Critical Review: The use of tympanic electrocochleography in the identification of Ménière's disease: What protocol offers the best sensitivity and specificity for diagnosis?

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Tympanic electrocochleography (TM ECochG) is a widely used objective technique for identifying the presence of Ménière's disease. Traditionally, an elevated ratio between the amplitude of the summating potential and the action potential (the SP/AP ratio) from alternating polarity clicks has been used as an indicator for the presence of Ménière's disease. However, likely due to the fluctuating nature of Ménière's disease, this measure alone provides limited sensitivity (e.g., Kim, Kumar, Battista, & Wiet, 2005). A number of approaches and analysis techniques have been proposed in the literature to be used in conjunction with the SP/AP amplitude ratio in order to improve the sensitivity and specificity of the electrocochleogram (see bibliography). However, there is need for greater consensus on what evidence-based protocol might be used in clinical practice.

Introduction

Ménière's disease (MD) is a vestibular disorder that is associated with symptoms including episodic vertigo, fluctuating hearing loss, aural fullness, and tinnitus, occurring in one or both ears. MD is idiopathic in nature, but is thought to be closely linked to endolymphatic hydrops (EH), which results from an excess of fluid (endolymph) in the inner ear (Vestibular Disorders Association, 2011). Given the strong association between MD and the presence of EH, the two terms will be used in combination (MD/EH) for the purposes of this critical review.

Electrocochleography (ECochG) is an objective approach for recording cochlear and auditory nerve potentials. A click stimulus is typically used to generate a response with ECochG (Ferraro & Durrant, 2006). The response typically occurs within 1-3 msec of the stimulus onset, making the response from ECochG an early-latency auditory evoked potential (AEP). ECochG recordings contain three major elements: the cochlear microphonic (CM), the cochlear summating potential (SP) and the auditory nerve action potential (AP; Margolis, Rieks, Fournier, & Levine, 1995). Given the capacity of ECochG to record cochlear and auditory nerve potentials in such close proximity to the actual generators, it has long been examined as a potential objective technique for assessing and monitoring the progression of MD/EH. Several recording techniques and analysis approaches for the detection of MD/EH have been evaluated in the literature. However, a consensus on an optimal clinical approach for identifying MD/EH has not yet emerged from the literature, and there continues to be considerable debate among researchers. This lack of agreement may be due, at least in part, to the inherent complexities of Ménière's disease. Its fluctuating nature, in addition to the fact that it typically involves damage to both auditory and vestibular structures, contributes to the considerable variability that can be seen both within and across individuals with MD/EH.

The most commonly used analysis technique for ECochG involves an examination of the ratio between the magnitude of the summating potential and the action potential (SP/AP). It is believed that the increase in endolymphatic fluid resulting from EH may introduce nonlinearities during transduction. The SP is sensitive to these distortions, and there is a considerable body of evidence demonstrating a tendency for patients with MD/EH to have abnormally elevated SP amplitudes (e.g., Levine, Margolis, Fournier, & Winzenburg, 1992). An enlarged SP/AP ratio is typically used to indicate MD/EH rather than the SP amplitude alone because the SP/AP amplitude ratio tends to have better consistency when a click stimulus is used (Ferraro & Durrant, 2006). The SP/AP ratio has a high level of specificity for MD/EH. However, the sensitivity of the ratio has been called into question in a number of investigations (e.g., Kim, Kumar, Battista, & Wiet, 2005). Typically, the sensitivity of the SP/AP ratio for detecting ECochG ranges from approximately 55% to 65% across the available literature, but has been even lower in some investigations (Ferraro & Durrant).

Ultimately, the SP/AP amplitude ratio alone does not provide adequate sensitivity for the correct identification of patients with MD/EH on a consistent basis. As such, other interpretation approaches have been proposed for improving the sensitivity of the ECochG. The clinical utility of analyzing the latency difference between rarefaction (RAR) and condensation (CON) click-evoked action potentials is one approach that has been examined in the literature (e.g., Levine, Margolis, Fournier, & Winzenburg, 1992). Area measurements (using SP/AP ratio, total SP/AP area, and SP area) have also been investigated using click stimuli (e.g., Al-momani, Ferraro, Gajewski, & Ator, 2009). The absolute SP amplitude for tone-burst stimuli has also been considered (e.g., Levine, Margolis, &

Daly, 1998). The available literature for these techniques has thus far failed to establish a gold standard approach for maximizing sensitivity and specificity. Due to the lack of consensus within the research community, a critical review of the literature examining the sensitivity of one (or a combination) of these techniques is necessary for determining the best method for identifying MD/EH.

An additional source of debate within the literature relates to the electrode placement used for the recording. With transtympanic (TT) ECochG, a myringotomy is performed to allow the needle electrode to pass through the tympanic membrane and rest on the cochlear promontory (Ferraro & Durrant, 2006). With extratympanic (ET) recordings, the electrode is placed against the skin of external auditory meatus. Tympanic (TM) ECochG is an additional extratympanic recording approach where the electrode is placed directly against the tympanic membrane. The waveforms generated through TT ECochG typically have a larger magnitude and are more reproducible (require less signal averaging) than the ET approaches. However, TT ECochG is far more invasive and must be performed by a physician (Ferraro & Durrant). ET and TM ECochG are of particular relevance to the practice of audiology because they can be performed by audiologists. For the present discussion, the diagnostic utility of different ECochG approaches will be analyzed for investigations using TM ECochG. As reviewed by Ferraro and Durrant, the TM ECochG approach provides an appropriate balance between accuracy (need for signal averaging) and invasiveness.

Objectives

The primary objective of this literature review is to analyze and critically examine the selected studies that have investigated approaches for maximizing the sensitivity and specificity of the ECochG for identifying MD/EH. The implications of using one or more of the reviewed analysis techniques will also be discussed, as well as clinical implications and potential future research directions.

Methods

Search Strategy

Electronic databases, including CINAHL, PubMed, MedLine, and Google Scholar were searched using the following key words: (Meniere's disease OR endolymphatic hydrops) AND (electrocochleography) AND (diagnosis OR assessment OR identification). The search was limited to English-language peer-reviewed studies investigating human participants. The reference lists of the located articles were also examined for additional articles of relevance.

Selection Criteria

Studies included in this critical review were required to examine the diagnostic utility of one or more ECochG analysis techniques for MD/EH. Only the studies using TM ECochG were selected for further review. No limits were set on the analysis techniques used or the demographics of the participants.

Data Collection

A review of the literature yielded five original journal articles consistent with the criteria indicated previously. The retrieved articles included four non-randomized clinical cohort studies (two prospective cohort studies and two retrospective chart reviews) which constituted a level 2b of evidence according to the experimental design – decision tree. The final article was a case-series (post-test only), which provided a level 3 of evidence.

Results

Prospective Cohort Studies

Study #1: Levine, Margolis, Fournier, and Winzenburg (1992) used a prospective, non-randomized cohort study to investigate the use of TM ECochG in the evaluation of EH. Two groups of patients were included: a control group consisting of 13 normal hearing individuals with no symptoms of MD, and a group of 66 patients (120 ears) presenting with one or more symptoms associated with MD. The ECochG response patterns for the normal subjects were analyzed to develop normative data for ECochG amplitude and latencies. Based on the normal response patterns, appropriate cutoffs were determined for the different analyses. The upper cutoff range of normal for the SP/AP amplitude ratio was determined using a 95^{th} percentile criterion (mean + 2SD; SP/AP>0.42 is abnormal), while the upper cutoff for the AP latency difference between rarefaction (RAR) and condensation (CON) clicks was set at 0.3 msec (mean + 3 SD, >0.3 msec is abnormal). When the SP amplitude was measured using a response to a 1-kHz tone-burst, a criterion of - 0.8 μv was used (SP < - 0.8 μv is abnormal, mean – 3 SD).

TM ECochG was also performed on the patients exhibiting MD symptoms. A case presentation format was used to illustrate the abnormal patterns of results in comparison to the normal response. For each of the main tests (SP/AP ratio, AP latency difference, SP amplitude for 1-kHz tone burst), the results indicated the percentage of cases where complete test results were obtained, in addition to the proportion of tests that

were abnormal according to the presented criteria. An SP/AP ratio was obtained for only 73% of the patients tested, while the 1-kHz tone-burst SP magnitude and the AP latency differences were obtained in 93% and 89% of the patients, respectively. The percentage of patients displaying abnormal results for the SP/AP ratio, SP amplitude for 1-kHz tone-burst, and AP latency difference was approximately 15%, 10%, and 35%, respectively.

Study #2: A later investigation by Levine, Margolis, and Daly (1998) provided a far-less optimistic view of the utility of TM ECochG in the diagnosis of MD. They evaluated the diagnostic value of TM ECochG using an existing diagnostic framework, which categorizes patients with MD into levels based on the severity of hearing loss, rather than the level of confidence in the diagnosis based on the patient's symptoms (i.e. certain, definite, probable, possible). Levine and colleagues used the click-evoked SP/AP amplitude ratio and AP latency difference between RAR and CON clicks, as well as the absolute SP amplitude for 1- and 2-kHz tone-bursts to evaluate 199 subjects (127 females, 72 males) suspected of having MD/EH. A variety of age categories were represented in the distribution of patients. Audiometric thresholds were also obtained for each patient. The inclusion criteria stipulated that the patient must have "some" of the common symptoms associated with MD/EH.

Averages for the different analyses were obtained for both affected and unaffected ears in the patients suspected of having MD/EH, and a two-tailed paired Student's t test was performed to compare the values. The results showed a significant difference between affected and unaffected ears for both the SP/AP amplitude ratio and the absolute SP amplitude for a 1-kHz tone-burst. No significant difference was found between the affected and unaffected ears for the AP latency differences between RAR and CON clicks, or the SP amplitude for a 2-kHz tone-burst. In a separate evaluation, the increasing duration of time since the onset of symptoms was not significantly correlated with an increasing proportion of abnormal ECochGs or abnormal 500Hz thresholds. In addition, chi-squared analysis revealed that the percentage of abnormal ECochGs did not increase according to the number of presenting symptoms of the patients. Moreover, the percentage of abnormal ECochGs did not significantly increase with increasing hearing loss of the patient (thought to indicate severity). Most discouragingly, only 28% of the patients with the four main symptoms associated with MD/EH had abnormal ECochG findings. Ultimately, Levine and colleagues (1998) concluded that TM ECochG is unhelpful in the diagnosis of MD/EH.

Case-Series (Post-Test Only)

Study #3: The aim of the investigation by Margolis, Rieks, Fournier, and Levine (1995) was to establish normative data for the ECochG responses to click and tone-burst stimuli. TM ECochG was performed on 53 subjects (34 female, 19 male). All participants were evaluated and found to have normal hearing levels and no symptoms of MD/EH.

Based on the normative data, test criteria for the SP/AP amplitude ratio, RAR-CON click-evoked AP latency difference, and SP amplitude for tone-burst stimuli (1- and 2-kHz) were created using 95% confidence intervals. Each of the conditions was presented at minimally two intensity levels in order to examine the optimal testing intensity for normal individuals. A chart was provided indicating the mean, standard deviation, 95^{th} percentile, and critical difference values of each of the analysis conditions across the tested stimulus levels. A cutoff criterion between 0.4 and 0.49 (depending on stimulus intensity) was suggested for evaluating the SP/AP ratio. For the AP latency difference, the cutoff criterion suggested was 0.38 to 0.74. For tone-burst stimuli, the SP amplitude cutoff was -1.78 to -1.35 for 1-kHz stimuli, and -2.25 to -1.32 for 2-kHz stimuli. Test-retest reliability co-efficients were provided using a similar chart. Higher test-retest reliability was associated with higher stimulus intensities. Through a working-model and a variety of case reports, Margolis et al. (1995) provided a qualitative illustration of the utility of their collected data.

Retrospective Chart Reviews

Study #4: The investigation by Kim, Kumar, Battista, and Wiet (2005) reviewed the TM ECochG results of 97 patients with definite (n = 60), probable (n = 5), or possible (n = 32) MD/EH, retrospectively. The inclusion criteria for each category were quite strict, such that even those in the possible MD/EH category had experienced episodic vertigo or hearing loss in combination with disequilibrium. The SP/AP amplitude ratio was calculated for each patient, and ratios exceeding 0.4 were considered abnormal. For analysis, the probable and possible MD/EH categories were combined to create a "less than definite" group. The analysis did not reveal a statistically significant difference between the proportion of patients with elevated SP/AP amplitude ratios in the definite and less than definite MD/EH categories, with sensitivity values of 66% and 53%, respectively.

The SP/AP ratios of the definite MD/EH patients were also examined to determine the proportion of patients with elevated ratios across the different stages of MD/EH, based on an audiometric four-tone average. The results revealed that patients in stage three (four-

tone average between 41-70 dB HL) were significantly less likely to have an elevated SP/AP amplitude ratio, compared to stage one and two (four-tone average 0-40 dB HL).

Study #5: The investigation by Al-momani, Ferraro, Gajewski, and Ator (2009) measured the amplitudes and areas of the SP and AP complexes using alternating polarity clicks in order to calculate both the SP/AP amplitude and area ratios. The AP latency difference between RAR and CON clicks was also investigated, as well as the SP amplitude for 1- and 2-kHz tone-bursts. The goal was to retrospectively evaluate several evaluation approaches, in order to arrive at an evidence-based protocol that provides optimal sensitivity and specificity for the identification of MD/EH using TM ECochG. Two groups of patients were included: a control group consisting of 20 normal hearing individuals with no symptoms of MD, and a group of 178 patients who were referred to an otolaryngology clinic because they presented with symptoms of MD/EH. The experimental subjects were further subdivided based on whether or not they had been given an actual MD diagnosis (MD or NMD), with the MD subjects having demonstrated additional red flags for MD/EH.

An analysis of variance (ANOVA) was performed to compare the means for the TM ECochG analysis techniques across the three groups investigated: the control group, and the two experimental groups (MD and NMD). Interestingly, while significant differences were found between the control group and the experimental groups (MD and NMD) for a variety of parameters (i.e., SP and AP amplitudes, SP/AP amplitude ratio, SP area, AP area, and SP/AP area ratio; all click-evoked), the results for two of the more commonly tested parameters (i.e., AP latency differences between RAR and CON clicks and SP amplitudes for tone-burst stimuli) were not significant. Of the parameters investigated, the SP area and AP/AP area ratio had the largest amount of statistical power. Post-hoc analyses revealed no statistically significant difference between the NMD and the control group for any of the parameters. However, the MD group was significantly different from both the NMD group and the control group. A logistic regression analysis revealed that the click-evoked SP amplitude, SP area, SP/AP area ratio, and the total area of the SP and AP had the largest impact on sensitivity and specificity of TM ECochG for MD/EH identification. Sensitivity and specificity ratings for the proposed protocol were also determined to reinforce the utility of the suggested approach. Using the proposed protocol, a sensitivity of 92% and a specificity of 84% was achieved.

Discussion

The investigation by Levine, Margolis, Fournier, and Winzenburg (1992) provided an important contribution to the evaluation of EH using TM ECochG. The majority of the research on ECochG techniques for assessing MD/EH thus far has focused on TT ECochG. By establishing normative data for a variety of analysis techniques for the lesser-researched TM ECochG, the data from Levine and colleagues provides some necessary guidelines for clinicians wishing to expand their analyses beyond the SP/AP amplitude ratio. Unfortunately, the sample size used to create the normative values was not adequate for the intended purpose. Without a minimum sample-size of 30, it cannot be assumed that the sample used was normally distributed. This limits the extent to which we can accept the normative criteria presented.

In the analysis of the possible MD patients, Levine and colleagues (1992) wisely chose to examine the percentage of cases where an interpretation was possible for each analysis approach. This consideration is not always investigated in the literature, but is highly clinically relevant. The finding that the SP/AP ratios could not be determined in nearly 30% of the patients evaluated reinforces the suggestion that the SP/AP ratio alone is not sufficient for assessing MD/EH. The proportion of patients with abnormal findings was quite low for all three tests. This was likely due to the exceedingly broad inclusion criteria utilized by Levine and colleagues, which only required that each subject display one or more symptoms of MD/EH. With so few restrictions placed within the inclusion criteria, it is impossible to estimate the percentage of the subjects tested that likely suffer from MD. As such, calculations of sensitivity and specificity for the different analyses would be unhelpful. However, Levine and colleagues achieved a conceptual breakdown of the patterns of abnormal results that can present themselves, which is nevertheless a useful, albeit qualitative, illustration for those in clinical practice. The high proportion of abnormal results for the AP latency difference analysis is promising, though the difference may not be the result of MD/EH (many of the possible MD patients presented with hearing loss, while the normal subjects all had normal hearing). Ultimately, the level of evidence for this study must be downgraded to a low-moderate level, in favour of other non-randomized clinical trials that present sufficient sample sizes and/or usable clinical protocols.

The investigation by Levine, Margolis, and Daly (1998) presented some important considerations for evaluating the diagnostic utility of TM ECochG for MD/EH that had not been considered previously. Ultimately, the results lead to questions about the value of using TM ECochG for evaluating MD/EH, and also indirectly

reinforced many of the complexities of MD/EH that are not always acknowledged in the literature. However, some of the inferences made from the data may have been premature; the aforementioned complexities of MD/EH were ultimately over-simplified despite efforts to address them within the investigation. For example, the decision to evaluate analysis techniques by comparing the results between affected and unaffected ears does not acknowledge the fact that unilateral MD/EH can subsequently extend to the other ear, becoming bilateral over time. The absence of symptoms in the unaffected ear does not necessarily mean that MD/EH is not present. Also, the inclusion criteria were vague, allowing patients with "some" symptoms of MD/EH to be included in the analysis. In fact, 38% of the ears included in the "affected" group presented with zero or one symptoms of MD/EH. Moreover, the inclusion criteria allowed some potentially misleading symptoms. For example, while vertigo is a characteristic symptom of patients with MD/EH, the description of the symptom did not separate vertigo from other descriptions more characteristic of dizziness (e.g. lightheadedness). in addition, the acceptance of "hearing loss" as a symptom fails to acknowledge the characteristic fluctuating nature of the typical hearing loss seen in MD/EH, particularly during the earlier stages. Thus, the finding that only 28% of patients with the four main symptoms for MD/EH had abnormal TM ECochG should be considered with caution.

Levine, Margolis, and Daly (1998) were ambitious in their attempts to represent the intricacies of MD/EH. However, they failed to acknowledge the major weaknesses of their study, which ultimately reduces the overall validity of their prospective cohort study to a moderate level.

The investigation by Margolis, Rieks, Fournier, and Levine (1995) provided well-needed normative data and cutoff criteria for identifying MD/EH using TM ECochG. Unlike previously mentioned investigations where the size of the normal groups were insufficient (e.g., Levine, Margolis, Fournier, and Winzenburg, 1992), the large number of subjects for this investigation was sufficient to assess normality. The inclusion of 95th percentile ratings and critical difference values for three common analysis approaches across more than one stimulus level provided future researchers with flexibility in the analysis of their data. However, as with any case-series, the level of evidence that can be derived from these results alone is very low. All of the subjects tested were grouped together and no manipulations were introduced.

Kim, Kumar, Battista, and Wiet (2005) aimed to differentiate definite from less-than-definite cases of MD/EH, as well as establish differences in the proportion of abnormal ECochG findings, depending on the patient's stage. The sensitivity of the measure was not statistically significantly different between the definite and less than definite MD/EH categories. However, as previously mentioned, the inclusion criteria used were strict enough that a large proportion of the patients in the less than definite category potentially had MD/EH. Thus, the determination that TM ECochG is not sensitive to MD/EH may be premature. Clearly investigators have a major challenge when it comes to determining appropriate inclusion criteria. Moreover, although 30% of patients in the definite category did not have abnormal electrocochleograms, the majority of them had later stages of MD/EH. These results suggest a need for further investigation into the presence of abnormal ECochG depending on the stage of MD/EH. The study by Kim, Kumar, Battista**,** and Wiet had fewer instances of bias compared to the previously mentioned cohort studies, and therefore represents a moderate level of evidence, despite the questionable inclusion criteria used for the study.

The investigation by Al-momani, Ferraro, Gajewski, and Ator (2009) is an important contribution to the available literature. It was carefully designed to include a number of statistical analyses that are helpful for interpretation, but which have often not been included in previous investigations (e.g., statistical power). It was also well-controlled within the confines of a cohort study (e.g., the Bonferroni correction was applied to account for the multiple comparisons). Through their design, Al-momani and colleagues also proposed an actual method, and made it possible to calculate the sensitivity and specificity values obtained with their approach. However, as with Levine, Margolis, Fournier, and Winzenburg (1992), the sample size for the normal group was not sufficient to assume a normal distribution.

Of the parameters investigated by Al-momani et al. (2009), the SP area and AP/AP area ratio had the largest amount of statistical power, suggesting that the inclusion of duration (part of the area measurement) may be beneficial in the identification of MD/EH. As acknowledged by the investigators, the increase in the sensitivity of TM ECochG for MD/EH identification occurred with an associated decrease in the specificity of the measure (compared to previous investigations). As such, presumably this protocol would be associated with a greater number of false-positives compared to some other available approaches. However, far more sufferers of MD/EH would be theoretically be identified using this approach, which is very encouraging.

Ultimately, the existence of an efficient and usable protocol that provides high levels of sensitivity and specificity for the identification of MD/EH is an ideal tool for clinical practice. However, given the insufficient sample size of the normal group, the level of evidence for this study must be downgraded from high to moderately-high.

Conclusions and Clinical Implications

The investigations included in this critical review have provided an excellent foundation for future research investigating the use of TM ECochG in the diagnosis of MD/EH. Inferences made based on these findings must be made with caution, however. As discussed, many of the reviewed studies had major limitations. Most were not designed in a way that generated reliable measurements of sensitivity and specificity, making it difficult to accurately evaluate the different techniques. Other studies failed to capture the inherent complexities of MD/EH in the study design. There is a clear need for more well-designed studies in this area so that a stronger body of evidence can be created. Moreover, there is a need for contributions from a larger group of researchers, since most of the articles discussed contained input from overlapping researchers.

Ultimately, the protocol presented by Al-momani, Ferraro, Gajewski, and Ator (2009) currently offers the best compromise between sensitivity and specificity for use in the identification of MD/EH, as well as the highest evaluated level of evidence. Al-momani and colleagues have provided an excellent model for future investigations. In future research, attempts should be made by other researchers (who may use different equipment, recording parameters, etc.) to replicate the results from the study, in order to further strengthen the validity of the protocol.

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