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AAO-HNS - Martha Entenmann Tinnitus Research Center Tinnitus Miniseminar 2013

New Concepts in Electrophysiology and Tinnitus

Location-Vancouver, CA.

INTRODUCTION

The theme of the AAO-HNS Martha Entenmann, Abraham Shulman, M.D., Barbara Goldstein, PhD International Tinnitus Miniseminar, 2013, was "New Concepts Electrophysiology and Tinnitus".

The goal was to provide to the otolaryngologist and all tinnitus professionals information of clinically applicable new and established methods of objective recording of electrical activity in both ear and brain which can serve as a basis for identification of electro physiologic correlate(s), for all clinical types of tinnitus, individual for each tinnitus patient.

The focus was on the clinical translation for tinnitus diagnosis and treatment based on: 1) State of the art clinical translation of electrophysiology of brain activity reflective of multiple brain functions in the presence of the tinnitus signal; and 2) Electrophysiology of cochleovestibular function reflective of endolymphatic hydrops, and sensorineural hearing loss.

Michael E. Hoffer, M.D. introduced the program to the well attended meeting. The program in 2013, "Electrophysiology and tinnitus", was presented as the fourth of a series of AAO-HNS Miniseminars, which over the past 4 years has had as its goal the providing to the AAO HNS membership and guests of state of the art tinnitus information, both clinical and basic science, for translation by the otolaryngology practioner to the patient for an increased accuracy for the tinnitus diagnosis and its translation for treatment.

The invited speakers included:

- Michael E. Hoffer, M.D. CAPT MC USN
- Guest of Honor: Leslie S. Prichep, PhD., Professor Psychiatry, Acting Director Brain Research Laboratories, New York University School of Medicine, NY, NY
- Carlos A Oliveira, MD, PhD., Professor and Chairman Department Otolaryngology, Brasília University Medical School Brasília, Brazil
- Tobias Kleinjung, M.D., PhD. University Zurich, Department Otorhinolaryngology, Switzerland
- Abraham Shulman, M.D. Professor Emeritus Clinical Otolaryngology, SUNY/Downstate.

The themes of the past miniseminars, the rationale for the order in the selection of the themes since 2010 were reviewed. The AAO-HNS tinnitus miniseminars, started in 2010, focused on tinnitus diagnosis and treatment, 2011 effects of Implants on Brain function, with a focus on the indication for tinnitus of the cochlear implant for attempting tinnitus relief/suppression; and in 2012 brain imaging and tinnitus with the take home message that clinical application of the brain imaging technologies of a) Nuclear medicine single photon emission tomography, brain SPECT, b) Photon emission tomography, brain PET; c) Functional magnetic resolution imaging, fMRI; d) Magnetic emission tomography (MEG), and e) Low frequency resolution electromagnetic tomographic analysis (LORETA), provide an objectivity for the diagnosis and monitor function for subjective aberrant sensory complaint, tinnitus.

The take home message and goal for the attendee of each miniseminar since 2010 has been the clinical translation of advances in neuroscience, sensory physiology, and auditory science for increasing both an accuracy of the tinnitus diagnosis and efficacy for treatment, for the ultimate benefit of the tinnitus patient. Diagnostic accuracy is reflected in the efficacy of treatment.

Specifically in 2013 the take home message was that translation of what is known of electrophysiology of the auditory system ear and brain, can with existing testing technologies, eg. ABR, otoacoustic emissions, P 300, functional brain imaging of nuclear medicine, single photon emission tomography, (SPECT), photon emission tomography (PET), and electrophysiology quantitative electroencephalography (QEEG) provide an objectivity for tinnitus, a subjective sensory aberrant auditory complaint, particularly for a predominantly central type severe disabling subjective idiopathic tinnitus.

Attendees were invited by Abraham Shulman, M.D. (Abe) to participate in support of the AAO-HNS International Tinnitus Miniseminar. Their participation was requested to continue the AAO-HNS Intl Tinnitus Miniseminars, planned for in perpetuity beyond 2014.

Initially, support for the costs of the meeting had been established by the Martha Entenmann tinnitus Research center (METRC) for the period 2010-2014.

A contribution, large or small, short or long term, to defray the cost of the meeting, was requested to be considered by attendees, colleagues, friends and patients, to continue to achieve the goal of the AAO-HNS, which is to provide state of the art tinnitus information to the Otolaryngology community for continuing education dedicated to tinnitus to provide state of the art quality care to our tinnitus patients.

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PRESENTATIONS

Each of the presentations focused on a methodology of ear and brain physiology and its translation for tinnitus, e.g. how to record, analyze, and interpret the data for diagnosis and treatment of severe disabling tinnitus.

The program was presented in two sections with adequate time for questions. Section 1. Electrophysiology of ear; and Section 2. Electrophysiology of brain. A question and answer session followed.

I. Michael E. Hoffer, CAPT MC USN presented an introduction and overview of the physiology of the peripheral and central auditory system with a focus on the P300 response and tinnitus.

The current diagnostics for tinnitus were reviewed which focus on the subjective nature of the tinnitus complaint. Specifically current emphasis is a medical audiologic team approach of otology/neurotology and audiology which is dependent on the subjective report by the patient of the tinnitus, its clinical course and response treatment. Audiology testing focuses on the psychoacustical and psychophysical scaling of the tinnitus percept. Questionnaires attempt to identify the characteristics of the tinnitus for quality, location, intensity, duration and masking characteristics, associated complaints of quality of life, depression, anxiety and severity. Treatment modalities, pharmacologic/instrumentation are inconsistent in subjective reports of efficacy.

The subjective nature and heterogeneity of the complaint for etiology, tinnitus characteristics, response to modalities of treatment, instrumentation/medication presents a dilemma to both, the tinnitus patient and professional health care providers, researchers compensation and disability organizations.

In general, identification of an electrophysiologic correlate(s) for any diagnostic category provides objectivity for a complaint and a target for treatment.

The presentations of the panel of international experts were charged with questions to be answered in their presentations:

1. Can electrophysiology provide us with more objective diagnostic information?
2. Can electrophysiology inform us about treatment modalities?
3. Can electrophysiology methods be utilized to treat tinnitus?

The P300 brain response in neuroscience is a neural evoked potential component of the electroencephalogram (EEG). It has been clinically applied in cognitive testing and in assessing progress of therapy, lie detection, computer interfacing. It can be universally elicited by varying stimuli. P300 potential is the neuronal correlation for attention, auditory differentiation capacity, short-term memory decision-making capacity.

Abnormalities in P300 reported in patients with cognitive disorders and tinnitus include the following:

1. Cognitive disorders: delayed latency time of wave P300, more predominant on left stimulations, a reduction of amplitude, and spatial variations in the formation of the potential. This is in keeping with the pathology. In the case of cortical atrophies and Alzheimer's disease, the temporospatial distribution of the potential prevails in frontal areas. In vascular pathological processes, temporospatial distribution of the potential prevails in temporoparietooccipital areas[1].
2. Abnormalities in P300 seen in tinnitus patients[2]. Increased latencies in individuals with tinnitus were reported in a controlled study of 30 individuals with tinnitus ages 29-50 and thirty matched individuals with no tinnitus. Bilateral abnormalities were identified in those with bilateral tinnitus[3].

In summary, the P300 results in selected tinnitus cases have been productive, however results have not been universal.

II. Carlos A Oliveira, MD, PhD., Professor and Chairman Department Otolaryngology, Brasília University Medical School Brasília, Brazil presented a summary of electrophysiology clinical studies of his entitled "Electrophysiology of tinnnitus in normal hearing patients with":

1. Transient and distortion product evoked oto-acoustic emissions (TEOAE/DPOAE),
2. ABR in normal hearing patients with and without tinnitus;
3. Preliminary data on the results of the mismatch negativity test (MMN); and
4. The relation of anxiety and depression with tinnitus annoyance, otoacoustic emissions and auditory evoked brainstem potentials.

The TEOAE and DPOAE results were compared in patients with/without tinnitus. TEOAE and DPEOAE tests showed that normal hearing patients with tinnitus have significantly more abnormal results in both tests than normal hearing patients without tinnitus. Tinnitus without hearing loss is associated to abnormal function of outer hair cells (OHC) evaluated by Otoacoustic Emission

tests. Factors such as clinical history, etiologic considerations, the degree of hearing loss and psychoacoustic measurements have not been linked to discomfort and the intensity of tinnitus in patients with hearing loss[4].

No correlation was identified between annoyance and tinnitus as measured by the tinnitus handicap inventory and the TEOEA or DPEOAE results.

No correlation was found between changes in the ABR and the level of anxiety and depression in tinnitus patients.

No correlation was found between the ABR changes and the tinnitus handicap results in the tinnitus patient group.

A correlation was identified between with degree of anxiety and/or depression as measured by the Beck anxiety index and depression scale (BAI/BDI).

Auditory brainstem short latency results, in patients with tinnitus and normal hearing compared with ABR results in normal hearing patients without tinnitus, demonstrated) a significantly prolonged latency of wave V in the study group when compared with the control group. The interpeak wave III-V latency was significantly ($p = 0.003$) enlarged in the study group when compared to control. Even though the average obtained in several analysed parameters were within normal limits the results in the study group differed from the control group suggesting changes in the brain stem auditory pathways. The significance of these changes must be further studied[5].

Reference was made to the report of long latency evoked auditory potentials studied in patients with tinnitus and/or hyperacusis who demonstrated altered latencies[6].

The altered latencies could be caused by different participation of the pre-frontal cortex (attention) and/or differences in sensibility (hyperacusis).

The mismatch negativity test (MMN) an objective method to quantify the central auditory process measures the temporal window of integration in the auditory perception[7].

Preliminary MMN testing results in patients with severe disabling tinnitus (SDT) and normal hearing were reported to demonstrate "altered pre-frontal cortex participation in the perception of the symptom (attention and habituation"). Further studies in this area were considered to be warranted since MMN seems to be able to objectively access tinnitus changes in the central auditory processing of sound stimulation.

Current conclusions included:

1. Tinnitus seems to be triggered in outer hair cells;
2. Tinnitus annoyance level as measured by the tinnitus handicap index does not correlate with the extension of lesions in the outer hair cells as measured with the TEOAE and DPOAE nor with the ABR;
3. Correlation of tinnitus annoyance with depression levels and changes in latencies in MMN tests point to higher levels. In the CNS as modulators of tinnitus intensity and annoyance.

III. Tobias Kleinjung, M.D., PhD. PD Dr. med. Leitender Arzt ORL Klinik University Zurich, Department Otorhinolaryngology, Switzerland, presented "The neuronal network of tinnitus and its implication for therapy".

The presentation started with the clinical profile of a typical tinnitus patient, i.e. otologic examination satisfactory, associated sloping bilateral symmetrical sensorineural hearing loss, and fluctuation in the intensity, annoyance, characteristics of the tinnitus.

Historically, reference was made to past experience of persistence of the tinnitus following transection of the auditory nerve.

The question posed was where in the brain is the tinnitus located and what are its neuronal correlates? The highlights of functional changes identified for tinnitus in animal models in the central auditory system at levels of brainstem, mid brain and cortex were presented.

1. Increased spontaneous firing rates of neurons,
2. Increase in burst firing,
3. Alteration of the tonotopic organization and involvement of non auditory brain areas. These findings provide the beginning of an understanding of a biology for tinnitus.

Neuroimaging and tinnitus was reviewed as a correlation of site of lesion in brain over milliseconds to days when imaging at levels of:

1. Whole brain,
2. Region of interest,
3. Neuronal population,
4. Single neuron and
5. Synapse.

Of clinical interest and application for tinnitus are:

1. Functional brain imaging, electroencephalography (EEG) and quantitative electroencephalography (QEEG),
2. Nuclear medicine brain imaging (PET/SPECT).

The brain wave activities, i.e. oscillations, delta 1-4Hz, theta 4-7Hz, Alpha 8-12 Hz Beta 13-30Hz, gamma 30-100 + Hz were presented as the "dialectics" of the brain. The advantages to the tinnitus patient of EEG include spatiotemporal localization of underlying neuronal generators, i.e. source localization, by the measurement of spontaneous activity.

Tinnitus patients demonstrate less Alpha and more Delta power in temporal cortex areas as compared to normal controls[8].

Tinnitus patients with high distress have been identified with increased alpha in subcallosal anterior

cingulate, parahippocampal gyrus, amygdala, middle temporal gyrus. Reduced alpha was demonstrated in posterior cingulate gyrus and precuneus[9].

Stronger connectivity between auditory and non-auditory (frontal, ACC) regions in tinnitus patients compared to controls[10].

Gamma-Band activity correlates with tinnitus-loudness in the contralateral auditory cortex[11].

A correlational approach helps to identify brain areas involved in tinnitus[12].

Neurofeedback (NF) was presented at time, as a clinical application of QEEG for attempting tinnitus relief. NF is a type of biofeedback that has been used for attempting tinnitus relief in the past. At this time the results of a study were presented of NF, as compared to repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for tinnitus related distress. The technique used realtime displays of EEG to illustrate brain activity and teach self-regulation to focally increase alpha power, found to be reduced I tinnitus patients. Only neurofeedback resulted in a significant decrease in tinnitus symptoms and an increase in alpha power for right auditory regions[13].

Future projections included development of individual treatment programs of a combination of NF and rTMS.

IV. Guest of Honor: Leslie S. Prichep, PhD., Professor Psychiatry, Acting Director Brain Research Laboratories, New York University School of Medicine, NY.

Introduction

Over the last 3 decades her academic focus has been on exploration of the pathophysiology of psychiatric/neuropsychiatric disorders using quantitative electrophysiology. At the present time she is the Associate Director of the Brain Research Laboratories and Professor of Psychiatry (current), and a Research Scientist at the Nathan S. Kline Institute for Psychiatric Research of New York State (retired 2011). She has been recognized as one of the pioneers in the field of quantitative electrophysiology, lectured internationally on this topic, and has published extensively in the field of human electrophysiology, clinically applied research, source and localization. Dr. Prichep is responsible for the Direction of the largest existing database of electrophysiological data from normal subjects, patients with various psychiatric/neuropsychiatric disorders, patients with loss of consciousness (both anesthetically induced and from injury), chronic pain patients, and patients with traumatic brain injury and post-concussive syndrome, and tinnitus and pain.

Due to a personal issue Dr. Prichep was not able to attend as planned and extended her apology to the attendees. The following sections of her were presented by A. Shulman:

The title of the presentation was *"Functional brain Imaging* QEEG/LORETA *and Tinnitus Present and Future"*.

Signal processing advances over the past decade has exponentially expanded the information about cortical and subcortical sources of scalp recorded EEG data. Such methods have enabled the pathophysiology of neurological and neuropsychiatric disorders to be studied and better understood.

Studies of QEEG in chronic pain patients have demonstrated significant abnormalities in regions of the "Pain Matrix" as identified by other neuroimaging methods (e.g., fMRI, PET and SPECT), and shown a relationship to severity of pain reported.

Why look at QEEG in Patients with Tinnitus?

Quantitative electroencephalography (QEEG), a spectral analysis of the raw EEG data may be a significant addition to the objective diagnosis of tinnitus and the optimization of treatment, including:

1. Objective identification of the central component of the tinnitus complaint;
2. Identifying a potential "biomarker" of the presence of the condition;
3. Provide an objective measure of "severity", which can be used to evaluate efficacy of treatment;
4. Lead to better understanding of the pathophysiology of tinnitus using source localization of scalp recorded EEG data and
5. Identification of heterogeneity within the diagnosis which may lead to more optimal treatment.

In this presentation the term tinnitus refers to a predominantly central type subjective idiopathic tinnitus patients of the severe disabling type.

Studies of Quantitative electroencephalography (QEEG) in tinnitus patients has demonstrated clear central abnormalities in this group, and suggest both similarities and differences from the chronic pain population.

Neurometrics - EEG Data Acquisition & Neurometric Analysis

The technique of EEG Data Acquisition & Neurometric Analysis was reviewed.

Neurometrics is a statistical technique that evaluates quantitatively the electrical activity in brain by extracting from the different electrophysiologic phenomena a common metric of relative probability[14,15].

Source localization is an EEG analysis technique used to identify the mathematically most probable underlying sources of the scalp recorded data, for a given neuropsychiatric diagnosis (using very narrow frequency spectra), i.e. NEUROMETRIC method of EEG quantification. NEUROMETRIC QEEG Norms have been established.

Normative data exists for ages 6-90, have been published and demonstrated to be culture-fair and to have high test-retest reliability. The potential effct of age on changes observed in the EEG is removed by describing the individuals EEG features in terms of deviations from age expected normal values (using z-scores).

The anatomical accuracy of QEEG source localization has been repeatedly confirmed by coregistration with other brain imaging modalities e.g. fMRI[16], PET[17,18]; and CT[19].

Included in the Neurometric normative EEG data base is that different normative equations exist for EEG across the human lifespan. The ground state of the brain is regulated by an anatomically extensive, genetically based neuro-physiologic homeostatic regulating system. Disturbances in this system result in abnormal ties and must be considered in the evaluation of results of EEG recordings.

The complexity of the pain matrix was reviewed differentiating between neuroanatomic substrates which serve the sensory and sensory motor component of the pain, e.g. somatosensory cortices, posterior insula, and others which may serve the affective cognitive and memory (e.g. orbitofrontal cortex, anterior insula cortex and cingulate) components of pain. Source localization of EEG with functional neuroimaging, in a population of 70 chronic pain patients (age range 20-92 yrs).clearly demonstrated activation in many regions of the Pain Matrix with maximum abnormality in the theta frequency band.

Clinical research QEEG, LORETA- the tinnitus signal, tinnitus and pain - similarities, and differences--preliminary report.

The protocol and preliminary results of a Neurometric analysis of tinnitus were presented. The study included 124 tinnitus patients; mean age was 48.29 yrs. Mean length of symptoms was 2 yrs. Criteria for inclusion in this study was identification with the medical audiologic tinnitus protocol (MATTP) of a predominantly central type subjective idiopathic tinnitus of the severe disabling type. Exclusion criteria included a clinical history of known CNS/otologic disease.

Preliminary results were reported as: A) Differences between tinnitus and normal for the delta, theta, alpha and beta bands; and B) Differences between tinnitus and pain:

1. EEG Source images of significance of differences between a) tinnitus and normal controls in the Delta band; b) significant differences with all showing more activation in the pain population in the delta band including: cingulate (anterior, mid and posterior), and parietal lobule.
2. EEG Source images of significance of the differences between Tinnitus and normal controls in THETA. Maximum regions with over activation in the theta band included: Insula, SMA, Medial Frontal cortex, S1 and hippocampus. b) less activation than pain was seen in tinnitus patients in the anterior cingulate.
3. EEG Source images of significance of differences between Tinnitus and normal controls in the ALPHA band. Maximum regions with over activation in the Alpha band included: Insula, Anterior Cingulate, thalamus, and hippocampus. b) less activation than pain in the left parietal lobule.
4. EEG Source images of significance of the differences between a) tinnitus and normal controls in the BETA band. Maximum regions with over activation in the Beta band included: DLPFC, Insula, S1, Cingulate cortex (anterior, mid and posterior), medial frontal cortex, SMA and hippocampus. b) Differences between Tinnitus and chronic pain: the most significant differences were seen in the Beta frequency band. c) maximum regions of difference showed tinnitus patents to have more activation in many regions, including: DLPFC, S1, Inferior Parietal Lobule, Cingulate, Medial frontal cortex. SMA; d) in other frequency bands there were many more similarities than differences, suggesting shared pathophysiology of tinnitus and pain. e) one difference of note was seen in the theta band where chronic pain had significant involvement of the cingulate compared to the tinnitus population.
5. EEG Source images of significance for the for Tinnitus population for particular frequency bands include a) 8.2 Hz sources (alpha) and b)15.6 Hz source (beta).
6. Tinnitus vs Pain in Beta band. Most significant differences show more activation in Tinnitus in superior temporal gyrus and thalamus.

Preliminary Conclusions highlights include:

1. Using EEG source localization clear abnormalities can be seen in the Tinnitus population, supporting a central component of Tinnitus;
2. QEEG features could be used to objectively measure and quantify the presence of tinnitus as part of the diagnostic process;
3. Future investigations will explore the QEEG heterogeneity of the Tinnitus population for pathophysiological subtypes, which may be differentially treatment responsive;
4. The similarities between chronic pain and tinnitus suggest a common matrix for both

tinnitus and pain i.e a final common pathway which demonstrates the integration of brain function of sensory/affect and motor components united by the establishment of a memory for both;

5. EEG source localization provides an increased accuracy for the tinnitus diagnosis, a monitoring tool for objective determination efficacy of treatment;
6. Memory consolidation dynamic range for pain exceeds that for tinnitus;
7. Tinnitus is the pain of the auditory system;
8. The resolution of electrophysiology functional brain imaging exceeds that of nuclear medicine, and a correlation has been established between both;
9. Metabolism of each frequency band of brain wave activity is directly proportional to the degree of neuronal synchronization, i.e. beta > alpha > theta > delta;
10. EEG source localization for tinnitus, i.e. electroencephalotinnitography (EETG/ETG) in 2013-2014 is clinically considered to be analogous to the EKG for cardiology in the 1930s.

V. Abraham Shulman, M.D., F.A.C.S. presentation: "Electrophysiology and Tinnitus QEEG/LORETA Update Present/Future: The presentation was transcribed for inclusion into AAO-HNS - Academy U.

A. The goals included:

To introduce the attendees to quantitative electroencephalography (QEEG) and low frequency resolution electromagnetic tomography analysis (LORETA) functional brain imaging and its application for tinnitus diagnosis; and to objectively monitor treatment efficacy.

To present a case report of a cochlear implant soft failure (CISF) to demonstrate its application for tinnitus diagnosis and to monitor the clinical course of tinnitus and treatment efficacy;

To present preliminary data obtained with electroencephalography (QEEG) and low frequency resolution electromagnetic tomography analysis (LORETA) functional brain of the similarities and differences between tinnitus and normals and tinnitus and pain; and

To recommend to attendees inclusion of functional brain imaging QEEG/LORETA into the evaluation of a predominantly central type subjective idiopathic tinnitus of the severe disabling type.

B. The historical background of our initial and ongoing experience since 1999 at SUNY/DMC Department Otolaryngology with Brain Electrical Activity QEEG and Tinnitus, and specifically its application with Transcranial Magnetic Stimulation: (TMS) and electrical stimulation attempting tinnitus relief was briefly reviewed. Since 1979, we have attempted to objectivize the subjective tinnitus complaint. It is reflected in numerous publications which include the following:

The medical audiologic tinnitus patient protocol (MATPP) which included cochleovestibular testing and identification of correlates of cochleovestibular function[20]:

ABR short latency responses[21];

Electrical Stimulation tinnitus control[22,23];

Transcranial magnetic stimulation[24,25];

Quantitative Electroencephalography (QEEG) 1999[26,27].

Dept Physiology NYU Tinnitus masking paradigm Magnetoencephalography (MEG) 2002[28].

Low resolution electromagnetic tomography analysis (LORETA) - 2005 - Brain Research Lab NYU John R, Prichep L., Pasqual R

- 2006 - BRL NYU Vareta-N-61 - presentation
- 2006 - QEEG Power analysis - presentation
- 2007 - BRL NYU - TMS-case report - presentation
- 2013 - BRL NYU Identification of the tinnitus signal in a predominantly central type tinnitus of the severe disabling type; similarities/differences tinnitus/pain[29].

C. Functional Brain Imaging and tinnitus Case Report

Advances in functional brain imaging technology and understanding of the electrophysiology for both ear and brain have been translated for the tinnitus definition, tinnitus theory, and clinical applications for tinnitus diagnosis and treatment. Metabolic and electrophysiologic functional brain imaging respectively with PET/SPECT brain imaging and QEEG/LORETA analysis are establishing a neurobiology for all clinical types of tinnitus.

Tinnitus in the past was defined as a perception of sound unrelated to an external auditory stimulus. The definition reflected a sensorineural approach wit a focus on the ear (and brain)[30].

A new and updated definition for tinnitus is a conscious, abnormal, auditory percept reflecting a dyssynchrony in development of, or neural transmission within, the peripheral and central cochleovestibular system. The focus is on EAR AND central BRAIN functions of perception, consciousness; attention, concentration, cognition, learning, memory, affect-behavior, and psychomotor activity - all in the presence of the tinnitus signal[31].

The translation of the principle of sensory physiology of components of sensations, i.e. sensory, affect behavior and psychomotor for all clinical types of tinnitus provides an understanding that what is being seen with both nuclear medicine brain PET/Spect and

QEEG/LORETA functional brain imaging are respectively metabolic alterations in neuroanatomic substrates reflective of multiple brain functions in the presence of the tinnitus signal, and alterations in synchronous brain wave frequency bands reflective of multiple brain functions activated in response to the initial dysynchronous tinnitus signal[32].

The hypotheses of Thalamo cortical oscillation (TCO) and Thalamocortical Dysrhythmia (TCD) are significant for all clinical types of tinnitus. Thalamo cortical oscillation: It is a term to describe the synchronous firing and interaction that occurs between thalamic and cortical neurons at specific brain frequencies, delta. 5-4Hz, theta 3.5-7.5Hz, Alpha 8-12Hz, Beta 12-24Hz, and Gamma 25-39Hz. in the thalamocortical system. Thalamo cortical dysrhythmia: Is a pathophysiologic model of brain wave activity of brain function proposed for neurogenic pain, tinnitus, abnormal movements, epilepsy, and neuropsychiatric disorders. It is hypothesized that a lesion results in deafferentation of excitatory inputs on thalamic relay cells which initiates tinnitus.

It is hypothesized for tinnitus that the spontaneous and constant gamma band of hyperactivity causes tinnitus: "In a dafferented state the thalamocortical columns fire in a burst mode of 4-7Hz which results in a decrease of lateral inhibition in adjacent areas and a halo activity in the gamma band (> 30Hz) called the edge effect[33]".

Functional brain imaging was explained to include different technologies each of which provides a 3 dimensional display of different metrics of response. Specifically 1) Nuclear medicine brain positron emission tomography (PET) and single photon emission tomography (SPECT) reflects alterations in brain metabolism, direct and indirect; 2) Functional Magnetic resonance imaging fMRI- blood oxygen level dependent; and 3) Low frequency resolution electromagnetic tomography analysis (LORETA) EEG provides source localization of the scalp recorded brain wave activities and neuronal connectivity. Quantitative electroencephalography (QEEG) is a spectral analysis of the raw electrophysiologic data of the electroencephalogram. The bands of frequencies of response of different brain waves in brain are displayed in multimetric topographic maps, i.e. the QEEG topographic maps are hypothesized to reflect multiple brain functions. For the QEEG raw power was transformed into a Z score against a normative database from BRL/NYU corrected for age and other factors A QEEG power score with a value greater than +1.96 or less than -1.96 would significantly differ at the 0.05 level from the mean of the age adjusted norm, i.e. 2 SD -95% confidence level.

The QEEG provides an objective measure of band waves of activity for display in brain of the influence of modality (-ies) of treatment attempting tinnitus relief.

The basics of the EEG technique, definition of the power spectrum and relative power in EEG and the significance of Z scores was reviewed[34].

The clinical and research applicability of functional brain imaging, PET and QEEG alone and/or in combination was presented with a case report of CISF and preliminary results of a study of similarities/differences between brain wave activity in tinnitus patients and normals, and tinnitus and pain patients.

D. Case report-Cochlear implant soft failure (CISF):

The case report was presented of a 74 yo female tinnitus cochlear implant patient, who in May 2008 sought consultation for an increase in tinnitus intensity and reduction in hearing.

This case demonstrates how the application of functional brain imaging, both nuclear medicine imaging brain PET and QEEG/LORETA analysis, which respectively reflect metabolic and EEG power tomographic display of the data, increased the accuracy of the tinnitus diagnosis, provided a basis for tinnitus treatment, and a method to monitor the clinical course of the tinnitus with the cochlear implant On and Off - all-based on objective metabolic and EEG power data. The clinical problem was a) diagnosis: to determine objectively if the tinnitus complaint was a "soft" failure of the implanted cochlear implant; b) to provide tinnitus relief.

Briefly, the tinnitus was clinically diagnosed with a medical audiologic tinnitus patient protocol (MATPP) to be a predominantly central type severe disabling tinnitus ear rt.

Initially the integrity of the CI was confirmed with the manufacturer of the device. The data, metabolic and electrophysiologic, was clinically considered to 1) Support the hypotheses of TCO and TCD; 2) Neural plasticity in brain between thalamus and frontal cortex; and 3) increased asymmetric metabolic and brain wave activity with between thalamus and cortex rt > lt, with the cochlear implant #1 On, and lt > rt with the CI #1 OFF. A clinical correlation was established between the metabolic and electrophysiologic objective data, and the subjective report of the tinnitus intensity increase with electrical stimulation with the CI #1 On. The patient was recommended removal CI #1 and replacement with a new CI #2. The CI #1 was removed and replaced with CI #2 6/09. The patient reported improvement in hearing and tinnitus relief wit CI #2. Follow up functional brain imaging PET/QEEG 11/09 demonstrated thalamocortical activation bilateral, and no excessive brain wave activity bilateral for the delta/theta/alpha/and beta frequency bands. Clinically a homeostasis of auditory function was reestablished with the CI #2.

In summary, 1) Tinnitus in an implanted CI patient may be a soft sign of CISF; 2) Serial functional

brain imaging results, metabolic and electrophysiologic, pre and post CI #1 removal and replacement with CI #2, provided serial objective metabolic and electrophysiogic data to monitor the efficacy of electrical stimulation with the CI between the time of initial consultation 5/08 and replacement with CI #2 in 6/09, and clinical basis for supplemental pharmacological therapy for tinnitus relief.

The PET brain and QEEG/LORETA images are available for review in Academy U. A publication is in preparation.

This case report clinically supports the significance of both functional brain imaging, both metabolic and EEG power based QEEG/LORETA. It is recommended: 1) Functional brain imaging, both metabolic and EEG power based QEEG/LORETA inclusion in selected cases of suspected CISF; and 2) The routine inclusion in the medical audiologic evaluation of a predominantly central type subjective idiopathic tinnitus of the severe disabling type.

Clinical research: Similarities/Differences Tinnitus normals/Pain

Preliminary results with QEEG/LORETA were presented of a study of 124 patients with a diagnosis of a predominantly central type subjective idiopathic tinnitus of the severe disabling type to establish differences between: 1) Tinnitus and the Neurometric normative database and 2) Differences between tinnitus and the pain matrix in brain.

EEG Source images were presented of the significance of differences between Tinnitus and normal controls in the THETA, Alpha, Beta band.

In other frequency bands there were many more similarities than differences, suggesting shared pathophysiology.

One difference of note was seen in the theta band where chronic pain had significant involvement of the cingulate compared to the tinnitus population.

E. Future for the tinnitus patient:

The future for tinnitus patients includes

1. Identification of the neurobiology, neuro biophysiology, and neurochemistry of synaptic neurotransmission for all clinical types/subtypes of tinnitus.
2. Molecular neuroimaging.
3. Source localization brain Stage 2 BRL - NYU - functional neuroimaging QEEG/LORETA - identification subtypes of a predominantly central type subjective idiopathic tinnitus of the severe disabling type.
4. Tinnitopharmacoproteogenomics/Tinnitopharmacology - the development of a pharmacology, individual, specific, and personalized for each tinnitus patient.
5. Surgery (Non Invasive transcranial MR guided high intensity focused ultrasound (tcMRgHIFU) utilizing source localization for tinnitus relief for a predominantly central type tinnitus[35].

F. Take Home messages:

The take home messages to attendees included the following

1. Tinnitus and the CI - its initiation and or increase - clinical consideration “soft” CI failure - Fulfills criteria consensus statement - “device malfunction is suspected but cannot be proven[36]”.
2. Outcomes evaluation for CI should include objective data reflecting brain function, i.e. Functional brain imaging metabolic PETCT brain, electrophysiology QEEG,
3. QEEG provides an objective evaluation of low frequency brain activity in the presence of the tinnitus signal for tinnitus diagnosis, treatment and monitor of efficacy of treatment.
4. Pet Data reflects the cytoarchitecture of the multiplicity of brain functions in the presence of the tinnitus signal (e.g. frontal, temporal, parietal, thalamus).
5. TCO proposed as a mechanism at cortex for tinnitus perception and is supported in this case report by PET brain nuclear medicine imaging and QEEG to improve the accuracy of the tinnitus diagnosis and provide a monitor function for treatment efficacy of the cochlear implant (CI).
6. Visualization methods of neuroanatomical regions that are the probable source generators in brain of changes in surface EEG activity are clinically reflective of the clinical course of the tinnitus and response to treatment.
7. QEEG provides an objective evaluation of low frequency brain activity in the presence of the tinnitus signal for tinnitus diagnosis, treatment and monitor of efficacy of treatment.
8. EEG source localization analysis identified clear abnormalities in the tinnitus population, supporting a central component for the tinnitus.
9. QEEG/LORETA recommended to objectively measure and quantify the presence of tinnitus as part of the diagnostic process in all predominantly central type subjective idiopathic tinnitus of the severe disabling type.
10. QEEG/LORETA identification of the pattern of the tinnitus signal by brain wave band (s) and frequency (ies) provide an electrophysiologic correlate for a predominantly central type tinnitus.

11. Significance - QEEG for otology and neurotology- clinically analogous to the introduction of the EKG in the 1930s for internal medicine and cardiology.

PRESENTATIONS EDITORIAL COMMENTS

1. Michael E Hoffer M.D.

Clinically, the P300 test may be of an increased significance when applied for a specific affective behavioral characteristic of the tinnitus patient for a specific clinical type of tinnitus, particularly of the severe disabling type. The heterogeneity of the tinnitus is one of the issues in the results with the P300 response reported in tinnitus patients.

2. Carlos P. Oliveira M.D.

ABR short latency results reported are similar to that reported initially in 1981[21].

The issue of heterogeneity of tinnitus and a need to identify the clinical type of tinnitus and parameter of tinnitus under investigation is demonstrated in the results reported in this excellent presentation with TEOAE, DPOAE ABR and MMN testing, i.e. clinically, a predominantly cochlear type tinnitus with a central component.

The associated complaints of tinnitus, anxiety and annoyance, are cortical brain functions. Significantly in this excellent presentation, central abnormalities were demonstrated with tests of electrophysiology of MMN and long (late) latency ABR recordings. The results provide a basis for recommendation for inclusion of these tests on an individual basis to provide objective data to improve the accuracy of the tinnitus diagnosis and evaluation of the efficacy of tinnitus treatment for these associated complaints.

Translation of the principle of sensory physiology of components of a sensation for tinnitus, i.e. sensory, affect and psychomotor is recommended to be specified for research investigations and to be combined with the diagnostic identification of the clinical type of tinnitus to avoid interpretation of negative results of investigations reflective in some degree to the heterogeneity of tinnitus.

Selection of a particular electrophysiologic testing modality for tinnitus is recommended to be based on the electrophysiologic site of lesion of the clinical type (e) of tinnitus and or associated complaint(s) under investigation.

3. Tobias Kleinjung, M.D., PhD.

To be considered in the interpretation of the brain wave activity at cortex is that they reflect not tinnitus but multiple brain functions in the presence of the tinnitus signal.

a) It is hypothesized that the development of a chronicity for tinnitus of all clinical types is reflected in the pattern of brain wave activities. Specifically an initial reduction in alpha followed by and or accompanied by an increase in delta. With increasing synchronization at cortex, over time, there is a maintenance of or increase in delta and beta. The significance of gamma - of different frequencies - remains to be established.
b) The underlying biophysiological process of neuromodulation is linked with Neuroplasticity and Neuro protection.

4. Leslie S Prichep, PhD; Abraham. Shulman, M.D.

QEEG provides an objective evaluation of low frequency brain activity in the presence of the tinnitus signal for tinnitus diagnosis, treatment and its translation to monitor efficacy of treatment.

Correlations in brain of activity in tinnitus and pain patients in multiple regions of interest have been reported between metabolic and electrophysiologic functional brain imaging

Similarities between chronic pain and tinnitus suggest the hypothesis of a final common pathway for tinnitus, pain and all sensations-aberrant/normal.

Otolaryngology and tinnitus professionals are recommended to introduce electrophysiologic functional imaging QEEG and LORETA to establish an accuracy for the tinnitus diagnosis, and to monitor efficacy of treatment modalities recommended for a predominantly central type severe disabling tinnitus.

The meeting was well attended until its conclusion.

We all look forward to the AAO HNS International Tinnitus Miniseminar 2014 Orlando, Fla September 21-24.

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