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Review

Idiopathic Sudden Sensorineural Hearing Loss: Should Otoacoustic Emissions Be Added to the Monitoring Protocol? A Systematic Review

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Abstract: Idiopathic sudden sensorineural hearing loss (ISSNHL) refers to a loss of hearing, most commonly unilateral, that occurs suddenly (≤72 h) with no identifiable cause or etiology. To date, there is no standard protocol to predict prognosis (hearing recovery) for patients with ISSNHL. However, studies have shown that changes in otoacoustic emissions (OAEs) often occur prior to changes in audiometric hearing thresholds. OAEs originate from the electrochemical motility of the outer hair cells (OHC) and reflect the integrity of the inner ear, specifically the cochlear amplifier. Therefore, OAEs may be useful as a prognostic predictive factor in patients with ISSNHL from the initial onset of symptoms through recovery. A systematic review of the literature was undertaken to assess the relationship between pure tone thresholds, OAEs, and subjective hearing improvement and/or recovery. Fourteen studies were identified for inclusion, and they overwhelmingly support the inclusion of OAEs in the protocol to monitor ISSNHL recovery. This finding supports the development of a standard diagnostic protocol that includes OAEs to predict patient hearing outcomes.

Keywords: idiopathic sudden sensorineural hearing loss; otoacoustic emissions; hearing; pure tone audiometry; hearing recovery

1. Introduction

Sensorineural hearing loss (SNHL) is defined as loss of sensitivity due to dysfunction in the cochlea or auditory nervous system, without comorbid dysfunction of the outer or middle ear systems. Sudden sensorineural hearing loss (SSNHL), also known as sudden deafness (SD), refers to a loss of hearing that occurs suddenly, either at once or within seventy-two hours or less. SSNHL is described as a hearing loss greater than or equal to 30 dB HL over at least three consecutive frequencies and is most commonly unilateral [1]. All audiometric configurations (flat, rising, sloping) have been reported in individuals with SSNHL [2]. Individuals with SSNHL may attribute their hearing loss to common conditions, such as allergies, a sinus infection, or occluding earwax, which may delay them from seeking medical treatment. It is recommended that SSNHL be considered a medical emergency and a visit to a medical professional should be a priority. Seeking treatment in a timely manner significantly increases the chance that a patient will recover at least some hearing, while postponing diagnosis may diminish the effectiveness of treatment. The National Institute of Deafness and other Communication Disorders (NIDCD), a member of the U.S. National Institutes of Health, notes that approximately half of patients with SSNHL regain some or all of their hearing spontaneously within one or two weeks of symptom onset [3].

The NIDCD reports that the prevalence of SSNHL occurs between one and six out of 5000 individuals per year, most commonly affecting adults in their late forties and early fifties [3]. Potential etiologies may

include viral/bacterial infections, head trauma, autoimmune disease, ototoxic medications, circulation issues, neurological disorders, and inner ear disorders. A definitive etiology is only found in about ten percent of SSNHL cases, with the majority having an unidentifiable etiology, otherwise known as *idiopathic* sudden sensorineural hearing loss (ISSNHL) [4].

The Massachusetts Eye and Ear Infirmary reports that a course of oral corticosteroids (prednisone or methylprednisone) is the standard treatment protocol for ISSNHL [5]. Steroids act to decrease swelling, while aiding the body in fighting illness in order to reduce overall inflammation. A typical course begins with a high initial dose followed by a taper over several days (e.g., 60 mg/day for 14 days followed by a five-day taper—50 mg, 40 mg, 30 mg, 20 mg, and 10 mg). This schedule is intended to create a balance between providing enough of the steroid to result in functional benefit without causing significant side effects. Administration of steroids should occur as soon as possible and is often recommended prior to receiving all test results, in the hopes of increasing effectiveness. Treatment that is delayed for more than two to four weeks is less effective in reversing permanent hearing loss [3].

Researchers at Massachusetts Eye and Ear Infirmary in 1980 reviewed the effectiveness of using a corticosteroid treatment for ISSNHL, and it has been widely used since. Over the past 15 years, administration of steroids through means of intratympanic injections (through the eardrum and into the middle ear space) has gained wider use, with the goal being to introduce a higher drug concentration to the ear while minimizing exposure elsewhere in the body. Other potential treatment options include antiviral medication, drugs to improve blood circulation, hyperbaric oxygen treatments, or gas inhalation. It is important to note that none of these alternative treatment options have been shown to be more effective than the standard treatment protocol of oral steroid administration. Timely and rapid treatment of ISSNHL with a tapered course of oral steroids has been correlated with an improvement in hearing in roughly 80% of patients [1,5]. Nearly all published studies have revealed a more positive outcome with earlier steroid treatment compared with delayed treatment.

Current monitoring protocols use behavioral audiometry to track detriment, stability, and improvement in hearing sensitivity during and after treatment for ISSNHL. However, studies using otoacoustic emissions (OAEs) [6] to track changes induced by high amplitude noise exposure [7] and ototoxic medications [8] have shown significant changes in OAEs, often occur prior to changes in audiometric hearing thresholds. Therefore, OAEs may be a useful prognostic predictive factor of hearing improvement in patients with ISSNHL from initial onset of symptoms through recovery.

OAEs are a low-level sound emitted by the inner ear either spontaneously or in response to an auditory stimulus as a byproduct of typically active cochlear amplification [6]. OAEs are closely associated with function of cochlear outer hair cells (OHCs) and reflect the integrity of the cochlea. Present OAEs denote that OHC function is normal or near-normal, which is often associated with normal to near-normal peripheral auditory function or hearing. When OAEs are present with known abnormal peripheral auditory function or hearing loss, this means that the OHCs are functioning and are not the main cause of the recorded hearing loss (e.g., inner hair cell loss, auditory neuropathy). Successful measurement of OAEs is also dependent upon a healthy middle ear system; middle ear dysfunction interferes with the measurement of OAEs by reducing the eliciting stimuli amplitude (when evoked) and attenuating the emission travelling through the middle ear to be recorded in the ear canal (see Zhao et al. for a review [9]).

Distortion product otoacoustic emissions (DPOAEs) are elicited by two simultaneous tones at closely spaced frequencies. DPOAEs may be used to evaluate both passive and active cochlear processing to determine auditory function. Active cochlear amplification is elicited with moderate intensity stimuli (e.g., 65, 55 dB SPL). Passive cochlear amplification is elicited with a stimulus of ≥70 dB SPL and is not dependent on the somatic motility of the OHC [10]. DPOAEs can be recorded in individuals with a mild to moderate hearing loss (thresholds of 40–50 dB HL), making them clinically useful for monitoring even those with mild to moderate cochlear dysfunction [11,12]. Transient evoked otoacoustic emissions (TEOAEs) utilize short duration stimuli to evoke a response, such as clicks or tonebursts. They are typically absent if pure tone thresholds exceed 30 dB HL [6], and thus are

clinically useful as a screening tool and in conjunction with DPOAE to characterize OHC health. Lastly, and unlike DPOAEs and TEOAEs, spontaneous otoacoustic emissions (SOAEs) are sounds emitted from the ear canal that occur without an evoking external stimulus. There are two main theories behind the origin of SOAEs, the global standing wave theory (GST) and local oscillator theory (LOT) [13]. GST suggests that the traveling wave of the basilar membrane between the stapes and cochlear duct creates reflections coupled to a standing wave; in turn, the standing wave vibrates the stapes and is transmitted into the ear canal via backward transmission [14,15]; LOT suggests the emission may be a result of instabilities of OHCs generating sinusoidal oscillations, without being coupled to a standing wave [16]. They are measurable in ~80% of ears with clinically normal hearing [17], but their absence is not an indicator of dysfunction. OAEs are highly reproducible, have high test–retest reliability, and have temporal/spectral properties that are unique to each individual [6]. They can be performed non-invasively, rapidly, and without the need for reliable behavioral responses [6].

A systematic review of the literature was undertaken to determine if hearing professionals should routinely include otoacoustic emissions in monitoring protocols for ISSNHL. More specifically, does the presence/absence and/or change in OAE characteristics improve clinicians' ability to predict long-term prognosis, that is, hearing recovery? Given that OAEs can objectively measure cochlear function, we predicted that evidence would support the use of OAE to track ISSNHL disease course and recovery.

2. Materials and Methods

2.1. Inclusion Time Period

This systematic review included studies published between the years of 1993 and 2018. The majority of the studies measured otoacoustic emissions using the ILO88 and/or ILO92 Analyzers [18], one study used the GSI-60 System [19], and one other used the Madsen Capella system [20] to measure DPOAEs and TEOAEs. Three articles did not report the equipment used; therefore, it was assumed they used similar equipment or non-commercially available systems. The release dates of the equipment correlate with the time frame of the studies included.

2.2. Search Strategy

A systematic search of records was accomplished utilizing five databases: PubMed, CINAHL Complete, Scopus, MEDLINE, and Google Scholar. The search queries were as follows:

1. (otoacoustic emissions) AND (sudden hearing loss)
2. (OAE) AND (sudden hearing loss)
3. (otoacoustic emissions) AND (sudden deafness)

The initial search yielded 341 studies; these studies' reference lists were examined, which identified an additional 28 studies. Each record's title and abstract were screened and subjected to inclusion criteria, summarized in Table 1, and duplicates were removed, yielding 43 studies. These 43 studies were read in their entirety, with an additional 29 excluded owing to language, population, diagnosis, or measurements used. Fourteen studies met all inclusion criteria and will be discussed. The selection of records was supported by the following resource, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement* [21]. Figure 1 summarizes the comprehensive search process.

2.3. Selection Criteria

Initially, the identified record titles and abstracts were screened to determine relevancy. The records that passed the preliminary screen were read in their entirety to classify the inclusion and exclusion criteria (Table 1). Briefly, inclusion criteria were as follows: diagnosis of idiopathic sudden sensorineural hearing loss, published in the English language, published on or after 1990, published in peer-reviewed sources, utilized OAEs (DPOAEs, TEOAEs, and/or SOAEs) as the primary physiologic outcome measure, and pure tone audiometry as the primary behavioral outcome measure.

Table 1. Study inclusion and exclusion criteria. DPOAE, distortion product otoacoustic emissions; TEOAE, transient evoked otoacoustic emission.

Variable	Inclusion	Exclusion
Population	10–86 years (mean 47.2)	
Language	English	All other languages
Publication Date	1991–2018	
Diagnostic Methods	Evoked otoacoustic emissions Pure tone audiometry	Did not include evoked otoacoustic emissions and pure tone audiometry
Report Type	Published in peer-reviewed sources, meta-analyses, randomized controlled trials, cohort studies, case control, cross-sectional studies, retrospective studies, and prospective studies	Theoretical papers, opinion-based editorials, reviews, qualitative studies, case studies, records with no statistical data reported, theses, and dissertations
Diagnosis	*Idiopathic* sudden sensorineural hearing loss (ISSNHL)	Sudden sensorineural hearing loss (SSNHL) with a known cause
Physiologic Measurements	Otoacoustic emissions (DPOAEs, TEOAEs, and SOAEs), Auditory Brainstem Response (ABR(, and Vestibular Evoked Myogenic Potential (VEMP(	
Behavioral Measurements	Pure tone audiometry thresholds; pure tone average (PTA)	

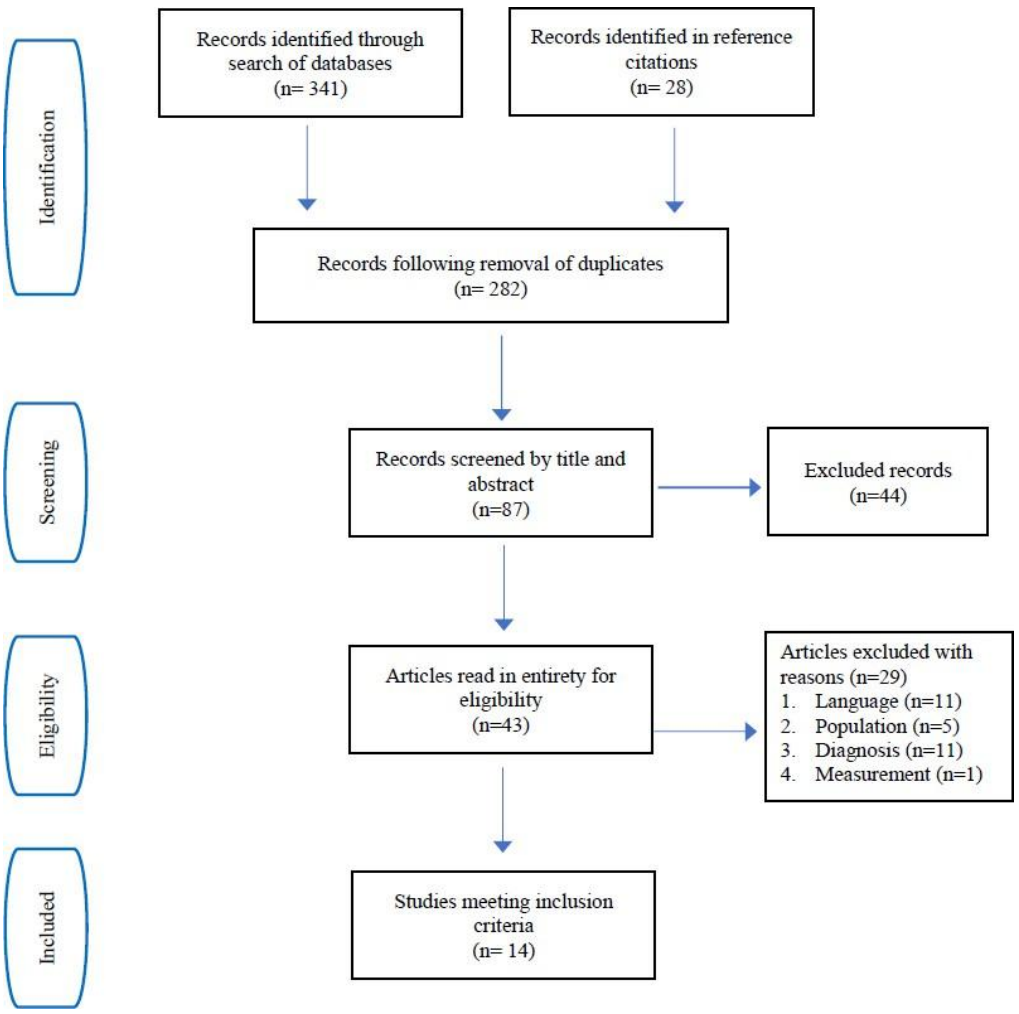

Figure 1. Comprehensive search process to identify included studies.

2.4. Level of Evidence and Quality Assessment

Each study meeting inclusion criteria was individually assigned a level of evidence and study quality. The level of evidence was identified according to the guidelines published by the Oxford Centre for Evidence-Based Medicine [22]. The fourteen included studies were each categorized as level 2c for outcomes research. The study quality was assigned using the protocol developed by the American Speech-Language Hearing Association (ASHA) National Center for Evidence-Based Practice in Communication Disorders. All studies that met the inclusion criteria received five points out of a possible nine for the following quality indicators: group/participant comparability, treatment fidelity, outcomes, significance, and intent to treat.

2.5. Data Synthesis

The methods, outcome measures, and statistical reporting varied across the selected articles, which prevented the completion of a meta-analysis. The time from symptom onset to diagnosis of ISSNHL was not homogenous across studies; treatment type and duration varied, and monitoring type and schedules differed. Data were summarized in tables and a narrative synthesis was completed to assess whether clinical use of OAEs should be recommended when attempting to predict prognosis in cases of ISSNHL. More specifically, we identified if the authors supported or rejected the use of OAEs as a prognostic indicator for this patient population, and whether they should ultimately be implemented into an ISSNHL monitoring protocol.

3. Results

Owing to its unknown etiology, a tapered course of oral corticosteroids is the primary means of treatment for ISSNHL. This systematic review focused on the use of OAEs as a clinical diagnostic tool for predicting hearing improvement in patients with ISSNHL, as changes in OAEs often precede changes in audiometric thresholds. Fourteen studies met the inclusion criteria found in Table 1. Table 2 summarizes patient characteristics across the articles, including the number of patients included (N), age range and mean, and gender. All fourteen studies included in this review reported physiological and behavioral results. All but four studies reported that these measurements were conducted in a sound proof or sound-attenuated booth. On the basis of this information, we presume the environments were similar for all patients across all studies. In all but three articles, patients were treated with a form of corticosteroid either alone or in combination with other treatment methods.

Table 2. Patient characteristics.

Authors	N	Age in Years (Mean)	Gender M/F
Bashiruddin et al. (2018) [23]	22	≥18 (NR *)	13/9
Canale & Lacilla (2005) [24]	20	19–77 (44)	9/11
Chao & Chen (2006) [25]	108	10–86 (45)	48/60
Chao & Chen (2010) [26]	200	10–86 (46)	98/102
Hoth (2005) [27]	25	20–73 (41)	15/10
Ishida et al. (2008) [28]	16	Group A: 18–58 (39.6) Group B: 35–57 (48)	10/6
Lalaki et al. (2001) [29]	30	NR	NR
Mori et al. (2011) [30]	78	16–80 (62.9)	42/36 W
Nakamura, et al. (1997) [4]	15	19–71 (50.8)	8/7
Nemati et al. (2011) [31]	26	25.3–55.8 (40.5)	16/10
Park et al. (2010) [32]	33	16–66 (38)	17/16
Schweinfurth et al. (1997) [33]	10	21–86 (51)	NR
Shupak et al. (2014) [34]	15	41.4–73.8 (57.6)	11/4
Truy et al. (1993) [35]	24	15–67 (41.25)	10/14

* NR = not reported.

3.1. Physiologic Measures

3.1.1. Distortion Product Otoacoustic Emissions

Twelve of fourteen included studies used DPOAEs as a physiologic outcome measure. At a minimum, these studies analyzed DPOAEs at frequencies between 1000 to 3000 Hz before and after treatment. Combined, five of the fourteen articles assessed DPOAE measures at octave and inter-octave frequencies from 500 to 12,000 Hz; the remaining six articles evaluated DPOAE between 500 and 6000 Hz (see Table 3).

Table 3. Monitoring procedures used by included studies. SOAE, spontaneous otoacoustic emissions.

Article	Monitoring Measurements	Monitoring Schedule
Bashiruddin et al. (2018) [36]	DPOAEs 500–12,000 Hz PTA	Before treatment and 15th day of treatment
Canale & Lacilla (2005) [24]	DPOAEs 1000–3000 Hz TEOAEs 500–5000 Hz SOAEs (present/absent) PTA	Before/after treatment
Chao & Chen (2006) [25]	DPOAEs 1093–5500 Hz PTA ABR VEMP	Every day for maximum of 7 days during hospital admission; every other week or monthly following discharge
Chao & Chen (2010) [26]	DPOAEs 1093–5500 Hz PTA ABR VEMP	Every day for maximum of 7 days during hospital admission; every other week or monthly following discharge
Hoth (2005) [27]	DPOAEs 1000–4000 Hz TEOAEs 1000–4000 Hz PTA	3–9 examinations (average) performed following symptom onset in intervals between 3 and 505 days (average of 53 days)
Ishida et al. (2008) [28]	DPOAEs 1000–6000 Hz PTA Tinnitus/Ear Fullness	Day of hospital admission and on a weekly basis until hearing stabilized
Lalaki, et al. (2001) [29]	TEOAEs 500–5600 Hz PTA	On admission, at least 2× during admission, 8–10 days after admission
Mori et al. (2011) [30]	DPOAEs 593–6031 Hz PTA	First hospital visit & one month post treatment
Nakamura, et al. (1997) [4]	DPOAEs 708–6299 Hz TEOAEs 1000–1500 Hz SOAEs 1000–6000 Hz PTA	Every 2–7 days during course of treatment

When reported, changes in DPOAE amplitudes were inversely related to increased pure tone thresholds [16–18,21]. More specifically, a hearing threshold increase of 20 dB corresponded with a 10 dB decrease in the DPOAE level, which agrees with other literature [18,21,26]. Larger DPOAE amplitudes within the first three days of ISSNHL onset were also shown to be a significant prognostic indicator for faster hearing improvement [16,17]. A better hearing prognosis was noted for those with a larger DPOAE emission shortly following acute damage, even with considerably elevated hearing thresholds [32].

Shupak and colleagues [28] reported that patients with detectable DPOAEs at the initial follow-up evaluation had a significantly higher average hearing improvement in comparison with patients with no measurable DPOAE response at first evaluation; the sensitivity and specificity of DPOAE ability to predict hearing improvement on the seventh day of follow up reached 83% and 100%, respectively [35]. Schweinfurth and colleagues found that three patients with intact DPOAEs upon presentation had an average improvement of 33 dB in their PTA at 500–2000 Hz in conjunction with steroid therapy, but, in contrast, five of seven patients with absent DPOAEs upon presentation had no improvement in hearing despite steroid therapy [35]. Park and colleagues reported that changes in DPOAEs and

hearing were associated with one another when the PTA was greater than 55 dB HL, however, the two were not correlated for patients with a PTA of less than 55 dB HL [34].

Hoth [33] recognized some exceptions to the above findings, in which emissions with small amplitudes were measurable in normal hearing ears and emissions with large amplitudes were noted in hearing impaired ears. Specifically, in some cases of ISSNHL, DPOAEs were more robust than expected from corresponding hearing thresholds at 1000, 1500, and 2000 Hz [28]. The authors speculated that, in these cases, the elevated hearing thresholds may be influenced by retrocochlear lesions, in addition to OHC damage [31].

Those patients that had the greatest change in DPOAE signal-to-noise ratio (SNR), at 8000 and 10,000 Hz, had the greatest changes in pure tone thresholds at those frequencies; however, no significant change was seen at 4000 and 6000 Hz for those individuals [28]. The authors noted these findings may reveal a greater impairment of cochlear cells at the mid frequencies in comparison with the higher frequencies [32]. On the other hand, it was found that the hearing improvement rate significantly correlated with DPOAE amplitudes at the f2 frequencies 3031 and 4812 Hz, but not at other f2 frequencies measured [24].

Two studies did not find a significant change in the mean overall DPOAE SNR and amplitude when comparing findings before and after treatment for patients with significant hearing recovery [15,22]. One study focused on the use of OAEs as a screening tool to predict recovery in specific cases of low frequency sensorineural hearing loss (LFNSHL) with no known etiology; the authors determined that the presence/absence of DPOAEs was not significantly correlated to prognosis following therapy for this specific patient population [4]. In this article, LFSNHL was considered to be ISSNHL that only affected low frequency hearing thresholds.

3.1.2. Transient Evoked Otoacoustic Emissions

Six of fourteen articles reported on transient evoked otoacoustic emissions (TEOAEs) as a physiologic outcome measure (see Table 3). At a minimum, all seven studies analyzed TEOAE measures at frequencies between 1000 to 4000 Hz, both before and after treatment. In combination, the seven articles assessed TEOAE measures at octave and interoctave frequencies of 500, 750, 1000, 2000, 4000, and 6000 Hz (see Table 3).

TEOAE measurements closely mirrored DPOAE results in patients with ISSNHL, as TEOAE amplitude was inversely related to increased pure tone threshold [18,21]. Lalaki and colleagues reported that approximately 61% of patients with recovered hearing had present TEOAEs or acceptable TEOAE peak amplitudes in at least some frequency bands at the first two measures, despite having thresholds worse than 40 dB HL [25]. Better hearing prognosis correlated with larger TEOAE amplitudes shortly following acute damage even in patients with worse hearing thresholds [1,18]. More specifically, Shupak and colleagues reported TEOAEs predicted significant improvement in hearing in 71% of patients and that a significantly larger number of patients with measurable TEOAEs at the second follow-up had hearing improvement of greater than 50% at at the three month follow up. [35]. Nemati and colleagues found a significant and positive change in the mean overall TEOAE SNR and reproducibility when comparing findings before and after treatment for patients with significant hearing recovery [35].

As with DPOAEs, Hoth [32] reported minimal exceptions to these findings, namely that small amplitude TEOAEs were measured in normal hearing ears and large amplitude TEOAEs were measured in hearing impaired ears. In some cases, TEOAEs were more robust than expected from corresponding hearing levels, specifically at 1000, 1500, and 2000 Hz [28].

Five out of the seven articles that assessed TEOAEs found them to be a significant prognostic indicator in cases of ISSNHL for predicting hearing improvement. Meanwhile, Truy et al. found the correlations to be too weak to recommend that TEOAEs could be clinically useful as a prognostic predictor in cases of ISSNHL [28]. Canale et al. reported that the majority of patients with present TEOAEs revealed greater hearing recovery; however, the findings were also too insignificant to suggest their usefulness in predicting prognosis in patients specifically with LFSNHL [36].

3.1.3. Spontaneous Evoked Otoacoustic Emissions

Two of fourteen articles monitored spontaneous evoked otoacoustic emissions (SOAEs) as a physiologic outcome measure for hearing recovery. SOAEs were measurable in four of fifteen cases when hearing thresholds returned to normal or a level of 25 dB or better; therefore, it was determined they are associated with normal ear function [25]. Canale et al. reported that SOAEs were recorded in only 20% of cases and never in patients with a pure tone average (PTA) worse than 37 dB. The presence/absence of SOAEs was not associated with PTA at 500, 1000, 2000, and 3000 Hz prior to therapy or with hearing outcome for ISSNHL affecting the low frequencies specifically [29].

3.2. Behavioral Measures

Pure Tone Audiometry

All fourteen articles included pure tone audiometry as their primary behavioral monitoring measurement. In combination, the authors obtained information regarding air conduction pure tone thresholds at octave and inter-octave frequencies between 125 and 12,000 Hz and at a minimum, before and after treatment. Bashiruddin et al. recognized a significant change in the average hearing thresholds across all octave and inter-octave frequencies from 250 to 10,000 Hz, with the exception of 12,000 Hz. The largest number of patients had hearing improvement at 2000, 3000, and 6000 Hz, whereas the lowest number of patients improved at 8000, 10,000, and 12,000 Hz [25]. The greatest PTA improvement was seen in the low to mid frequencies, with smaller improvements observed at high frequencies [29]. The authors noted that patients with poor hearing improvement tended to have absent OAEs and persistent tinnitus/aural fullness [29].

Furthermore, Chao and Chen [16,17] recognized that a PTA from 250 to 4000 Hz of greater than or equal to 65 dB was associated with a poorer hearing prognosis; however, they noted duration from onset to treatment could not be ruled out as a confounding factor [24,26]. Schweinfurth et al. noted an average improvement of 33 dB in the PTA from 500 to 2000 Hz in conjunction with steroid therapy, which was also associated with intact DPOAEs [27]. In contrast, Lalaki et al. reported no statistical difference in the initial PTA threshold between recovered and non-recovered patients [34]. Chao and Chen also discussed audiometric configurations in regards to prognosis. The authors recognized a poorer prognosis for patients who had absent responses at the limits of the audiometer at all frequencies and for those who had cookie-bite audiometric configurations in comparison with flat configurations [26,30].

A few articles discussed discrepancies in the findings regarding pure tone thresholds and ISSNHL. Nakamura et al. speculated that OHC damage presumably existed in all ISSNHL cases; however, in some cases, pure tone thresholds at 1000, 1500, and 2000 Hz did not correlate with DPOAE and TEOAE measures [27]. The authors postulated that, in these cases, the elevated hearing thresholds may have been more greatly influenced by retrocochlear lesions in addition to OHC damage [31]. Hoth found a poor, yet significant correlation between OAE level and hearing threshold; however, the author also recognized numerous exceptions of nearly normal hearing ears with small emissions as well as hard-of-hearing ears with large emissions [31]. Canale et al. reported that, although there was a relationship between the presence/absence of OAEs and pure tone improvement after therapy, there was not a specific correlation for LFSNHL [28].

4. Discussion

Table 4 summarizes the main findings, conclusions, and whether each study supports or rejects the use of OAEs as a predictive prognostic indicator in cases of ISSNHL. All but two studies supported the use of OAEs as a diagnostic tool for predicting hearing improvement in this patient population.

4.1. Aggregate Analysis

All seven articles that solely assessed DPOAEs supported their clinical value as a predictive prognostic indicator for hearing improvement in cases of ISSNHL. Four of five articles that evaluated the use of both DPOAEs and TEOAEs supported the clinical use of both types of OAEs as a predictive prognostic indicator for hearing recovery. The fifth article that evaluated both DPOAEs and TEOAEs determined TEOAEs to be an objective, efficient, and sensitive diagnostic tool for the prediction of hearing improvement in ISSNHL; however, their evidence was not significant enough to support the use of DPOAEs. One of two articles that solely evaluated the use of TEOAEs supported their clinical value as a predictive prognostic tool for hearing recovery; however, the second article noted their findings to be insignificant. Finally, Canale et al. evaluated the use of DPOAEs, TEOAEs, and SOAEs, and while they supported their use as an indicator of inner ear functional status, the authors did not support their use in predicting hearing improvement, specifically for cases of LFSNHL [25].

The seven articles that solely assessed DPOAEs came to the following conclusions: the relationship between treatment-induced change in hearing threshold is reflected in DPOAE SNR changes, specifically at frequencies of 8000 and 10,000 Hz, therefore, this physiologic measure may aid in predicting hearing outcome for individuals with ISSNHL at those frequencies [25]; DPOAE amplitude is largest at f2 frequencies of 3031 and 4812 Hz for patients with the most significant hearing improvement; and a significant association between DPOAEs measured before and after treatment in predicting prognosis was determined [35].

Park et al. found that the functional state of OHCs is relatively spared in ears with an initial mild-to-moderate hearing loss, and recovery of measurable DPOAEs is not related to hearing improvement, whereas functional improvement of OHCs is important for recovery in those with an initial moderately-severe to profound hearing loss [4]. The authors noted that, for those with an initial moderately-severe hearing loss, changes of DPOAE sum values positively correlated with hearing improvement; although presence of initial DPOAE responses indicated good prognosis, absence did not always indicate poor prognosis.

The rate of improvement for patients with flat audiometric configurations and larger increases in DPOAE amplitudes within the first three days displayed faster recovery [16,17]. On the basis of this finding, the authors developed a mathematical model to compare treatment options and predict the curve of improvement for patients with ISSNHL within a specific time frame. In summary, both articles supported the value of DPOAEs as a predictive prognostic indicator [16,17].

Schweinfurth et al. concluded that patients with intact DPOAEs had a significant improvement in their PTA in conjunction with steroid therapy, whereas the majority of patients with absent DPOAEs had no hearing recovery, despite treatment [33]. The authors suggested that DPOAEs may be a useful prognostic tool as they are positively associated with hearing improvement in ISSNHL cases. Ishida et al. supported this finding as ISSNHL patients with significant hearing recovery tended to have present DPOAEs, whereas, when hearing recovery was not complete, DPOAEs did not reappear [34]. Overall, all seven articles that solely assessed DPOAEs determined them to be a valuable tool for predicting hearing outcome for ISSNHL patients.

Four of the five articles that supported the use of both DPOAEs and TEOAEs came to the following conclusions: Hoth found that monitoring TEOAE and DPOAE measures in patients with ISSNHL throughout and after treatment provides an understanding of the recovery course of OHC function in relation to subjective hearing improvement; however, their findings also revealed instances where OAEs were surprisingly large in the presence of poor pure tone thresholds [29]. Shupak et al. reported that patients with present DPOAEs and TEOAEs in the acute stages revealed the greatest improvement in hearing. Furthermore, the sensitivity and specificity on the seventh day of follow-up in predicting hearing improvement was significant for both DPOAEs and TEOAEs, supporting their role for use in predicting outcome [28]. Nakamura et al.'s findings suggested that the function of OHCs deteriorated when hearing threshold was elevated, and their activity recovered in correlation with hearing improvement in ISSNHL cases with positive outcomes. The authors also recognized that ears

with ISSNHL did not show significant differences in OAEs when compared with ears with other forms of SNHL [35]. The fifth article that analyzed both DPOAE and TEOAE measures determined TEOAEs to be a significant prognostic indicator in cases of ISSNHL, however, their findings regarding the value of DPOAEs were deemed insignificant [31]. Overall, the articles as a whole concluded that DPAOEs and TEOAEs are clinically valuable in predicting the outcome in cases of ISSNHL.

The two articles that focused solely on the use of TEOAEs as a diagnostic tool in predicting outcome for cases of ISSNHL had different conclusions. Lalaki et al. found that present TEOAEs in the acute stages of ISSNHL in patients with hearing thresholds greater than 40 dB HL indicated a positive prognosis, determining this physiological measure may be useful in predicting hearing recovery. However, the authors did not find a specific correlation between TEOAE amplitude and hearing improvement [32]. On the contrary, Truy et al. determined that correlations between TEOAE amplitude and hearing recovery were too weak to support the clinical use of TEOAE measures in predicting outcome in cases of ISSNHL. However, of all seven articles that assessed the use of TEOAEs, only one did not support their clinical use for predicting prognosis [30].

Finally, Canale et al. was the only article that included all three types of OAE measures (DPOAEs, TEOAEs, and SOAEs) and focused solely on ISSNHL affecting low frequency hearing. The authors supported the idea that all three forms of OAEs can be useful in assessing inner ear functional state; however, they concluded that they would not be valuable as a prognostic indicator in cases of LFSNHL in regards to hearing recovery or treatment significance.

4.2. Limitations

Using OAEs to monitor auditory status will always be limited by their reliance on healthy outer hair cells and a functioning cochlear amplifier. Thus, they will never be useful to characterize the status of other auditory structures or higher level auditory processing. However, their role as a part of a comprehensive test battery to determine site of lesion should not be ignored, particularly for ISSNHL. Measurable OAEs in the presence of more than a moderate SNHL should prompt referral for imaging to assess retrocochlear function [36]. OAE's utility as a monitoring tool is also limited by their absence with greater than moderate SNHL. The majority of ISSNHL cases occur in middle age individuals [1], while the prevalence of hearing loss increases with age and measurable OAE declines [1].

A second category limiting OAE's ability to monitor auditory status relates to the equipment currently available to clinicians. Commercially available OAE measurement systems (which were used in all of the studies reviewed herein) limit the frequency regions tested (up to ~4000 Hz for TEOAE and ~8000 Hz for DPOAE). Commercial equipment typically also has relatively high system distortion levels (e.g., −10 dB SPL at many frequencies and up to −5 dB SPL using moderate level stimuli), which means that a DPOAE must be >−5 dB SPL in level to be designated as present. Many commercial systems have licensed the normative data published by Gorga et al. [37], and display their 95% confidence intervals for the DPOAE level. However, the commercial system's high system distortion essentially eliminates the possibility of monitoring smaller amplitude DPOAE, labelled "present but reduced" in this normative data set [38]. Lastly, monitoring OAE within the same patient over time is still hampered by commercial systems calibrating stimulus levels at the plane of the OAE probe, which does not control for the effect of individual ear canal acoustics [38–40]. Small changes in OAE probe insertion depth from one test to another can result in ±20 dB differences in stimulus level arriving at the eardrum [41].

4.3. Developing an OAE Monitoring Protocol for ISSNHL

No two studies in this review used the same OAE protocol. Obviously, further investigation to develop the most sensitive OAE protocol to cochlear ISSNHL and its recovery will be needed. We recommend universally screening for the presence of TEOAE and DPOAE as part of the initial site of lesion assessment. OAE protocols used to monitor noise- and ototoxicity-induced hearing loss have been refined over time to identify the most sensitive frequency regions: for ototoxic agents,

monitor the highest frequencies with pre-exposure responses [42]; for noise-exposure, monitor the OAE frequency region $\frac{1}{2}$ to 1 octave lower than the frequency with significant threshold shift [8]. Refining an ISSNHL OAE monitoring protocol will be hampered by the variety of audiometric configurations that occur, and the unlikelihood of having baseline measurements. With these factors in mind, we recommend measuring both TEOAE and DPOAE over as wide a frequency region as possible, with the hopes that future systematic reviews may identify the most sensitive frequency region to monitor. For all serial OAE monitoring, we would caution against using OAE SNR as a criterion for significant change, as was used by Canale and Lacilla [7]. DPOAE amplitude changes were reported to be the best predictor of pure tone threshold changes in patients receiving potentially ototoxic chemotherapy [25,43]. Konrad-Martin et al. suggest establishing a clinic test–retest amplitude criterion [8]; we suggest using the patient's own unaffected ear to establish the test–retest amplitude criterion for unilateral ISSNHL.

Table 4. Evidence of intervention benefit and support for use of OAE when monitoring auditory recovery. OHC, outer hair cell.

Article	Conclusions	Support/Reject
Bashiruddin et al. (2018) [44]	Significant changes in DPOAE SNR at 1500, 2000, and 8000 Hz; Significant associations between SNR change and hearing threshold at 8000 and 10,000 Hz; Relationship between treatment-induced change in hearing threshold and DPOAE SNR may help predict outcome at certain frequencies	Support
Canale & Lacilla (2005) [24]	The relationship between pre-treatment presence/absence of SOAEs, DPOAEs, and TEOAEs and thresholds was not significant; The study supports that OAEs can be an indicator of inner ear functional state, but they cannot be used as a prognostic test in cases of LFSNHL	Reject
Chao & Chen (2006) [25]	Results showed that a greater DPOAE amplitude was a significant prognostic indicator; Established a model that revealed prognostic value of DPOAEs for ISSNHL patients; The model can be used for comparison of different treatment protocols	Support
Chao & Chen (2010) [26]	Results showed that a greater DPOAE amplitude was a significant prognostic indicator; Established a model that revealed prognostic value of DPOAEs for ISSNHL patients; The model can be used for comparison of different treatment protocols	Support
Hoth (2005) [27]	Greater OAE levels following the drop in hearing thresholds were correlated with better outcome; Monitoring TEOAEs and DPOAEs in patients with ISSNHL during/after treatment gives insight into the recovery process of OHC function parallel to subjective hearing improvement, but also reveals paradoxical cases where OAEs are unexpectedly large compared with thresholds	Support
Ishida et al. (2008) [28]	ISSNHL patients with significant hearing improvement tended to have OAE responses; Greater recovery was seen in the low-mid vs. high frequencies; When hearing recovery was not full, OAEs did not reappear	Support
Lalaki et al. (2001) [29]	Presence of TEOAEs in early stages of ISSNHL in those with hearing thresholds >40 dB HL indicates a positive prognosis; No significant correlation between TEOAE peak amplitude and pure tone improvement; TEOAEs may serve as a clinical tool for prediction of recovery in ISSNHL cases	Support
Mori et al. (2011) [30]	DPOAE amplitude in patients with hearing improvement rate of >50% was significantly larger compared with those with hearing improvement rate of 50% at frequencies of 3031 and 4812 Hz; Significant correlation between DPOAEs before treatment and hearing recovery indicates they are a potentially useful means for predicting prognosis	Support
Nakamura et al. (1997) [4]	Amplitudes of TEOAEs and DPOAEs increased concurrently with recovery of hearing threshold; In 27% of cases, SOAEs were detected when hearing recovered; Results suggest that the function of OHCs deteriorated when thresholds were elevated and recovered as hearing improved to nearly normal levels in ISSNHL cases with a good outcome	Support
Nemati et al. (2011) [31]	No significant change in DPOAE SNR or amplitude when comparing findings before/after treatment for patients with significant hearing recovery; Significant and positive change in TEOAE SNR and reproducibility when comparing findings for patients with significant hearing recovery; TEOAEs are an objective, rapid, and sensitive tool in the course of ISSNHL	Support TEOAEs; Reject DPOAEs
Park et al. (2010) [32]	Function of OHCs is spared in ears with initial mild-to-moderate hearing loss and recovery is not related to hearing improvement; Function of OHCs is impaired in ears with initial moderately-severe to profound hearing loss and OHC improvement is important for recovery; Although presence of initial DPOAE responses indicated good prognosis, absence did not always indicate poor prognosis	Support
Shupak et al. (2014) [33]	Three patients with intact DPOAEs at presentation had an average improvement of 33 dB in the PTA at 500–2000 Hz in conjunction with steroid therapy, whereas five of seven patients with absent DPOAEs had no improvement in hearing despite therapy. The presence of DPOAEs may be a useful prognostic indicator that positively correlates with recovery from ISSNHL	Support
Schweinfurth et al. (1997) [35]	Function of OHCs is relatively spared in ears with initial mild-to-moderate hearing loss and recovery is not related to hearing improvement; Function of OHCs is impaired in ears with initial moderately-severe to profound hearing loss and functional improvement of OHCs is important for recovery; Although the presence of initial DPOAE responses indicated good prognosis, absence did not always indicate poor prognosis	Support
Truy et al. (1993) [34]	The TEOAE amplitude at initial follow-up was correlated with improvement in thresholds at the second follow-up at 2000 Hz. Weak correlations between TEOAE amplitude at 1200 Hz and recovery of hearing. Overall, correlations were too weak to form the basis for a predictive test that could be clinically useful; TEOAE presence is not considered a good prognostic indicator in cases of ISSNHL	Reject

Only two reviewed studies monitored SOAEs and reported limited utility of their inclusion. However, recent studies in animal models have described the emergence of SOAE following cochlear trauma or genetic dysfunction [44]. Further development of this line of research may become fruitful for clinical applications.

5. Conclusions

- Twelve out of fourteen studies in this systematic review support the use of OAEs as a prognostic indicator for hearing improvement in cases of ISSNHL.
- OAEs are an important component of a diagnostic and monitoring auditory test battery to help determine site of lesion, make proper diagnostic referrals (e.g., for imaging), and predict benefit from aural rehabilitation.
- No unifying OAE protocol was identified in this systematic review. The choice to use TEOAE, DPOAE, or both measures should be based on available equipment, patient age, and pre-existing hearing loss (which, in unilateral cases, may be inferred from the unaffected ear).
- Further research may lead to predictive models of hearing recovery in ISSNHL based on factors such as treatment type, duration from onset to treatment, OAE measures, pure tone thresholds, and audiometric characteristics [26,36].

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Acronyms: ABR = Auditory Brainstem Response; DPOAE = Distortion Product Otoacoustic Emissions; GST = Global Standing Wave Theory; HL = Hearing Loss; ISSNHL = Idiopathic Sudden Sensorineural Hearing Loss; LFSNHL = Low-Frequency Sensorineural Hearing Loss; LOT = Local Oscillator Theory; OAE = Otoacoustic Emissions; OHC = Outer Hair Cells; PTA = Pure Tone Audiometry; SOAE = Spontaneous Otoacoustic Emissions; SNHL = Sensorineural Hearing Loss; SNR = Signal to Noise Ratio; SPL = Sound Pressure Level; SSNHL = Sudden Sensorineural Hearing Loss; TEOAE = Transient Evoked Otoacoustic Emissions; VEMP = Vestibular Evoked Myogenic Potential.

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