lead an independent normal day to day life. So periodic,regular ENT examination with OAE screening and BERA may be recommended in RA patients.

SUMMARY

Otoacoustic Emissions test is a simple, effective and non-invasive screening tool for the evaluation of the functional integrity of the cochlear hair cells .BERA is an effective procedure to differentiate peripheral and central auditory pathology. Both in combination can be used to assess the cochlear functions in toto.

The present study was conducted at the Institute of Physiology and Experimental medicine, Madras Medical College, Chennai, to assess the role of OAE & BERA in patients with active RA .The study also involves the integral role of ACPA as a biomarker of active disease.

30 active RA patients satisfying DAS 28 >5.1 and 30 normal subjects participated voluntarily in the study .They were subjected to OAE & BERA and their serum levels of ACPA was measured by ELISA. On OAE screening,all controls showed PASS indicative of normal hair cell function.Out of 60 ears of active RA patients ,41 ears showed REFER indicating hair cell abnormalities requiring diagnostic OAE .Statistically significant prolongation in absolute latency of wave I with normal waves II,III & V was observed in active RA patients indicating hair cell dysfunction and thus peripheral auditory pathology .The serum ACPA levels were significantly higher in active RA patients when compared to controls & showed a positive correlation with latency of wave I in both ears , that the active RA affects the hair cells of the cochlea .

Hair cell abnormalities are detected at an earlier stage by OAE &BERA. Periodic ENT examination with audiological assessment to be

encouraged in these patients to prevent hair cell damage & protect them thus preventing hearing disability enabling them to accomplish a better lifestyle in the society.

However, the study has got its own limitations as the above findings needs to be confirmed with a larger sample size. The patients with OAE abnormalities on screening are to be subjected to diagnostic OAE for measuring their amplitude & reproducibility to comment on the extent of hair cell damage. . Further research is required to reveal the mechanism of hair cell damage like assessment of anticochlear antibodies which may be helpful in establishing the diagnosis at an earlier stage. Measures aimed at the same may protect hair cells and prevent its damage.

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Yun Ye Su-Liang Li Ming Xie Ping Jiang

90. Anti-citrullinated peptide antibodies (ACPA): Possible role in determining disease activity and severity in rheumatoid arthritis of less than one year duration Dr Shyam Sundar Lakshkar , Dr Laxmi Kant Goyal , Dr Renu Saigal Former Senior Resident, Department of Medicine, SMS Medical College, Jaipur 2Assistant Professor, Department of Medicine, Consultant, Rheumatology Services SMS Medical College, Jaipur 3 Professor & Head,

Department of Medicine, IMSRC, Jaipur Former Senior Professor, Head Department of Medicine, Former In-Charge, Rheumatology Services, SMS Medical College, Jaipur

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ANNEXURES

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.R.Bhuvaneswari
Postgraduate M.D.(Physiology)
Madras Medical College
Chennai 600 003

Dear Dr.R.Bhuvaneswari,

The Institutional Ethics Committee has considered your request and approved your study titled **"Evaluation of Otoacoustic Emissions and brainstem evoked response audiometry and serum levels of anti cyclic citrullinated protein antibodies in patients with active rheumatoid arthritis" No.21072015.**

The following members of Ethics Committee were present in the meeting held on 07.07.2015 conducted at Madras Medical College, Chennai-3.

1.	Prof.C.Rajendran, M.D.,	: Chairperson
2.	Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.Sudha Seshayyan, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC	: Member
5.	Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6.	Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7.	Prof.Baby Vasumathi, Director, Inst.of O&G, Ch-8	: Member
8.	Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
9.	Prof.Saraswathy, M.D., Director, Inst. Of Pathology, MMC	: Member
10.	Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC	: Member
11.	Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
12.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
13.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆய்வு தலைப்பு :

முடக்கு வாத நோயாளிகளிடம் ஆட்டோ அகோஸ்டிக் எமிஷன்ஸ் மற்றும் இரத்த எசிசிபி (ACCP) அளவு பற்றிய ஆய்வு.

ஆராய்ச்சியாளர் பெயர் : மரு. இரா. புவனேஸ்வரி

ஆராய்ச்சி நடக்கும் இடம் : சென்னை மருத்துவக் கல்லூரி.

பெயர் : வயது :

பாலினம் : ஆண்/பெண் பங்கு பெறுபவரின் அடையாள எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு, எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

நான் மேற்குறிப்பிட்ட ஆராய்ச்சியில் பங்குபெற்று ஆட்டோ அகோஸ்டிக் எமிஷன்ஸ் கொண்டு செவி திறன் பரிசோதனை மற்றும் இரத்த எசிசிபி அளவு பரிசோதனை செய்து கொள்ளவும் முழு சம்மதம்.

இந்த ஆராய்ச்சியில் இருந்து நான் எந்த நேரமும் பின் வாங்கலாம் என்றும், அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புரிந்து கொண்டேன். நான் செவி திறன் குறித்த இந்த ஆராய்ச்சியின் விவரங்கள் கொண்ட தகவல்களை பெற்றுக் கொண்டேன்.

இரத்த எசிசிபி அளவு பரிசோதனைக்கு ஊசி மூலம் இரத்தம் எடுக்க சம்மதிக்கிறேன். இரத்தம் எடுக்கும் போது வலி, அரிப்பு, மயக்கம் போன்ற பின் விளைவுகள் ஏற்படலாம் என்று தெரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சம்மதத்துடன் ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கின்றேன்.

ஆய்வாளர் கையொப்பம்

தேதி :

பங்கேற்பாளர் கையொப்பம் /
இடதுகை பெருவிரல் ரேகை

தேதி :

INFORMED CONSENT FORM

Title of the study: " Evaluation of Otoacoustic emissions,Brain stem evoked response audiometry and serum levels of Anticyclic Citrullinated Protein Antibodies in patients with active Rheumatoid arthritis "

Name of the Participant:

Name of the Principal Investigator: Dr.R.Bhuvaneswari.

Name of the Institution:

Institute of Physiology and Experimental Medicine,

Madras Medical College and Rajiv Gandhi Govt. General Hospital,

Chennai - 3

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in

" Evaluation of Otoacoustic emissions,BERA and serum levels of ACPA in patients with active rheumatoid arthritis"

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have informed the investigator of all the treatmentsthat I am taking or have taken in the past _____ months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past _____month(s).

9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigator to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I understand that my identity will be kept confidential if my data are publicly presented.

14. I had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

For adult participants

Name and signature / thumb impression of the participant (or legal representative if participant is incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his/ her representative obtaining consent:

Name _____ Signature_____

Date_____

PROFORMA

1. Name :
2. Age:
3. Sex:
4. Address :
5. Occupation :
6. Complaints/duration:
7. History of present illness:
8. Past history:
9. History of ear disorders /previous surgeries:
10. Family history of hearing problems:
11. History of drug intake:

Investigations :

1. Brain stem evoked response audiometry
2. Otoacoustic emissions test
3. Serum ACPA's

General examination:

Temperature:

Pulse rate:

Blood pressure:

Systemic examination:

Cardiovascular system:

Respiratory system:

Gastrointestinal system:

Central nervous system:

ENT Examination:

MASTER CHART - OAE, BERA & ACPA VALUES IN CONTROLS

S.NO	AGE (yrs)	SEX	RIGHT EAR LATENCY (in msec)						LEFT EAR LATENCY (in msec)						OAE SCREENING		ACPA (RU)
			Wave I	WAVE II	Wave III	Wave V	IPL I-III	IPL I-V	Wave I	WAVE II	Wave III	Wave V	IPL I-III	IPL I-V	RIGHT EAR	LEFT EAR	
1	35	f	1.62	2.83	3.64	5.3	2.19	4.6	1.6	2.81	3.25	5.69	2.12	4.84	PASS	PASS	4
2	36	m	1.64	2.79	3.63	5.6	2.76	3.78	1.67	2.79	3.59	5.62	1.89	3.99	PASS	PASS	3.16
3	45	f	1.67	2.69	3.88	5.49	1.99	4.09	1.66	2.83	3.19	5.79	1.87	5.86	PASS	PASS	1.36
4	44	m	1.42	2.78	3.22	5.54	2.27	5.81	1.67	2.78	3.21	5.52	3.59	4.13	PASS	PASS	1.49
5	42	f	1.54	2.78	3.67	5.39	2.44	5.07	1.5	2.78	3.62	5.5	2.64	3.84	PASS	PASS	1.36
6	37	f	1.54	2.69	3.67	5.54	2.12	3.74	1.34	2.79	3.71	5.39	2.64	5.13	PASS	PASS	1.77
7	39	f	1.59	2.71	3.9	5.39	2.61	5.2	1.65	2.89	3.8	5.64	3.71	4.08	PASS	PASS	1.51
8	44	m	1.61	2.74	3.94	5.54	2.51	4.81	1.67	2.69	3.99	5.38	2.69	4.64	PASS	PASS	1.62
9	42	f	1.64	2.89	3.76	5.69	2.47	5.12	1.8	2.9	3.99	5.71	2.72	5.12	PASS	PASS	1.08
10	35	f	1.6	2.69	3.69	5.59	2.56	4.51	1.6	2.81	3.97	5.8	3.01	5.21	PASS	PASS	1.28
11	32	f	1.67	2.89	3.81	5.72	1.89	4.5	1.64	2.77	3.52	5.81	2.24	4.64	PASS	PASS	1.48
12	33	m	1.69	2.79	3.87	5.74	2.36	4.44	1.68	2.89	3.71	5.79	2.41	3.87	PASS	PASS	2.44
13	38	f	1.6	2.69	3.94	5.56	2.39	4.39	1.64	2.76	3.81	5.84	2.39	3.64	PASS	PASS	3.16
14	37	f	1.5	2.68	3.99	5.67	2.5	4.52	1.65	2.79	4.12	5.06	2.25	3.76	PASS	PASS	3.55
15	37	f	1.65	2.89	3.89	5.79	2.54	4.49	1.74	2.87	3.77	5.01	2.25	3.81	PASS	PASS	1
16	42	f	1.45	2.75	3.98	5.61	2.53	4.44	1.67	2.9	3.64	5.77	2.16	3.78	PASS	PASS	1.59
17	38	f	1.6	2.68	3.94	5.6	2.39	4.39	1.65	2.88	3.91	5.75	2.31	3.99	PASS	PASS	1.86
18	43	f	1.66	2.79	3.87	5.79	2.19	4.39	1.63	2.85	3.99	5.72	2.5	3.98	PASS	PASS	1.83
19	40	m	1.64	2.84	3.88	5.74	2.21	4.52	1.69	2.68	3.81	5.64	2.61	3.81	PASS	PASS	1.48
20	39	f	1.67	2.71	3.7	5.69	2.64	4.49	1.63	2.65	3.72	5.56	2.69	4.01	PASS	PASS	2.52
21	40	f	1.59	2.69	3.98	5.72	2.59	4.69	1.54	2.91	3.62	5.89	2.34	4.02	PASS	PASS	1.69
22	35	f	1.6	2.84	3.7	5.84	2.64	4.39	1.68	2.69	3.51	5.69	2.39	4.61	PASS	PASS	1.88
23	29	f	1.65	2.89	3.87	5.84	2.31	4.42	1.54	2.78	3.69	5.74	2.42	4.64	PASS	PASS	1.2
24	33	f	1.67	2.89	3.78	5.88	2.43	4.5	1.6	2.84	3.68	5.74	2.52	4.8	PASS	PASS	2.1
25	28	f	1.54	2.79	4	5.89	2.46	4.3	1.5	2.81	3.72	5.69	2.64	4.31	PASS	PASS	2.21
26	43	f	1.55	2.9	3.94	5.76	2.53	4.8	1.66	2.86	3.81	5.49	2.71	4.32	PASS	PASS	3.07
27	39	f	1.6	2.89	3.86	5.69	2.52	4.12	1.65	2.84	3.94	5.48	2.5	4.64	PASS	PASS	1.9
28	42	f	1.6	2.83	3.87	5.61	2.37	4.11	1.67	2.76	3.81	5.34	2.59	4.67	PASS	PASS	1.3
29	42	f	1.71	2.68	3.88	5.79	2.54	4.67	1.54	2.79	3.84	5.4	2.61	5.08	PASS	PASS	1.2
30	40	f	1.72	2.87	3.9	5.69	2.67	4.57	1.69	2.78	3.81	5.76	2.64	4.41	PASS	PASS	1.8

MASTER CHART - OAE, BERA & ACPA VALUES IN ACTIVE RA PATIENTS

S.NO	AGE (yrs)	SEX	DURATION (MONTHS)	RIGHT EAR LATENCY (in msec)						LEFT EAR LATENCY (in msec)						OAE SCREENING		ACPA(RU)
				Wave I	WAVE II	Wave III	Wave V	IPL I-III	IPL I-V	Wave I	WAVE II	Wave III	Wave V	IPL I-III	IPL I-V	RIGHT EAR	LEFT EAR	
1	37	F	5	1.7	2.56	3.62	5.57	2.1	4.68	1.59	2.81	3.2	5.78	2.21	4.71	PASS	PASS	54.88
2	35	M	5	1.79	2.58	3.65	5.7	2.73	3.88	1.99	2.84	3.62	5.55	1.99	3.89	REFER	REFER	56.88
3	42	F	4	1.91	2.72	3.9	5.5	1.95	4.03	2	2.7	3.21	5.7	1.97	5.91	REFER	REFER	64.57
4	34	F	3	1.62	2.81	3.12	5.5	2.25	5.9	1.61	2.79	3.12	5.43	3.51	4.09	PASS	PASS	53.87
5	32	M	4	1.72	2.89	3.64	5.42	2.39	5.03	1.89	2.83	3.67	5.53	2.73	3.99	PASS	REFER	53.7
6	37	F	2	2.1	2.79	3.71	5.43	1.99	3.89	2.1	2.82	3.6	5.42	2.51	5.08	REFER	REFER	185
7	39	F	3	1.69	2.81	3.91	5.61	2.51	5.1	1.62	2.74	3.72	5.59	2.56	3.97	PASS	PASS	54.28
8	46	F	3	1.61	2.84	3.98	5.52	2.49	4.91	1.59	2.77	3.91	5.41	2.52	4.52	PASS	PASS	54.27
9	44	F	4	1.74	2.82	3.73	5.74	2.5	5.07	1.92	2.8	3.9	5.62	2.81	5.01	REFER	REFER	4-Mar
10	40	F	2	2.1	2.68	3.65	5.71	2.51	4.51	1.9	2.79	3.92	5.69	3.06	5.12	REFER	REFER	200
11	30	F	5	1.68	2.75	3.9	5.52	1.97	4.44	1.6	2.81	3.64	5.7	2.12	4.51	PASS	PASS	53.24
12	45	M	1	1.7	2.81	3.92	5.61	2.31	4.39	1.9	2.79	3.78	5.72	2.52	3.98	REFER	REFER	67.21
13	43	F	3	2	2.78	3.91	5.75	2.34	5.1	2.3	2.78	3.99	5.81	2.41	3.72	REFER	REFER	125.33
14	36	M	4	2.2	2.69	3.96	5.57	2.41	5.12	2	2.74	4	5	2.36	3.88	REFER	REFER	122.63
15	32	F	5	1.7	2.68	3.84	5.59	2.51	4.67	1.9	2.82	3.76	5.02	2.62	3.96	REFER	REFER	96.6
16	38	F	5	1.98	2.79	3.71	5.81	2.49	4.71	2	2.84	3.62	5.8	2.12	3.84	REFER	REFER	102.8
17	41	F	2	2	2.8	3.94	5.69	2.31	4.59	2.3	2.79	3.92	5.79	2.21	4.12	REFER	REFER	200
18	44	F	1	1.61	2.76	3.99	5.64	2.25	3.96	1.58	2.81	3.94	5.65	2.42	4.21	PASS	PASS	11.95
19	46	F	5	1.87	2.74	3.9	5.74	2.16	4.42	1.77	2.83	3.78	5.52	2.51	3.9	REFER	PASS	123.56
20	42	M	3	1.64	2.9	3.67	5.81	2.56	4.34	1.59	2.77	3.61	5.49	2.64	4.45	REFER	REFER	97.8
21	29	F	6	1.97	2.81	3.78	5.86	2.54	4.62	1.89	2.78	3.54	5.81	2.26	4.52	REFER	REFER	102.01
22	39	F	4	1.9	2.79	3.73	5.89	2.59	4.59	1.87	2.84	3.59	5.62	2.29	4.43	REFER	REFER	68.76
23	37	F	4	1.62	2.62	3.64	5.88	2.25	4.29	1.67	2.91	3.62	5.67	2.34	4.56	PASS	PASS	54.34
24	36	F	2	2.2	2.59	3.91	5.7	2.39	4.57	2	2.88	3.64	5.67	2.56	4.64	REFER	REFER	200
25	28	F	5	1.79	2.78	3.89	5.64	2.41	4.56	1.99	2.78	3.78	5.65	2.61	4.16	PASS	REFER	58.67
26	43	F	4	1.98	2.89	3.79	5.59	2.47	4.61	1.99	2.74	3.91	5.59	2.64	4.21	REFER	REFER	96.45
27	44	F	5	1.81	2.83	3.43	5.71	2.47	4.32	1.75	2.84	3.94	5.54	2.52	4.51	REFER	REFER	94.45
28	41	F	4	2.23	2.81	3.74	5.64	2.31	4.39	1.98	2.79	3.88	5.42	2.5	4.5	REFER	REFER	145.67
29	36	F	5	1.79	2.8	3.69	5.67	2.5	4.54	1.8	2.8	3.72	5.31	2.51	5.1	REFER	REFER	67.89
30	38	F	4	1.64	2.67	3.98	5.69	2.7	4.55	1.62	2.89	3.76	5.8	2.6	4.32	PASS	PASS	89.95