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REVIEW ARTICLE

Secondary autoimmune immune ear disease (AIED): a systematic review and meta-analysis on vestibular manifestations of systemic autoimmune and inflammatory disorders

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Abstract

Secondary autoimmune inner ear disease (AIED) is often bilateral and asymmetric in patients presenting with audiovestibular symptoms due to a systemic autoimmune disease. This systematic review and meta-analysis are aimed at identifying and highlighting patterns in prevalence of vestibular dysfunction, symptom presentation, and diagnostic methods in extant literature by combining clinical context from case reports with quantitative analyses from cohort studies. Screening of articles by title, abstract, and full text was completed by four reviewers (K.Z., A.L., S.C., and S.J.). In this study, we grouped secondary AIED and systemic autoimmune diseases by pathophysiologic mechanism: (1) connective tissue disease (CTD), (2) vasculitides (VAS), (3) systemic inflammatory disorders (SID), and (4) other immune-mediated disorders (OIMD). The search for AIED disease identified 120 articles (cohorts and case reports) that met the final inclusion criteria. All 120 were included in the qualitative review, and 54 articles were included for meta-analysis. Of these 54 articles, 22 included a control group (CwC). Ninety individual cases or patient presentations from 66 articles were included for analysis in addition to the 54 cohort articles. Secondary AIED does not have a diagnostic algorithm for managing vestibular symptoms. The management of audiovestibular symptoms requires close collaboration between otolaryngologists and rheumatologists to preserve end-organ function of the ear. To improve our ability to understand the impact on the vestibular system, vestibular clinicians need to develop a standardized reporting method. Clinical presentation should frequently be paired with vestibular testing to contextually investigate symptom severity and provide higher quality care.

Keywords Autoimmune ear disease · Caloric · Immune-mediated ear disease · Nystagmus · PTA · Vertigo · Vestibular testing

Introduction

Secondary autoimmune ear disease (AIED) due to a systemic autoimmune disease is often bilateral and asymmetric and presents with sensorineural hearing loss (SNHL) [1]. Harris et al. initially proposed a classification of AIED based on five principal causes (see Table 1) [2]. Secondary AIED typically occurs concurrently with rheumatic diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), vasculitis (e.g., Behcet disease), systemic inflammatory diseases (SID), or other autoimmune pathologies (OIMD). This article will focus on audiovestibular outcomes in secondary AIED according to the Harris classification.

In McCabe's initial 1979 report, unsteadiness and ataxia were more frequently reported than vertigo in his cohort of patients [6]. This finding corroborated a similar progressive, bilateral, and simultaneous decline of vestibular end-organs to hearing loss [6]. Since then, diagnosis has been dependent on history and limited clinical findings [7].

Generally, AIED accounts for less than 1% of all cases of hearing impairment or dizziness [9]. In addition to SNHL, concurrent conductive hearing impairment may

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Table 1 Harris classification

(1) Primary AIED (ear-specific or localized AIED)
(2) Secondary AIED (due to a systemic autoimmune disease)
(3) Immune-mediated Meniere's disease
(4) Immune-mediated inner ear disease (IMIED) associated with inflammatory diseases (chronic otitis media, Lyme disease, otosyphilis)
(5) IMIED associated with other discrete organ disease (e.g., Cogan syndrome, relapsing polychondritis)

also be present, as found in otitis media with effusion or with presence of granulation tissue in autoimmune pathologies (i.e., GPA) [11, 12]. Per the CDC, more than 95% of hip fractures are a result of falls, typically sideway falls. Balance dysfunction can lead to 2.6-fold increase in the odds of falling, while clinically symptomatic patients (i.e., reported dizziness or vertigo) had a 12-fold increase in falls [10]. Thus, vestibular symptoms secondary to autoimmune diseases are important to identify and define to prevent high morbidity and mortality from increased fall-risk in the short as well as long term.

For patients suffering from secondary AIED, hearing loss can range from slowly progressive to rapidly progressive, as opposed to primary AIED, which is usually rapidly progressive and bilateral [3]. Damage due to AIED can occur directly from an uncontrolled, immune response toward inner ear antigens (i.e., ECM protein cochlin) or indirectly by immune-complex deposition in the inner ear apparatus, causing an array of otologic and vestibular symptoms secondary to endocochlear injury [4, 5].

Ralli et al. [11] published a comprehensive review on audiovestibular symptoms in systemic autoimmune disease describing various clinical presentations of AIED patients and postulated that identifying audiovestibular symptoms early could help with diagnosis and tracking of disease progression and can prove crucial to the prognosis of the inner ear function. However, this review did not encompass vestibular testing methods and diagnostic work-up [11].

Due to the varying presentations of secondary AIED in the setting of their systemic rheumatologic disorders, there is little consensus in the diagnostic algorithm and treatment [5]. Research has placed a larger emphasis on audiologic deterioration and outcomes, often overlooking vestibular presentations.

Ciobra et al.'s [5] review of diagnostic approaches to AIED determined that there are no standard diagnostic criteria or pathognomonic tests for a diagnosis of AIED; rather, the diagnosis is based on clinical symptoms, laboratory findings, and responsiveness to treatment with steroids, without the need for vestibular testing [5]. This systematic review and meta-analysis are aimed at highlighting patterns in prevalence of vestibular dysfunction and symptom presentation and identifying employed and effective diagnostic methods in extant literature.

Methods

Search strategy

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A detailed search strategy was developed in the following four databases: PubMed (National Library of Medicine, National Institutes of Health), Scopus (Elsevier), CINAHL (EBSCO), and Cochrane Library (Wiley). Databases were searched from conception to February 6, 2022, using a combination of medical subject headings and keywords. The full search strategy with a list of systemic autoimmune diseases is shown in the Appendix.

Screening of articles by title, abstract, and full text was completed by four reviewers (K.Z., A.L., S.C., and S.J.), and any disagreements were resolved by consensus. To identify additional studies, the reference lists of relevant articles were manually searched. A flow diagram detailing selection of studies with inclusions and exclusion criteria is shown in PRISMA Fig. 1 [13–118].

AIED classification rationale

In this study, we chose to classify secondary AIED and systemic autoimmune diseases by pathophysiologic mechanism (Table 2): (1) connective tissue disease (CTD), (2) vasculitides (VAS), (3) systemic inflammatory disorders (SID), and (4) other immune-mediated disorders (OIMD). We hope this classification helps highlight patterns in vestibular presentations and diagnostic work-up in vestibular testing [8].

Vestibular testing data were extracted for nystagmus (central positional, gaze-evoked, abnormal optokinetic, head-shaking induced, peripheral positional, spontaneous, and positional not otherwise specified (NOS)), caloric response (decreased/diminished/paresis, absent, and total/unspecified (NOS), canal paresis (%), and directional preponderance (%)), Dix-Hallpike testing, oculographic testing (abnormal saccadic movement, smooth pursuit), cVEMP (absent, total abnormal/NOS), cVEMP amplitude ratio, and electronystagmography (ENG)/videonystagmography (VNG). Central positional and peripheral positional nystagmus were included in the positional total/(NOS) categories.

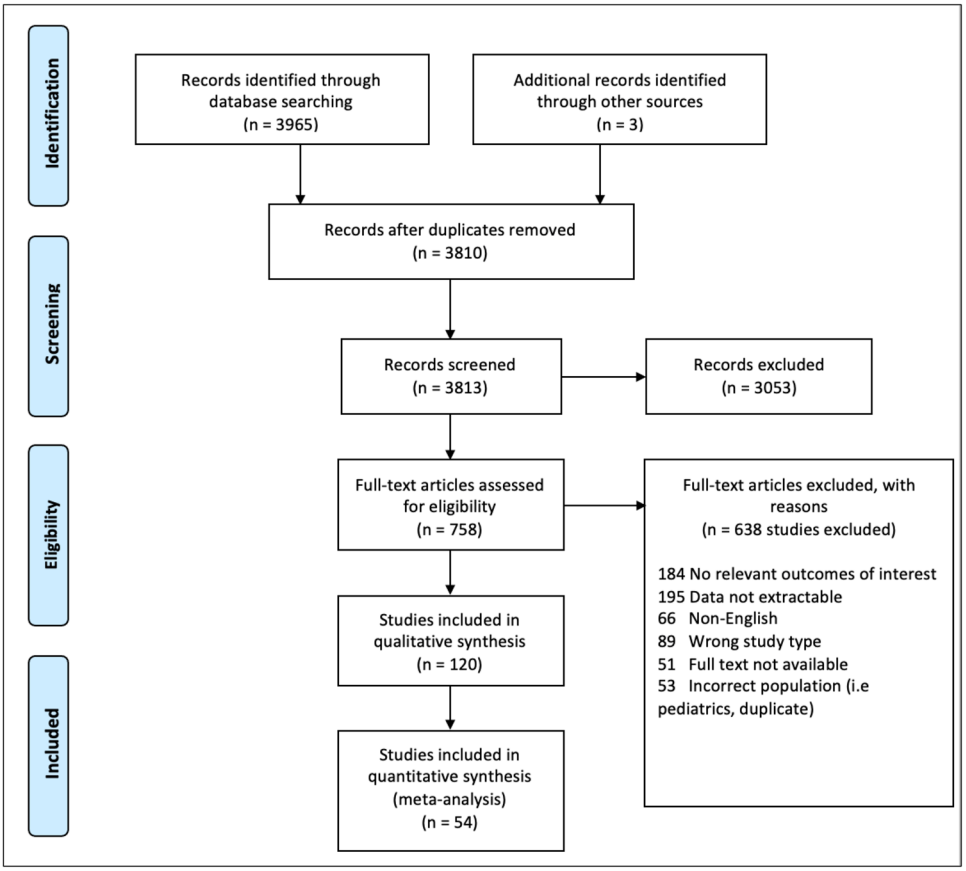

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) schematic for vestibular manifestations in AIED [13–118]

Table 2 Classification of secondary AIED cohort studies

	Connective tissue disease (CTD)	Vasculitides (VAS)	Systemic inflammatory disorders (SID)	Other (OIMD)
Studies [$n = 54$]	18	26	4	6
Disease [*n* studies]	Scleroderma (5) SLE (5) SJO (3) RA (5)	GCA (2) BHD (10) Cogan syndrome (8) GPA (3) EGPA (1) OMAAV (2)*	PMR (2) Sarcoid (2)	UC (1) HT (1) RP (2) VKH (2)

*OMAAV, subtype of GPA taking traction in recent literature; OMAAV can be a complication of GPA

SLE, systemic lupus erythematosus; *SJO*, Sjogren's syndrome; *RA*, rheumatoid arthritis; *GCA*, giant cell arteritis; *BHD*, Behcet's disease; *GPA*, granulomatosis with polyangiitis; *EGPA*, eosinophilic granulomatosis with polyangiitis; *PMR*, polymyalgia rheumatica; *UC*, ulcerative colitis; *HT*, Hashimoto's thyroiditis; *RP*, relapsing polychondritis; *VKH*, Vogt-Koyanagi-Harada

While there is an American National Standard Procedure highlighting specific procedures for conducting Basic Vestibular Function Test Battery (spontaneous, gaze-evoked, positional/positioning nystagmus, saccade test, pursuit testing, and caloric testing), there is no standardized procedure for reporting these results. Given the heterogeneity of reporting methods, we organized the results according to Table 3. When available, data for the following audiologic testing modalities was extracted: pure tone audiometry (PTA), auditory brainstem response, tympanometry, word recognition testing, speech recognition thresholds, auditory recruitment, and reflex decay. Any discrepancies were resolved by consensus between the authors.

Quality assessment

Level of evidence for each selected article was evaluated with the Oxford Center for Evidence-Based Medicine [119]. The risk of bias for non-randomized studies was assessed according to the Cochrane Handbook for Systematic

Table 3 Clinical definitions of vestibular evaluation and testing

1) Central nystagmus
   a. Central positional [121]
      i. A triggered nystagmus (pure vertical, pure torsional) generated by change in head position. Lesion centrally located and suspected if peripheral counterpart suspected.
   b. Gaze-evoked nystagmus (GEN) [95]
      i. Centrifugal nystagmus or rhythmic oscillation of the eye when attempting to maintain an extreme eye position.
   c. Optokinetic nystagmus [95]
      i. Multi-direction nystagmus (vertical, horizontal, torsion) occurring due to moving or rotational visual fields or objects. Slow phase ipsilateral to aggravating stimuli. No fast phase.
2) Peripheral nystagmus
   a. Peripheral positional (BPPN)
      i. Positioning nystagmus often with vertigo characterized by torsional and upbeat (posterior canal), horizontal (horizontal canal), or mixed horizontal-torsional depending on etiology.
   b. Spontaneous nystagmus
      i. Nystagmus that is peripheral and lateralizing due to abnormal vestibular tone between nerves and labyrinth.
3) Spontaneous nystagmus [95]
   a. Consistent nystagmus with fixed central gaze position when stationary, upright, and neutral positions.
4) Dix-Hallpike test
   a. Rotation of the head left or right in a hanging position at a 45° angle as fast as possible. Assesses presence of otoliths in posterior and anterior semicircular canal. Torsional nystagmus with symptoms of vertigo considered abnormal.
5) Head shaking test [122]
   a. Nystagmus resulting from quick and passive head shaking followed by a sudden stop. Unilateral vestibular impairment seen if nystagmus (horizontal, torsion) ipsilateral to non-affected labyrinth. Central impairment seen if horizontal shaking triggers vertical nystagmus (cross-coupling).
6) Caloric testing [77]
   a. Determines the responsiveness of the vestibular system (only horizontal canal) and symmetry via canal stimulation of varying temperatures. Cohorts included in this review utilized water-based caloric test except four studies [123–126]. Paresis often defined as greater than 25–26% is a pathological sign.
   b. Classified by decreased function/paresis/hypoactive labyrinth or absent function. Hypoactive labyrinth grouped into canal paresis as both are indicative of horizontal canal weakness
7) VEMPs
   a. cVEMP is a clinical test to assess saccule and inferior vestibule nerve function.
   b. oVEMP used to determine utricle and superior vestibular nerve function.
8) vHIT test [127]
   a. Evaluation of the horizontal canals. Patient's head usually positioned at 20°. After horizontal canal tests, vertical tests are conducted rotating the head sharply to assess RALP and LARP canals.
   b. Normal rate of VOR gain accepted for horizontal canals (>0.8) and 0.7 for vertical canals (anterior and posterior).
9) Oculographic testing [128]
   a. Abnormal saccadic movement.
      i. Gaze jumps rapidly from one fixation point to another. Abnormalities assessed in peak velocity, latency and accuracy and classified by the following patterns: inappropriate, inaccurate (hypermetric, hypometric), too slow, too fast, or poorly initiated.
   b. Abnormal smooth or faze pursuit.
      i. Assesses integrity of neural brainstem pathways involved in extrinsic ocular movement. Inability for the eye to follow a moving target is abnormal.

Reviews of Interventions [120]. The Joanna Briggs Institute (JBI) critical appraisal checklist (8 questions) was used to assess the quality of case reports.

Statistical analysis and synthesis of results

The cohorts in this study were analyzed in two distinct groups: (1) all AIED cases and (2) AIED cases with controls (CwC). Each group was further split into the classification detailed in the above methods to ascertain subgroup trends and variations (group 1: CTD, group 2: VAS, group 3: SID, group 4: OIMD).

Statistical analyses were performed on case reports data with SPSS 28.0.1.0 (IBM Corporation, Armonk, NY). Continuous variables were summarized by mean ± standard deviation (SD) or median and interquartile range (IQR

25–75th) when appropriate. All continuous variables were tested for normal distribution as determined by the Kolmogorov–Smirnov test. Comparisons between continuous variables were performed with a *t*-test or Mann–Whitney test as appropriate. Categorical variables were summarized by frequency (*N*) and percentage (%). Comparisons between categorical variables were performed with a Fisher's or chi-square test. The strength of association in cohorts with AIED cases and controls was estimated using odds ratios (ORs) and 95% confidence intervals (CIs) by the exact method.

In addition, meta-analysis of continuous measures (comparison of means and standard deviations) and odds ratios (comparison of events) between treatment and control were performed with Cochrane Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020). If median and range were provided for a continuous variable, a mean and SD were estimated using the quantile estimation method [129]. Due to the homogeneity of the studies, $I^2 < 50\%$, the fixed-effects model was used in this study. If homogeneity of studies or $I^2 > 50\%$, the random-effects model was used. Finally, the Sterne and Egger tests were performed for further assessment of risk of publication bias. Potential publication bias was evaluated by visual inspection of the funnel plot [130, 131]. In a funnel plot, treatment effect is plotted on the horizontal axis, and the standard error is on the vertical axis. The vertical line represents the summary estimate derived using fixed-effect meta-analysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 standard error) around the summary effect for each standard error on the vertical axis. These show the expected distribution of studies in the absence of heterogeneity or selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot. A *p* value of < 0.05 was used to indicate a statistically significant difference for all statistical tests.

Results

Overview

The search for AIED disease identified 3810 unique abstracts; 758 articles underwent full-text review of which 120 articles (cohorts and case reports) met the final inclusion criteria. All 120 were included in the qualitative review, and 54 articles were included for meta-analysis. Of these 54 articles, 22 included a control group (CwC). The remaining 32 studies did not have a control group. Most of the included articles were either prospective cohort studies ($N = 42$) or retrospective cohort studies ($N = 12$). Ninety individual cases or patient presentations from 66 articles were included for analysis in addition to the 54 cohort articles. A complete list of cohort studies and case reports with bibliographic information is available in the Appendix. Critical appraisal of studies indicated an acceptably low risk of bias for the majority of included studies (Appendix). A funnel plot with Egger test (4.48, 95%CI 1.58 to 7.39, $p = 0.04$) demonstrated that most studies were within the funnel with little asymmetry, suggesting little publication bias (Fig. 2).

Demographics

A total of 54 cohort studies were included with 2195 patients. Demographic information by subgroup is detailed in the Appendix for all AIED cases (cohort studies). Of note, the AIED CwC ($n = 814$) are included in all AIED cases included in the Appendix ($n = 2195$). The youngest cohort of patients was the VAS group with mean age of 42.5 ± 3.47 (18–81) years old. With the most included studies, CTD and VAS cohorts yielded sufficient data for a case vs. control analysis (CwC). CTD patients were significantly more likely to be female (90.7%) when compared to control patients (65.0%) ($p < 0.001$). Patients with VAS pathologies had a shorter disease duration at the time of the study at 1.87 ± 0.63 years in comparison to CTD patients at 5.15 ± 1.06 years.

Vestibular symptoms

The presence of any vestibular symptom was the highest in the VAS cohort in 466 (63.0% [47.4–77.4%]) patients, followed by 245 (34.1% [21.7–47.6%]) patients in CTD, 43 (20.3% [4.7–43.2%]) patients in SID, and 44 (17.5% [13.1–22.3%]) patients in the OIMD cohort as shown in Table 4. The VAS subgroup had the highest prevalence of vertigo in 220 (50.3% [35.4–65.1%]) patients, dizziness/lightheadedness in 112 (34.3%) patients, and imbalance in

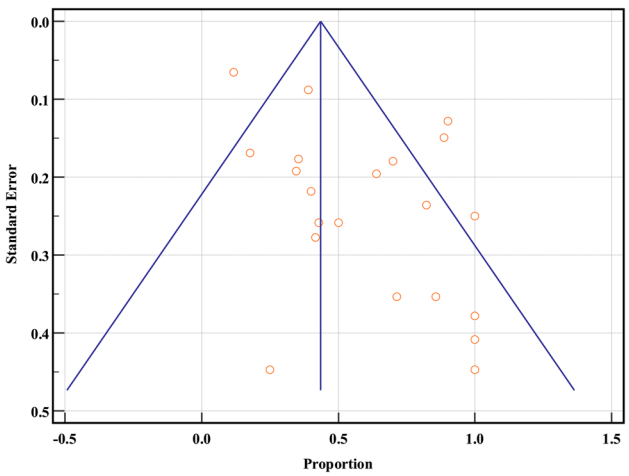

Fig. 2 Funnel plot indicating publication bias among included studies

Table 4 Indicating prevalence of vestibular and audiologic symptoms among each autoimmune disorder

	Connective tissue disease (CTD)	Vasculitides (VAS)	Systemic inflammatory disorders (SID)	Other (OIMD)
Vestibular symptoms				
Any vestibular symptom	245 (34.1% [21.7–47.6%])	466 (63.0% [47.4–77.4%])	43 (20.3% [4.7–43.2%])	44 (17.5% [13.1–22.3%])
Vertigo	210 (33.3% [20.9–47.0%])	220 (50.3% [35.4–65.1%])	43 (20.3% [4.7–43.2%])	11 (13.9% [7.2–22.3%])
Imbalance	24 (19.0% [2.9–44.3%])	161 (54.8% [49.0–60.5%])	51 (24.2% [34.9–52.0%])	24 (19.0% [2.9–44.3])
Audiologic symptoms				
Hearing loss	259 (39.5% [24.7–55.4%])	351 (63.0% [45.0–79.4%])	N/A*	175 (77.3% [23.2–99.5%])
Tinnitus	164 (42.7% [28.0–58.0%])	272 (45.9% [29.4–63.0%])	72 (36.1% [23.8–49.5%])	26 (42.8% [30.9–55.1%])
Total included in study (*n*):	CTD = 838	VAS = 824	SID = 216	OIMD = 217

*Insufficient sample size to include

161 (54.8%) patients among the subgroups. In the SID subgroup, 43 (20.3% [4.7–43.2%]) and 51 (24.2% [34.9–52.0%]) patients screened for vertigo and imbalance, respectively, reported symptoms. The proportion of patients presenting with imbalance is significantly higher in the VAS cohort 162 patients (54.8% [49.0–60.5%]) compared to the CTD cohort (24 patients (19.0% [2.9–44.3])). The most significant findings between CwC and controls were presence of vertigo for CTD cohort (OR = 69.4 [23.5, 205.3]) and imbalance in the VAS cohort (OR = 61.6 [8.2, 460.3]) indicating a greater than 60 times likelihood for both CTD and VAS compared to controls.

Vestibular testing

Scarce and inconsistent reporting was notable when obtaining nystagmus, caloric testing, cVEMP, ENG/VNG results, and the rotational chair exam. The VAS cohort had the highest prevalence of after headshake nystagmus (AHSN) with 24.2% [1.7, 61.6] patients affected. Spontaneous and positional (NOS) nystagmus was the most prevalent in the OIMD subgroup with 22 (32.3%) of patients positive, followed by 35 (16.2%) patients in VAS and was rare in CTD with 2 (0.8%) patients. Positional nystagmus in the OIMD cohort was seen in 12 (29.5%) patients in the OIMD subgroup, followed by 20 (19.9%) patients with VAS and 25 (9.2%) patients with CTD.

Prevalence of abnormal caloric testing (total/NOS), highlighting a peripheral vestibulopathy, was the highest in the VAS cohort with 84 (42.8%), followed by 46 (20.9%) patients with CTD and 25 (47.3%) patients in the OIMD subgroup. Most abnormal caloric testing results in the VAS and CTD cohorts were due to decreased response or paresis on testing: VAS 55 (47.3%), CTD 45 (20.4%), and OIMD 8 (38.1%). Caloric testing was more likely to yield absent findings in the VAS subgroup (24 [71.1%]) compared to the CTD cohort (1 [3.57%]). cVEMPs were only reported for one study in the CTD cohort [132]. In the VAS subgroup, cVEMPs were abnormal (total/NOS) in 16 (16.6%) and absent in 3 (4.84%). Rotational chair testing was mentioned in 6 of 54 included articles of which five were VAS and one was OIMD [125, 133–136]. Results for rotational chair testing were too heterogenous to pool. Sensory organization test (SOT) and clinical test of sensory integration and balance (CTSIB) were only reported in one study each [133, 137].

Only CTD and VAS cohorts were able to undergo analysis for vestibular testing due to insufficient reporting and low sample sizes in SID and OIMD subgroups. In the VAS cohort, AHSN (OR = 47.5 [9.7, 232.5]) and spontaneous nystagmus (OR = 19.6 [4.0, 96.6]) were significantly more likely to be present in CwC patients than controls. Positional nystagmus (NOS) was not significantly more notable in either CTD or VAS groups compared to controls. There also is no significant difference in abnormal Dix Hallpike test in CTD CwC patients and controls. However, CTD CwC patients were 12.5 times more likely to have an abnormal (total/NOS) caloric test (OR = 12.5 [3.9, 39.5]). Within oculographic testing, abnormal saccadic movement was OR = 3.7 [1.6, 8.8] times more likely to be present in CwC CTD patients versus controls. cVEMPs (total/NOS) were significantly abnormal in the CwC VAS group versus controls (OR = 6.9 [2.0, 23.6]). Only one study reported oVEMPs; thus, there was insufficient data for pooling [138].

Audiologic symptoms

Hearing loss and tinnitus were the most reported otologic symptoms while headache was also reported in the above AIED cohorts. In the CTD cohort, headaches were reported in 83 (57.5% [49.1–65.6%]) patients, tinnitus in 154 (42.7% [28.0–58.0%]), and hearing loss (total/NOS) in 259 (39.5% [24.7–55.4%]). In the VAS cohort, headaches were present in 74 (60.2% [32.3–84.9]), tinnitus in 272 (46.0% [29.3–63.0%]), and hearing loss in 351 (63.1% [45.0–79.4%]) patients as shown in Table 4. Hearing loss (total/NOS) was proportionally greatest in OIMD

175 (77.3%), followed by VAS 351 (63.1%) and CTD 259 (39.5%) subgroups. Tinnitus was reported in approximately 40% across all subgroups (ranging 38.3–46.0%), indicating it may be a nonspecific symptom. Only one study reported 15 (25.0%) patients with oscillopsia [139].

Hearing loss (total/NOS) is significantly more likely to be present in CwC patients with CTD (OR = 9.1 [6.3–13.1]) or VAS (OR = 10.0 [4.5–21.8]) pathologies. CwC CTD patients were significantly more likely to present with subjective hearing loss (OR = 31.7 [2.4–425.3]). VAS CwC patients are significantly more likely to present with tinnitus (OR = 37.5 [5.2–267.8]) compared to controls.

Cogan syndrome

Though a hallmark otolaryngologic pathology, typical CS is unique in affecting the vestibular system and the cochlear system [140]. In our study, 8 of the 26 VAS cohorts were CS. A sub-analysis of the VAS subgroup was completed to isolate the confounding effects of CS versus other vasculitis pathologies. The presence of any vestibular symptom, vertigo, and imbalance were significantly more prevalent in CS cases. Upon removing CS patients from the VAS cohort, rates of vertigo in the non-CS cohort (29.8%) were comparable to the CTD subgroup (33.3%). Yet, prevalence of any vestibular symptom, dizziness/lightheadedness, and imbalance are still higher in non-CS cases compared to controls, with up to a third of patients endorsing a complaint of vertigo.

While vestibular testing results were limited by small sample size post-stratification, absent caloric response and abnormal results (total/NOS) were significantly higher in the CS cohort (24, 71.1%) versus non-CS (60, 34.7%) and CTD cases (46, 20.9%). The CS subgroup likely skewed and, naturally, predominated audiologic symptoms in the overall VAS cohort. Prevalence of audiologic symptoms for non-CS cases was comparable to CTD subgroup in the absence of CS cases. However, it is still noteworthy that a third of vasculitis (without Cogan syndrome) and a fifth of CTD subjects had peripheral vestibular abnormalities on objective reflexive testing, confirming that the vestibular labyrinth had been affected.

Descriptive analysis of individual cases

A total of 66 articles were included with 90 respective patients or case presentations. Patients were a mean age of 44.0 ± 16.9 (18–85) years old and 62.2% female ($n = 56$). Of the 90 patients, 17 (18.9%) were identified as white, 3 (3.3%) as black, 4 (4.4%) as "other," and 66 (73.3%) were not identified by race. Five (5.6%) patients had a history of connective tissue disease, 58 (64.4%) had a history of vasculitis, 13 (14.4%) had a history of systemic inflammatory disorder, and 14 (15.6%) had a history of autoimmune pathology not otherwise specified. Three (3.3%) patients presented with a history of Behcet's disease, 13 (14.4%) patients with sarcoidosis, 36 (40.0%) patients with Cogan syndrome, 5 (5.6%) patients with Vogt-Koyanagi-Harada (VKH) disease, 19 (11.1%) patients with granulomatosis with polyangiitis, 3 (3.3%) patients with systemic lupus erythematosus (SLE), 1 (1.1%) patient with IgG4 disease, 8 (8.9%) patients with relapsing polychondritis, 1 (1.1%) patient with systemic sclerosis, 1 (1.1%) patient with rheumatoid arthritis, 2 (2.2%) patients with polyarteritis nodosa, 1 (1.1%) patient with antiphospholipid syndrome, and 3 (3.3%) patients with giant cell arteritis.

On clinical presentation, 28 patients (31%) complained of SNHL, 24 (27%) experienced tinnitus, 29 (32%) reported a history of vertigo episodes, 12 (13%) experienced disequilibrium/imbalance, 5 (6%) experienced headache, and 4 patients (4%) experienced otalgia. Upon examination, 34 patients (38%) displayed uveitis or keratitis, 75 (83%) indicated hearing loss (23 unilateral and 52 bilateral), 47 (52%) reported tinnitus, 7 (8%) reported headache, 52 (58%) displayed vertigo, 11 (12%) displayed dizziness, 18 (20%) displayed imbalance, 2 (2%) displayed oscillopsia, 19 (21%) displayed nausea and/or vomiting, 2 (2%) displayed hyperacusis, and 10 (11%) displayed aural fullness. Of the 46 patients who underwent cranial imaging (27 MRI, 23 CT, 5 X-Ray), 21 (45.7%) were described as "abnormal"; most commonly present were hyperintensities on MRI (2 VAS, 1 SID), cerebellar atrophy (1 SID), recent hemorrhage, infarction, or stenosis (3 VAS, 1 CTD), enhancements in the labyrinthine (1 VAS), inner ear (1 VAS, 1 OIMD), or posterior region (1 OIMD) or nonspecific mucosal thickening in mastoid region (2 VAS, 1 SID).

Central nystagmus was present in 3 patients (one positional, one gazed-evoked, one unspecified), peripheral nystagmus was present in 12, and spontaneous nystagmus was present in 15 patients. Audiometry found SNHL in 47 patients (unilateral in 15 and bilateral in 33).

Treatment regimens were carried out over a mean duration of 4.3 ± 3.9 (0.3–15) months. The most frequently utilized treatment was corticosteroids ($n = 66$), methotrexate ($n = 10$), azathioprine ($n = 10$), cyclophosphamide ($n = 7$), cyclosporine ($n = 5$), acetylsalicylic acid ($n = 3$), antihistamine ($n = 3$), and intravenous immunoglobulin ($n = 2$). Tetracyclines, vestibular rehabilitation therapy, plasmapheresis, rituximab, and mycophenolate mofetil were each used in one patient.

Out of the 91 patients, treatment response was recorded in 79. Sixty-four (81.0%) patients were classified as "recovered" if resolution occurred of their presenting symptom which included, but is not limited to, hearing loss, dizziness, imbalance, and/or tinnitus. Fifteen (19.0%) were classified as "not recovered." Within the recovery group, 24 (38.1%)

underwent a full recovery, 39 (61.9%) underwent a partial recovery, and 1 (1.5%) was not specified. Post-audiometry treatment was reported for 24 (31.2%) patients, and 8 (10.9%) patients underwent cochlear implantation.

Discussion

Diagnostic criteria or reliable pathognomonic tests for the diagnosis of secondary AIED are not standardized. For this study, we reviewed audiovestibular manifestations in systemic autoimmune or secondary AIED.

Particularly, the discussion of vestibular symptoms and methods of investigating in patients with AIED is scarce, especially given that the ear is an organ system providing a crucial function for patients. Agrawal et al. [141] reported that loss of vestibular function extended beyond just balance function and resulted in decreased performance in vision, speech, dexterity, and emotion while significantly decreasing overall quality of life [141]. This is the first review to collectively pool and quantify the prevalence of vestibular symptoms in the above pathologies. Identification of vestibular testing by subgroup type may highlight which methods are common or preferred in certain disease processes. In our study, presence of any vestibular symptom, vertigo, and imbalance were all most common in the VAS subgroup with almost 2/3 of the patients (63%) having those symptoms and 50% having vertigo. After excluding CS cases (which skewed vestibular presentations of the overall subgroup), non-CS VAS cases had a higher overall vestibular symptom, dizziness, imbalance, nystagmus, and abnormal caloric testing rate compared to the CTD subgroup. Discussions with patients regarding symptoms of dizziness and vertigo should be incorporated by rheumatologists when managing VAS patients, and a multidisciplinary approach should be initiated by timely referral to an otolaryngologist [142]. Latency in referral can lead to fibrosis and irreversible damage to the inner ear [143]. This is further emphasized by this study's finding that CTD and VAS patients have > 60 times likelihood of experiencing vertigo or imbalance when compared to control patients.

VAS and CTD groups had the highest prevalence of peripheral vestibulopathy as found on vestibular testing (42.8% and 20.9%, respectively). The presence of a spontaneous nystagmus and AHSN is often a marker of uncompensated, asymmetric input of the peripheral vestibular system, but may also reflect alterations in central vestibular end organs. These findings were more prevalent in VAS patients (OR of 19.6 and 47.5, respectively) simply due to compromised arterial flow, secondary to inflammation, to central or peripheral vestibular systems. OIMD patients also showed the highest rate of spontaneous, positional nystagmus, and abnormal caloric testing (32.3%, 29.5%, and 47.3% respectively). Although these are not specific findings, the decreased or absent response on caloric testing in OIMS, CTD, and VAS patients indicate that the peripheral vestibular system may indeed be involved and a major contributing factor toward audiovestibular symptoms [144]. This emphasizes the need for vestibular testing in those patients.

Preferences in vestibular testing methods and reporting may change with time and be dependent on the availability of vestibular testing resources in a particular clinical setting, institution, or country. Figure 6 in the Appendix further highlights this temporal distribution of study publication between included cohort studies and case reports. The first included cohort study in this review was approximately 30 years after the first included case report (1980 versus 1952) [145, 146]. Commercially available equipment has gotten more accessible for vestibular testing since their inception in the early 2000s [147].

Hearing loss, particularly at lower frequencies, has been shown to be more common in patients with CTD and VAS in congruence with the increased odds (OR = 9.1) demonstrated in our study [148, 149]. In patients with ulcerative colitis, sensorineural hearing loss is the most common auditory symptom as reflected in the present study with 77.3% of included patients experiencing symptoms. Fousekis et al. [150] also found that patients with AIED secondary to IBD has minimal to no response to steroid treatment [150]. The propensity of multiple autoimmune disorders occurring in patients makes pinpointing the true cause of secondary AIED difficult. Subjective symptoms such as hearing loss should be investigated upon presentation in patients as hearing loss could represent an early sign of autoimmune disease.

Even when excluding Cogan syndrome cases, a third of patients with VAS and a fifth of patients with CTD have a confirmed vestibular pathology. It is very likely that this is even underrepresented given the heterogeneity of vestibular testing and the fact that most articles may not have conducted or reported a complete panel of vestibular testing, including VNG, rotational chair, video HIT, and VEMPs. While those symptoms could be related to neuropathy or cardiac/hemodynamic involvement or secondary to treatment side effects, identifying a vestibular dysfunction early may help initiate targeted treatment or vestibular rehabilitation sooner [151–153].

Though an array of vestibular testing is available, abnormal findings on vestibular testing may not always translate to a loss of function. Abnormal results should always be correlated with clinical symptoms. Standardized vestibular reporting will allow clinicians to properly understand and better relay information about the vestibular system which may help early detection of dysfunction and early referral to vestibular rehabilitation if needed to minimize risk of falls.

The author, country of publication, and audience toward which the work is directed are all factors which influence the clarity of vestibular reporting (Appendix). Only 64% of authors were otolaryngologists or neurologists by training, calling into the question if vestibular symptoms, signs, and testing have been appropriately interpreted. Thus, the importance of defining vestibular terms cannot be overlooked. An organized checklist or system including, but not limited to, standardizing the way vestibular results and terms are reported in academic journals, regardless of specialty, to better pool data can better facilitate understanding among physicians of various specialties. Identifying vestibular dysfunction early can change quality of life and reduce morbidity in these patients.

Limitations and future directions

This review highlights that audiovestibular pathologies are frequent in patients with systemic rheumatologic disorders. While otolaryngologists are the specialists most likely to interface with audiovestibular symptoms, the treatment of these patients is often multidisciplinary, and management should be done in collaboration with a rheumatologist. Increasing visibility of this problem to rheumatologists screening for organ involvement of the systemic diseases they are treating is primordial. While vital organs should continue to be monitored, the inner ear should also be investigated with emphasis on treating audiovestibular manifestations in a timely way to help reduce risks of complete failure. Many studies have linked loss of hearing and vestibular function to detrimental quality of life impact [141, 154].

One of the major limitations of this paper is the heterogeneous reporting of vestibular data (symptomatic and objective data). The word dizziness is a very nonspecific marker that could implicate vestibular and nonvestibular diagnoses, and our results likely underrepresent the subjects with vestibular diagnoses. Furthermore, making sense of the grouped results of vestibular testing is difficult in the absence of a clear understanding of what the finding is. For instance, while positional nystagmus can reflect benign paroxysmal positional vertigo, it can also be a central vestibular finding, and reviewed papers did not always allow for that determination. Our results further emphasize the need for a standardization in reporting vestibular results. This standardization would allow for greater comparison between independent samples and studies, increase reproducibility, and would increase power when studies are pooled. Due to changing standards in vestibular testing, the addition of new technologies, and the availability of resources in individual clinics, it is difficult to compare disease diagnostics overtime. Furthermore, autoimmune conditions are already rare pathologies, and studies often have small sample sizes. In such scenarios, quality of reporting in these studies should be held to a higher standard. Often, a mismatch exists between what the authors sought in their methods and what the articles ultimately report in their results. Thus, there is a need for a published standard of reporting for vestibular results, akin to those in place for audiometric standards (i.e., New Hearing Reporting Standard for clinical trials) [155]. Pooling is difficult if only "processed results" (i.e., standardized mean differences) are provided without access to raw values.

As previously mentioned, this study included a two-pronged approach. The cohort studies added power to our analysis, but the individual stories of the patients and complete clinical picture of vestibular disease process are lost. It is difficult to categorize a patient into a vestibular pathology in the absence of other clinical information. Additionally, it is important to note the varying exclusion criteria for these studies. Although authors largely excluded baseline otologic disease that may not have been due to autoimmune pathology, confounding factors such as another non-autoimmune otologic comorbidity could have been present. Abnormal oculographic findings are normal and non-pathologic in older patients, but, in a cohort design with pooled analysis, this is difficult to ascertain. To build this clinical context, a summary of case reports was utilized.

Conclusion

Vestibular symptoms are often overlooked in the setting of secondary AIED with no clear-cut diagnostic algorithm. Thus, it is likely that vestibular dysfunction is likely underdiagnosed in patients suffering from AIED. Primary care providers, rheumatologists, and otolaryngologists should collaborate to manage patients presenting with potential cochlear and vestibular involvement. Undergoing multiple workups for diagnosis of autoimmune disorders can be a difficult journey for patients; however, with early identification of audiovestibular issues, early intervention may improve quality of life and reduce morbidity. Pairing clinical data with audiometric and vestibular testing can help guide both otolaryngologists and rheumatologists with accurate diagnosis and more precise management. To improve our ability to understand the impact on the vestibular system, vestibular clinicians need to develop a standardized reporting method that can improve communication and reporting across specialties. Early identification can also aid in tracking disease progression and quality of life for patients.

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