Review Article

Audio-vestibular symptoms in systemic autoimmune diseases

Massimo Ralli MD, PhD [1], Vittorio D'Aguanno MD [2], Arianna Di Stadio MD, PhD [3], Armando De Virgilio MD [4], Adelchi Croce MD [5], Lucia Longo MD [2], Antonio Greco MD [2], Marco de Vincentiis MD [1]

1) Department Oral and Maxillofacial Sciences, Sapienza University of Rome, Rome, Italy
2) Department of Sense Organs, Sapienza University of Rome, Rome, Italy
3) San Camillo Hospital IRCCS, Venice, Italy
4) Humanitas Clinical and Research Center. Via Alessandro Manzoni 56 - 20089 Rozzano (MI), Italy
5) Department of Otolaryngology, Università Gabriele d'Annunzio Chieti, Italy

Corresponding Author:

Vittorio D'Aguanno, MD

Department of Sense Organs, Sapienza University of Rome

Viale del Policlinico 155, 00100 Rome, Italy

E-mail: vitdaguanno@libero.it

Phone Number: +39 0649976808

Conflict of Interest of all authors: the authors report no conflict of interest

Funding source: the authors report no funding sources for this article

Abstract

Immune-mediated inner ear disease can be primary, when the autoimmune response is against the inner ear, or secondary. The latter is characterized by the involvement of the ear in the presence of systemic autoimmune diseases. Sensorineural hearing loss is the most common audio-vestibular symptom associated to systemic autoimmune diseases, although conductive hearing impairment may also be present. Hearing loss may present in a sudden, slowly or rapidly progressive or fluctuating form, and it is mostly bilateral and asymmetric. Hearing loss shows a good response to corticosteroid therapy that may lead to near-complete hearing restoration. Vestibular symptoms, tinnitus and aural fullness can be found in patients with systemic autoimmune diseases; they often mimic primary inner ear disorders such as Menière's disease and mainly affect both ears simultaneously. Awareness of inner ear involvement in systemic autoimmune diseases is essential for the good response shown to appropriate treatment. However, it is often misdiagnosed due to variable clinical presentation, limited knowledge, sparse evidence and lack of specific diagnostic tests. The aim of this review is to analyse available evidence, often only reported in the form of case reports due to the rarity of some of these conditions, of the different clinical presentations of audiological and vestibular symptoms in systemic autoimmune diseases.

Keywords: autoimmune disease, immune-mediated inner ear disease, hearing loss, vertigo, tinnitus.

Introduction

The inner ear has been considered for a long time an immune-privileged site, spared from organ-specific autoimmunity and rarely involved in systemic autoimmune diseases thanks to the blood-labyrinthine barrier [1]. Lehnhardt [2] was the first to hypothesize that sudden or rapidly progressive sensorineural hearing loss (SNHL) could be the result of an autoimmune process against the inner ear. McCabe [3] showed the success of steroid and cytotoxic treatment in a cohort of patients with bilateral progressive SNHL, suggesting an autoimmune pathogenesis. Recently, several studies showed inflammatory cells in the inner ear, describing the presence of resident cochlear macrophages in animal models and the recruitment of inflammatory macrophages to the cochlea [4]. In 2016, McKenna et al. identified cells with staining characteristics and morphology consistent with macrophage/microglia in the human cochlea [4]; the presence of these cells in patients with autoimmune diseases suggests that they may have an important role in inner ear pathology due to the increased level of pro-inflammatory cytokines and reactive oxygen species (ROS) induced by microglia [4].

There is growing interest for inner ear involvement in systemic autoimmune diseases [5, 6], a condition that should be considered in patients with audio-vestibular dysfunction presenting a constellation of symptoms consistent with systemic autoimmunity, or with a pre-existing diagnosis of autoimmune disease [7, 8]. This should be distinguished from primary autoimmune inner ear disease, a condition in which the autoimmune response acts directly against the inner ear [6, 7].

Inner ear involvement in autoimmune diseases is estimated to account for less of 1% of all cases of acquired hearing loss [7] and follows gender and demographic characteristics of autoimmune disorders, with higher prevalence in female patients between their thirties and fifties [5].

A correct identification of inner ear involvement in patients with systemic autoimmune diseases is essential for the possibility of near-complete hearing restoration with appropriate treatment [9]; however, it is often misdiagnosed due to variable clinical presentation, limited knowledge, sparse evidence and lack of specific diagnostic tests.

The aim of this review is to analyse the available evidence, often only reported in the form of case reports due to the rarity of some of these conditions, of the different clinical presentations of audiological and vestibular symptoms in systemic autoimmune diseases.

Main Text

Pathophysiology of inner ear involvement in autoimmune diseases

Pathophysiology of inner ear involvement in systemic autoimmune diseases is still unclear and may be related to circulating antibodies against a number of inner ear antigens leading to antibody-dependent cell-mediated cytotoxicity, the activation of the complement system, a direct action of cytotoxic T cells, or to immune complex-mediated damage [5, 7, 8, 10-14].

The immune complex deposition seems to play a central role in inner ear involvement; it leads to vasculitis of inner ear vessels that determines atrophy of the stria vascularis and SNHL. The deposition of immune complexes reduces the calibre of the auditory arteries with a consequent decrease in blood flow; blood flow reduction induces an oxygen deficit that increases ROS level responsible for damage to the hair cells and spiral ganglion [15-17]. This pathogenic mechanism appears to be the major factor involved in cochlear and vestibular damage in systemic autoimmune diseases, especially when affecting the labyrinthine artery, the common trunk of the inner ear vascularization system [18].

Temporal bone studies clearly explain the mechanism of damage. The vascular ischemia, underlying vasculitis, initially determines the atrophy of the stria vascularis and hair cell death; the progression of the inflammation initiates bone inflammatory processes such as necrosis or cochlear fibrosis [8], more evident in the final stages of the disease [19].

Audio-vestibular symptoms in systemic autoimmune diseases

Audio-vestibular dysfunction in systemic autoimmune diseases may have different clinical presentations with elevate inter-individual variability [20]. Hearing loss is the most common condition, followed by tinnitus and vertigo [8].

Characteristics of hearing impairment are extremely variable. The hearing loss is typically sensorineural, affecting mainly the high frequencies [8, 9], although low and mid-frequencies hearing loss is common in case of vasculitis [20]. The general pattern of SNHL is rapidly progressive over a period of weeks to months, with great timing variability among different systemic diseases [21]; fluctuations in hearing are common, although the overall course is a progressive deterioration of auditory function [9]. Hearing loss is mainly bilateral and asymmetric; however, cases of unilateral SNHL that manifests in the contralateral ear after a variable time have been described [21]. In some cases, a temporary and acute blood flow reduction in the inner ear may be related with the onset of Sudden Sensorineural Hearing Loss (SSNHL), with complete or partial recovery after restoration of normal perfusion. SSNHL is common in patients with inner ear involvement following systemic autoimmune diseases, and it may be the presenting symptom in some cases [5, 20]. Despite hearing loss is mainly sensorineural, autoimmune diseases can also induce a conductive hearing loss (CHL). In these cases, CHL may follow the effusions of the middle ear and the inflammation of Eustachian tube mucosa or involve the ossicular chain [22-24].

Tinnitus in systemic autoimmune diseases is mainly found in association to hearing loss. It has been established that the decrease of peripheral input following hearing loss can trigger neuroplastic reactions up to the auditory cortex responsible for the onset of tinnitus. Therefore, it is probable that peripheral auditory dysfunction could initiate central changes that eventually lead to tinnitus onset in patients with autoimmune diseases [25-28].

Vestibular symptoms, such as rotational vertigo or disequilibrium, may follow temporary occlusion of the labyrinthine or the anterior vestibular artery [1, 11] and they often mimic primary inner ear disorders such as Menière disease [3, 21].

A list of systemic autoimmune diseases that have been reported to be associated to audio-vestibular symptoms, along with relevant literature references, is shown in *Table 1*.

Table 1: Systemic autoimmune diseases associated to audio-vestibular symptoms

Autoimmune Disease	Prevalence of audio-vestibular involvement	Classification	Literature Reference
Systemic Lupus Erythematosus	6-70%	Systemic autoimmune rheumatic disorders	15,16,18; 29-37; 133
Cogan Syndrome	31-45%	Systemic vasculitis	38-43; 134
Sarcoidosis	5-96%	Systemic granulomatous diseases	44-48; 135
Rheumatoid Arthritis	25-72%	Systemic autoimmune rheumatic disorders	24; 49-51
Antiphospholipid Syndrome	Case reports only	Autoimmune hypercoagulable condition	52-57
Polyarteritis Nodosa	Case reports only	Systemic vasculitis	58-67; 137
Behcet's disease	12-80%	Systemic vasculitis	68-73; 134
Takayasu's Arteritis	Case reports only	Systemic vasculitis	74-81; 138; 145
Relapsing Polychondritis	40-54%	Autoimmune connective tissue disorder	23; 82-87; 139
Wegener's Granulomatosis	8-65%	Systemic vasculitis	88-91
Susac's Syndrome	Case reports only	Systemic vasculitis	92-97; 141
Sjögren's syndrome	22-46%	Systemic autoimmune rheumatic disorders	22; 98-103; 142
Myasthenia Gravis	22-34%	Autoimmune condition affecting neuromuscular junction	104-113; 143
Multiple Sclerosis	1-28%	Autoimmune inflammatory demyelinating disease	4,15; 114-122; 144

Hashimoto Thyroiditis	Case reports only	Autoimmune thyroid disease	123
Mixed Cryoglobulinemia	22%	Systemic vasculitis	124
Giant Cell Arteritis	7-100%	Systemic vasculitis	125-127
Vogt-Koyanagi-Harada's Disease	48-62%	Systemic granulomatous diseases	128
Ulcerative Colitis	2-5%	Autoimmune inflammatory bowel disease	129,130

Summary of systemic autoimmune diseases that have been reported to be associated to audio-vestibular symptoms, along with reported prevalence of audio-vestibular involvement, classification and relevant references.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiorgan involvement and an incidence higher in women (82%-96%) than in men (4%-18%) [29].

The audio-vestibular symptoms that present in patients with SLE may follow antibody/antigen direct reactions, cytotoxic action or immune complex deposition [15]. Vasculitis following immune complex deposition is the major cause of cochlear and vestibular damage in SLE patients. Immune complexes deposit in the auditory artery reducing the vessel calibre with a consequent decrease in blood flow and oxygen deficit; this stimulates the release of ROS that damage the hair cells and the spiral ganglions with consequent hearing impairment [16].

SNHL is the most common audio-vestibular symptom in SLE, with a prevalence between 6% and 70% [15]. Hearing loss may be bilateral or unilateral; slowly progressive or sudden; it mainly affects high frequencies, mimicking the typical presbycusis pattern, but may also involve the low and middle frequencies [15]. Maciaszczyk et al. [30] and Roverano et al. [18] described progressive, bilateral SNHL involving the high frequencies. Khalidi et al. [31] reported unilateral SNHL involving mid and high frequencies (500, 1000, 2000, and 3000 Hz) associated with a 16%-word discrimination score as demonstrated by speech audiometry. Sperling et al. [32] described both bilateral and slowly progressive SNHL and unilateral SSNHL in patients with SLE.

Tinnitus is often associated with hearing loss in SLE, most probably following peripheral deafferentation [33-35].

The vestibular system could be involved in SLE, but vertigo and dizziness have rarely been reported [35, 36]. Balance disorders as a consequence of SLE have been observed also in children [37]. However, the incidence of vestibular symptoms may be underestimated due to their slowly progressive onset and consequent compensation by the somatosensory system and vision.

Cogan's Syndrome

Cogan's Syndrome (CS), first described in 1934, is a rare autoimmune disorder characterized by ocular and audio-vestibular symptoms [38]. CS develops in young adults, mostly during their first three decades of life [39, 40]. The origin of CS is still unclear. Antibodies against Cogan peptide have been found in serum of patients with CS. Also, this peptide antigen shares sequence homology with CD148 and Connexin 26, both involved in congenital deafness [41].

CS includes a large spectrum of clinical manifestations. Haynes et al. [42] defined two types of CS, a typical and an atypical variant. Typical CS is defined by ocular symptoms, classically presenting as non-syphilitic interstitial keratitis (IK); audio-vestibular symptoms similar to those of Ménière's disease (recurrent episodes of hearing loss, tinnitus and vertigo); and an interval between the onset of ocular and audio-vestibular manifestations of less than 2 years. Atypical CS is characterized by different inflammatory ocular manifestations, with or without IK; audio-vestibular symptoms (usually progressive hearing loss); and, most important, a delay of more than 2 years between the onset of ocular and audio-vestibular manifestations. In many cases, it is difficult to differentiate between the two types of CS because some patients do not present IK at the onset of the disease or, alternatively, they develop this condition during the following years. Systemic manifestations are much more frequent in atypical CS and can be used in the differential diagnosis between the two types [40].

Inner ear involvement in CS has been reported with a prevalence between 31 and 45% [39-43]. The most common audio-vestibular manifestations in CS are hearing loss, vertigo, tinnitus, ataxia and oscillopsia [40]. These symptoms can appear at any time during the course of the disease [43]. Hearing loss may be both unilateral or bilateral, often presents as SSNHL with fluctuations or progressive worsening over time. Progression to complete bilateral hearing loss has been reported in almost 50% of patients during the follow-up period, whereas permanent hearing loss in one ear was observed in 20% of patients [43].

Tinnitus usually follows auditory deafferentation [40].

Abnormal vestibular function is found in 90% of patients with CS; at least 20% of the patients present spontaneous or gaze-induced nystagmus. Rarely, patients present with clinical symptoms of vestibulopathy that lasts for days or weeks from the time of onset without spontaneous resolution that frequently results to hospitalization [43].

Sarcoidosis

Sarcoidosis is an inflammatory multi-system disease with unknown origin. CNS involvement is reported in about 5-7% of patients with systemic sarcoidosis, called neurosarcoidosis (NS) [44].

A cranial nerve neuropathy affecting the facial and optic nerves is a common finding in up to 80% of NS patients; the eighth crania. nerve involvement is seldom reported [44, 45].

Audio-vestibular involvement is common in sarcoidosis. In a review of 50 patients with NS [46], a high incidence of audio-vestibular manifestations was noted. Hearing loss was present in 49/50, unilateral in 25% and bilateral in 75% of the patients. Tinnitus was reported in 30 patients (61%) and vestibular impairment was recorded in 32/50 (64%) including vertigo, dizziness and benign paroxysmal positional vertigo. A complete vestibular function testing was performed in 24 patients found abnormalities in 23 (96%). Of those, six (25%) had unilateral alterations; 16 (67%) had bilateral alteration and one (8%) had a non-localizing dysfunction. In another review, Babin [47] reported SNHL in approximately 90% of reported cases, characterised by sudden or rapidly progressive onset,

and vestibular symptoms with abnormal vestibular functioning tests in a similar percentage of cases. In almost 50% of the cases, at least partial hearing recovery was achieved after high-dose systemic steroid administration, while balance disorders recovered either spontaneously or after treatment [47]. A recent study [48] reported two new cases of SSNHL due to probable NS, each having a quite different clinical course. In one case, unilateral SSNHL and facial palsy were the presenting symptoms of NS, while in the second, unilateral SSNHL occurred despite ongoing immunosuppressive treatment for NS.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting about 1% of the general population [49]. Principal symptoms referred by patients are articular and periarticular, although RA can involve other organs including heart, lung, skin, and eye [49].

Several events can lead to audio-vestibular alterations during the course of RA; thus, a wide variation in the prevalence of different types of hearing impairment in RA patients may be found [50]. SNHL is the most common type of hearing impairment in RA patients ranging from 25% to 72% [50]. Conductive and mixed hearing loss have also been reported, although less frequent [50].

A prospective case-control study [24] compared hearing disturbances in patients with RA with a control group. In 60% of the RA patients, SNHL was observed and the difference was statistically significant at 500 Hz, 1 kHz, and 2 kHz in both ears. CHL was reported in 17.1% of the RA patients compared to 5.7% of patients in the control group, with a statistically significant difference.

Pathogenesis of CHL in RA is still poorly understood; several hypotheses have been proposed. A laxity of the middle ear transducer mechanism [51] was proposed although others authors [24] suggested increased stiffness of the ossicular system.

Antiphospholipid syndrome

The antiphospholipid syndrome (APS) is an acquired disorder characterized by the presence of antiphospholipid antibodies such as anticardiolipin (aCL) and lupus anticoagulant (LAC) antibodies causing hypercoagulability. The characteristic triad of the disease is the is the association of specific antibodies, arterial or venous thrombosis and/or pregnancy morbidity and mortality [52]. APS is associated with microthrombosis, causing cutaneous manifestations like purpuric eruptions, livido reticularis, and skin ulcerations. The involvement of retina may cause amaurosis fugax [53].

The involvement of the inner ear has been reported in APS, and is related to antibodies targeting the small vessels of the labyrinthine circulation. Endothelial cells within the cochlear circulation might be activated by antiphospholipid antibodies directly or by inducing the formation of free radicals that, secondarily, damage the endothelium. These upregulated endothelial cells would initiate local microthrombus formation and subsequent ischemia to the target organ [54].

The association of aCL or LAC antibodies and SSNHL was firstly reported by Naarendorp and Spiera [53] in six patients with SLE or a lupus-like syndrome. Toubi et al. [55] studied sudden and progressive SNHL in 30 patients showing that in control group no one had aCL antibodies, whereas 27% of the patient group had aCL antibodies in low to moderate concentration. In a subsequent study, Toubi [56] reported that 31% of patients with idiopathic SSNHL were positive for aCL, compared with only 6% of matched control subjects. A prospective study [57] including 168 patients with progressive SNHL undergone a screening panel of blood tests for autoimmune disease including aCL antibodies, anti-B2 glycoprotein, and LAC. In this population, forty-two patients (25%) had at least one elevated antiphospholipid antibody marker and twenty patients had two or more positive test results, suggesting that antiphospholipid antibodies could be involved in the pathogenesis of some forms of inner ear dysfunction, related to a microthrombus formation in the labyrinthine vasculature.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that mainly affects medium sized arteries, although small arteries may also be involved [58]. The incidence of PAN ranges from 0 to

1.6 cases per million, and the prevalence of this disease is approximately 31 cases per million [59]. PAN affects men more frequently than women and occurs in all ethnic groups; the average age at onset is approximately 50 years [60].

The pathogenesis of idiopathic PAN remains enigmatic, although the clinical response to immunosuppressive therapy suggests that immunological mechanisms play an active pathogenic role. As in other forms of vasculitis, the presence of impaired endothelial function could reflect direct endothelial cell activation and damage resulting from primary inflammatory vasculitis or proinflammatory cytokines or antibodies [59].

Clinical manifestations of PAN include non-specific constitutional manifestations, such as sickness, weight loss, fever, arthralgia and myalgia. Dysfunction or damage of target organs may produce specific symptoms, often caused by occlusion or rupture of inflamed arteries. The most frequently involved territories are the skin and peripheral nervous system [59].

SNHL is often reported in PAN [61-63] and, in rare instances, may occur as the presenting symptom of the disease [64, 65]. Hearing loss is typically bilateral and symmetrical, with sudden onset [64, 66] or a rapidly progressive course [62, 67]. Alterations found in Auditory Brainstem Responses (ABR) suggest an inner ear involvement, and the involvement of low frequencies may resemble those found in endolymphatic hydrops [66]. Tinnitus, vertigo and occasional nausea and vomiting may also be found in patients with PAN [64].

Behcet's disease

Behcet's disease (BD) is a chronic systemic relapsing syndrome affecting young adults and characterized by the presence of recurrent oral and genital ulcers, ocular inflammation and skin lesions caused by a vasculitis involving small vessels [68].

Hearing loss is a common compliant in BD, it is mainly bilateral and predominantly affects high frequencies; several studies have reported SNHL following cochlear impairment ranging from 12% to 80% in BD patients [68, 69]. No relationship has been found between the age or the disease

duration and inner ear involvement [69, 70]. A recent survey [71] of 65 BD patients reported that audio-vestibular complaints were found in 47% of patients. The most common symptoms were tinnitus (11%), hearing loss (10%), vertigo (8%); a case of unilateral SSNHL was also reported.

Nearly half of BD patients report orthostatic disequilibrium [68]. Studies of the vestibular function [69, 70] showed that BD mainly causes a peripheral lesion rather than a damage to the central vestibular tracts, although another study [72] showed a higher prevalence of central vestibular syndrome in BD patients. Magnetic resonance studies did not show any degenerative conditions of basal ganglia and brainstem atrophies in BD patients with abnormal vestibular function tests [71, 72]. Neural involvement in BD (Neuro-Behcet) may appear with dizziness or vertigo as initial symptoms, mimicking a vestibular neuritis [73].

Takayasu's arteritis

Takayasu's arteritis (TA), also known as aortitis syndrome, is a vasculitis that mainly affects large elastic arteries with symptoms caused by organ ischemia, aneurysm formation, and inflammation. TA is more prevalent in women of reproductive age and clinical features usually reflect limb or organ ischemia that follow gradual stenosis of the involved arteries [74, 75].

The aetiology of hearing impairment in TA remains unknown [75]; it has been hypothesized that hearing loss follows the elevation of serum immune complexes that deposits in the inner ear or reversible circulatory disturbances with hypercoagulability in response to the arterial disease [76]. Although TA involves medium and large caliber arteries, Noel reported that the occlusion of small retinal vessels is a rare and severe microcirculatory complication in TA; common immunopathology mechanisms with hearing loss could be hypothesized [77]. Moreover, Maruyoshi speculated that hearing loss in TA could have a vascular background based on reversible circulatory disturbances due to vasculitis and/or some autoimmune pathogenesis in the inner ear, involving especially hair cells [76].

Only a few cases in the literature reported an association of TA with SNHL [78-80]. Hearing loss is often progressive, although it can be stable or fluctuating, is usually bilateral and asymmetric, develops over several weeks to months and mainly involves high frequencies. SNHL may also present as a SSNHL. A good response to corticosteroid therapy has been reported for SNHL in TA, although it may also persist despite therapy [76]. Recently, Ralli et al. described a case of a 36-year-old woman with TA who had two episodes of SSNHL involving one ear at a time with an 11-month delay between each episode treated Hyperbaric Oxygen Therapy associated to corticosteroids, with significant improvements in both ears [81].

Relapsing polychondritis

Relapsing polychondritis (RP) is a rare connective tissue disorder, affecting organs containing collagen, such as the eye, cartilage tissue and skin. The diagnosis is based on clinical features and no specific test for this disease is available, thus definitive diagnosis takes a long time and often the prognosis is poor [82]. Recurrent bouts of inflammation may lead to a permanent destruction of involved structures such as cartilage of the ears, nose, larynx, tracheobronchial tree and cardiovascular system [83]. McAdam et al. [84] proposed diagnostic criteria for RP when three or more of the six clinical features are present: recurrent chondritis of both auricles; non-erosive, seronegative inflammatory polyarthritis; chondritis of the nasal cartilages; ocular inflammation (conjunctivitis, keratitis, scleritis, uveitis); respiratory tract chondritis affecting laryngeal and tracheal cartilages; cochlear and/or vestibular dysfunction (SNHL, tinnitus, vertigo).

Auricular chondrite is a quite specific sign of RP. It is present in 20% of patients at the onset of the disease and in 90% during the course of the disease [85]. One or both ears can be affected. The concha is swollen, red, or less often purplish, hot, and painful even at the slightest contact. The ear lobe, which does not contain the cartilage, is spared.

Audio-vestibular impairment is reported in 40-54% of all patients with RP [86]. These changes can represent the initial symptoms heralding the outbreak of the disease or appear after the onset of other

symptoms. Typical manifestations can be bilateral or unilateral, are usually of sudden onset and appear as perceptive deafness or tinnitus combined with or without vertigo and nausea [84]. CHL can be a result of a serous otitis following chondritis of the eustachian tube [23]. Further, the SNHL in RP patients has been suggested to be the result of inflammation of the internal auditory artery or its cochlear branch [87], or due to autoantibodies against the cochlea and vestibular organ [86]. This could explain the near-complete hearing recovery in patients after treatment with corticosteroids.

Wegener's granulomatosis

Wegener's granulomatosis (WG) is an autoimmune disease of unknown aetiology characterized by necrotizing granulomatous inflammation of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis that affects predominantly small vessels.

Although the pulmonary, nasal, and renal manifestations of WG are well described, hearing symptoms are less appreciated. Studies available in the literature report a prevalence of audiovestibular symptoms in 8-65% of patients with WG, mainly auditory symptoms with SNHL [88, 89] or CHL in cases of WG involving the middle ear [90]. Audiometric patterns of WG have been described as typically flat, although sometimes additional high frequency losses may coexist and differential diagnosis with noise exposure or age-related hearing loss may be difficult [90]. Hearing impairment may also present as SSNHL; Bakthavachalam [91] identified hearing loss in 56% of patients suffering from WG and SSNHL was the most common form, occurring in 47% of cases.

Hearing loss may be a presenting symptom of WG, and in some cases the primary complaint. SNHL in WG is believed to be largely irreversible, therefore potentially adding to the patient’s cumulative disability [90]. SNHL evaluation and monitoring is therefore recommended for appropriate patient management and could suggest a worsening of disease that may address to a specific treatment like cyclophosphamide rather than either methotrexate or azathioprine [88, 89].

Susac's syndrome

Susac's syndrome (SS) is a rare immune disease characterised by encephalopathy, branch retinal artery occlusion and sensorineural hearing loss [92]. SS has a higher prevalence in females, with a male:female ratio of 1:3.5 [93].

The pathophysiology of SS is not entirely clear. Anti-endothelial cell antibodies (AECAs) in SS have been recently documented [93]. Potential targeted antigens suggested in other studies focusing on AECAs include cytoskeletal proteins (β-actin, α-tubulin, and vimentin), glycolytic enzymes (glucose-3-phosphate-dehydrogenase and α-enolase), and the prolyl- 4-hydroxylase β subunit, a member of the disulfide isomerase family [94].

Clinical manifestations of SS are thought to be caused by autoimmune-mediated occlusions of microvessels in the brain, retina and inner ear, that lead to a characteristic clinical triad of central nervous system (CNS) dysfunction [95]. At clinical onset, the most common manifestations are CNS symptoms, observed in two-thirds of patients, followed by visual symptoms and hearing disturbances. Unfortunately, only a small number of patients (around 13%) show the characteristic symptoms of SS at disease onset, thus definitive diagnosis is often delayed [95].

Hearing loss can be a dramatic and severely debilitating feature of SS. Hearing loss may be mild and insidious, or may be fluctuating, mimicking Meniere's disease [96]. A loss of the low or middle frequencies is typical, suggesting a vulnerability of the cochlear apex to microinfarction; loss of high frequencies can also occur [97]. Hearing loss often occurs overnight and may affect both ears. Dörr et al. refer to this clinical behaviour as the “bang-bang hearing loss” [95]. Severe hearing loss is often accompanied by vertigo and a roaring tinnitus; the occlusion of cochlear and vestibular arterioles may be the cause of these symptoms [93]. In these patients, that often develop severe/profound SNHL and can no longer benefit from hearing aid amplification, cochlear implantation is a valid therapeutic option.

Sjögren’s syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by xerostomia and xerophthalmia due to lymphocyte infiltration of both salivary and lacrimal glands. It may also occur as a systemic disease involving kidneys, lungs, liver, vessels and lymph nodes. pSS mainly affects women in the fourth-fifth decade of life and presenting symptoms are often oral and ocular [98]. In this context, autoantibodies to cardiolipin and M3 muscarinic receptors (mAchRs) in the serum of pSS patients are suspected to play a pathogenic role in the onset of progressive hearing loss and neurological complications [98].

Audio-vestibular involvement in patients with pSS has been reported in the literature qith a prevalence ranging from 22% to 46%. Boki et al. [99] reported in a pSS patient the presence of SNHL affecting preferentially the high frequencies. Tumiati et al. [100] reported SNHL in 46% (14/30) patients with pSS. Ziavra et al. [101] diagnosed SNHL in 22.5% (9/40) of pSS patients. Hearing loss as presenting complaint in pSS is quite uncommon and only limited to case reports [22]; SSNHL was recently reported in a 62-year-old female treated with high-dose methylprednisolone (250 mg) infusion for 5 days with successful hearing restoration [102].

The high prevalence of cranial neuropathies is a known condition in pSS, therefore symptoms and signs of the eighth cranial nerve disorder could be present [103].

Although pSS patients tend to have a higher prevalence of SNHL compared to the general population, no evidence of damage to the central auditory pathways was reported [100]. However, the prevalence of audio-vestibular symptoms in pSS might be underestimated, suggesting that their association with pSS was not previously made because it had not been actively sought [100].

Myasthenia gravis

Myasthenia gravis (MG) is the most common autoimmune disorder affecting the neuromuscular junction, characterized by muscle weakness and fatigue [104]. Weakness, the typical clinical symptom of MG, affects facial, ocular, bulbar, respiratory or limb muscles and worsen after muscular activity [105].

In healthy subjects, acetylcholine (ACh), the primary neurotransmitter of the efferent auditory system, has been found to enhance the electromotility of Outer Hair Cells (OHC) binding to acetylcholine receptors (AChRs), which are localized on the post-synaptic membrane of OHC [106]. In patients with MG, autoantibodies against AChRs were reported to bind to AChRs on OHCs, inducing a progressive loss of AChRs that decreases OHC electromotility [107]. This cascade of events induces apoptosis in all three rows of OHCs, evolving into a clinically evident hearing loss in some cases [108]. The efferent auditory system has been investigated using contralateral acoustic stimulation (CAS) [109]. CAS produces physiological suppression of otoacoustic emissions [110] protecting the hair cells from noise of moderate to high intensity [111]. A reduced CAS effect has been reported in patients with MG compared to control subjects, suggesting a possible role of the progressive reduction of beta subunits of nicotinic AChRs associated to the destruction of the basal membrane and OHCs due to prolonged exposure to autoantibodies [107, 109].

At MG onset, patients do not refer hearing loss and Pure Tone Audiometry (PTA) is often within normal range. A specific test studying the activity of the OHC, otoacoustic emissions (OAE), may show some abnormalities, as OAE have been found to exhibit greater sensitivity to incipient cochlear damage compared to PTA, particularly for high frequencies [108, 112]. A study on 16 MG patients reported a clinical hearing loss in 30% of the patients, while 100% of the patients exhibited abnormal distortion product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs) [113]. Therefore, OAE should always be performed in MG patients because they can early detect the MG related effects on the ACh-innervated auditory system [104].

Additional audiological symptoms, such as tinnitus, should be always considered and investigated although seldom reported [27].

Vertigo, also reported in patients with MG, seems to be more related to musculoskeletal alterations rather than to vestibular impairment [105].

Multiple sclerosis

Multiple sclerosis (MS) is traditionally considered an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). The autoimmune pathogenesis of MS is still debated; recently it has been hypothesized that it may be a homogeneous degenerative process analogous to primary neurodegenerative diseases [114]. As an exacerbating and remitting immune-mediated disorder of interfascicular oligodendrocyte produced myelin, MS can impair acutely and transiently any CNS neural system, including the auditory pathways [115].

The evidence of a clear presence of macrophages in human temporal bone of patients affected from autoimmune diseases [15] support the hypothesis that in MS the autoimmunity mechanisms also affect the structures of the inner ear; hair cells, auditory and vestibular spiral ganglion neurons may be subject to the attack of lymphocytes and their damage may present with SNHL and vertigo. The microglia, a cell population that belongs to the macrophage family and that is normally represented in brain, has been shown to be active in aggressive forms of MS (phenotype M1). Temporal bone studies could suggest that microglia can migrate to the internal auditory canal and to the cochlea [4]. M1 microglia can demyelinate cochlear and vestibular structures causing SSNHL or vertigo; such episodes may be temporary due to the relapsing-remitting phases of MS that activates and inactivates the M1 microglia.

In the literature, several reports showed MS-related hearing deficits. Hearing loss may occur when MS involves both the peripheral and the brainstem auditory pathway [116]; however, in some case, MS lesions involving the auditory pathways may not determine a clinically evident hearing impairment [117]. In rare cases, SSNHL may be the only presenting symptom of MS, and may appear early in the course of the disease with good prognosis and little or no residual hearing deficit [118].

MS patients typically report a difficulty in speech perception, especially in noise [119]. This alteration is due to an abnormal auditory processing, such as problems with dichotic listening tasks and auditory temporal processing [119]. Performance of chronic MS subjects in speech reception threshold (SRT) is normal in the standard clinical level (70 dB above the SRT); however, when lower levels are used, performance significantly decreases compared to age-matched controls suggesting a deficit in

cognitive processing, such as attention and auditory discrimination, which is especially required in binaural integration of sound. [120]

Furthermore, studies have shown that 40-55% of individuals with MS have at least an episode of dysarthria or speech alteration characterized by slowness, slurring, or difficulties in production or comprehension [120].

Disequilibrium in MS is often related to internuclear ophthalmoplegia and multiple nystagmus constitute the most typical vestibular signs of MS, although peripheral equilibrium may coexist [121]. Multidirectional nystagmus without latency may be an atypical central sign, and differential diagnosis with peripheral disorder, such as benign paroxysmal positional vertigo, can be more difficult, although adaptation and fatigue of nystagmus play a central role in differential diagnosis. When the clinical findings are not clear and ex-adjuvantibus criteria cannot be adopted, vestibular evoked myogenic potential (VEMP) may be proposed for the differential diagnosis of positional vertigo in association with careful clinical history and otoneurologic examination [121].

Audio-vestibular symptoms in young, neurologically normal subjects, especially when spontaneous recovery occurs, could represent an early sign of MS even when no demyelinated plaques are visible in the central nervous system; it would be recommended to evaluate these subjects with clinical, radiological and electrophysiological test to exclude peripheral incipient MS [122].

Other autoimmune conditions

Other autoimmune diseases associated to audio-vestibular symptoms include Hashimoto's thyroiditis, Mixed cryoglobulinemia, Giant Cell Arteritis (GCA), Vogt-Koyanagi-Harada's disease, and Ulcerative Colitis.

Thyroid autoimmunity seems to affect the inner ear, particularly inducing hearing loss at lower frequencies [123].

In mixed cryoglobulinemia, unilateral SNHL has been found in 22% of patients following immune complex deposit in labyrinthine vessels determining both audiological and vestibular symptoms [124].

Hearing loss has been reported with a prevalence ranging from 7 to 100% in several case series of patients with GCA, a multi-systemic vasculitis mainly involving large and medium-sized blood vessels [125]. In a series of 44 patients with GCA, PTA at the time of diagnosis showed auditory dysfunction in all patients [126]. In some patients, hearing loss was progressive and appeared as an initial manifestation [127].

Bilateral rapidly progressive SNHL and tinnitus and vestibular manifestations have been observed in 48-62% of patients with Vogt-Koyanagi-Harada's disease [128].

In a retrospective study, SNHL was found in about 2% of patients with ulcerative colitis [129]. In these patients, OAE play a central role as they may indicate a cochlear involvement even when normal hearing thresholds are present [130].

Audio-vestibular diagnostic workup in systemic autoimmune diseases

The audio-vestibular symptoms in systemic autoimmune diseases are often related to the entity of the autoimmune damage, as they may follow an inflammatory process in the inner ear or a direct macrophage aggression of the inner and – mainly - outer hair cells [15].

Current literature agrees that SNHL is the most common auditory symptom of systemic autoimmune diseases [131], but due to the different presentation forms (sudden or progressive) and severity (mild to severe) of SNHL, an early correlation between the symptom and the systemic autoimmune disease may be difficult. Furthermore, audio-vestibular symptoms found in autoimmune conditions are also common to other pathologies such as diabetes and hypertension. For these reasons, a correct differential diagnosis of the cause of the audio-vestibular involvement is of utmost importance.

The diagnostic process in patients presenting with a variety of audio-vestibular symptoms should begin with individual medical and family history followed by traditional audio-vestibular tests. The

most important audiological test battery in all cases should include Pure Tone Audiometry possibly extended to the high frequency region, Transient-Evoked and Distortion Product Otoacoustic Emissions, and Auditory Brainstem Responses [122,131]. Vestibular testing should include a basic vestibular exam integrated with caloric test, Video Head Impulse Test and VEMPs [122]. The aforementioned test batteries should be performed at the onset of the audio-vestibular symptom and during follow up to monitor the course of the disease. Audio-vestibular examination should be integrated, when an autoimmune condition is suspected, with specific blood tests as summarized in *Table 2* [132].

Table 2: Blood tests commonly used in patients with audio-vestibular symptoms suggestive for a systemic autoimmune condition.

Test	Classification
Red and white cell count	General blood test
Coagulation test (aPTT, PT)	General blood test
Creatin Kinase (CK)	General blood test
Alanine Transaminase (ALT)	General blood test
Aspartate Aminotransferase (AST)	General blood test
Erythrocyte sedimentation rate (ESR)	Inflammatory markers
C-reactive protein (CRP)	Inflammatory markers
Ferritin	Inflammatory markers
Enzyme-Linked Immunosorbent Assay (ELISA)	Immunologic analysis
Rheumatoid Factor (RF)	Antibody
Anti-Cyclic Citrullinated peptide antibody (CCP)	Antibody
Anti-Nuclear Antibody (ANA)	Antibody
Anti-double stranded DNA (anti-dsDNA)	Antibody
Anti-extractable nuclear antigen (anti-ENA)	Antibody
Anti-signal recognition particle (anti-SRP)	Antibody
Anti-Mi2	Antibody
Antineutrophil cytoplasmic antibody (ANCA)	Antibody
Lupus Anticoagulant (LAC)	Antibody

Antiphospholipid autoantibodies (aPL)	Antibody
Anti-cardiolipin (aCL)	Antibody
Complement (C3, C4 and B)	Complement
Cryoglobulins	Immunoglobulin

Summary of most relevant blood test used to investigate a possible autoimmune condition.

Treatment approaches to audio-vestibular symptoms in systemic autoimmune diseases

The treatment of audio-vestibular symptoms should first aim to preserve the function, such as hearing preservation and/or restoration in patients with SNHL, then to solve disability, distress and quality of life. If an underlying autoimmune disease is suspected, treatment should be started after complete blood exams; in fact, steroid therapy, that is commonly used as first-line treatment for SSNHL and other audio-vestibular symptoms, may have an effect on the underlying autoimmune systemic disease and delay its diagnosis.

In patients with a diagnosis of systemic autoimmune disease, the treatment of the audio-vestibular symptoms is usually strictly related to that of the systemic condition. Common treatment options for systemic autoimmune diseases that may present an audio-vestibular involvement are summarized in *Table 3*.

Table 3: Common treatment for systemic autoimmune diseases with audio-vestibular involvement

Disease	Treatment	Reference
Systemic Lupus Erythematosus (SLE)	SLE without major organ manifestations: antimalarials and/or glucocorticoids. Nonsteroidal anti-inflammatory drugs may be used judiciously for limited periods of time in patients at low risk for drug-induced complications. In non-responsive patients, immunosuppressive agents such as Azathioprine, Mycophenolate Mofetil and Methotrexate should also be considered.	133
Cogan's Syndrome (CS)	Prednisone 1mg/kg/day for two weeks and then tapered over 3 to 6 months. Methotrexate for long term treatment. Alternative treatments are Cyclophosphamide, Azathioprine, Tacrolimus and Rituximab.	134
Sarcoidosis	High dose of corticosteroids (20-40 mg/daily) for 6 to 18 months. High-dose intravenous n-methyl-prednisone with doses of up to 30 mg/kg for 1-5 days has been commonly recommended for	135

	treatment of refractory neurosarcoidosis. In addition, Methatrexate, Azathioprine and TNF-alpha antagonists.	
Rheumatoid Arthritis (RA)	Methotrexate at disease onset (10-15 mg/week) then 20 mg/week for 4-8 weeks. It is possible to use Prednisolone at high dosage (40-60 mg) tapering to 7.5 mg at week 6 for a total of 12 weeks.	136
Antiphospholipid Syndrome (APS)	Chronic treatment with low dose of Acetylsalicylic acid	133
Polyarteritis Nodosa (PAN)	PAN without viral syndrome: Prednisone 1mg/kg/day then tapering when remission is reached.	137
Behcet's Disease (BD)	Steroid treatment with Azathioprine. For resistant cases, Azathioprine + Interferon + TNF-a antagonists.	134
Takayasu's Arteritis (TA)	Prednisone 1mg/kg/day. Additionally, it is possible to use immunosuppressants such as Methotrexate, Azathioprine, Mycophenolate Mofetil, Leflunomide, Tacrolimous, TNF-alpha antagonists.	138
Relapsing Polychondritis (RP)	Corticosteroid treatment at high dosages. In addition, Colchine, Methotrexate, Azathioprine, intravenous immunoglobulins, Mynocicline, Lefunomide.	139
Wegener Granulomatosis (WG)	Prednisone or equivalent 1mg/kg/day, sometimes preceded in severe cases by intravenous Methylprednisolone pulses (7.5-15 mg/kg/day) for 1-3 consecutive days. After two weeks tapering with a decrease of 10% every two weeks for a total of 6 months. In case of long term treatment (>2 years) 5 mg/day. Is also possible to use Cyclophosphamide and Rituximab for maintenance therapy.	140
Susac Syndrome (SS)	High dosage corticosteroids. Additionally, intravenous Immunoglobulin, plasma exchange Azathioprine, Mycophenolate Mofetil, Methotrexate, Cytochrome P450 Enzymes and Cyclosporin A.	141
Sjogren Syndrome (pSS)	Cyclosporin A for local treatment of eye disease. Colchine and steroid treatment are used. Controversial use of Rituximab.	142
Myasthenia Gravis (MG)	Immunosuppressant therapy. In addition, treatment with Insulin, thyroid hormones and Pyridostigmine.	143
Multiple Sclerosis (MS)	Immunomodulating therapy: T-cell suppressor (Alemtuzumab, Daclizumab); B-cell modulators (Rituximab, Ocrelizumab); Unique anti-inflammatory agents (Laquinimod); Hormones (Estriol); 3-Hydroxy-3-Methylglutaryl–Coenzyme A Reductase Inhibitors; Vitamin D.	144

Treatment options for systemic autoimmune conditions, along with relevant references.

The most common treatment for SSNHL is systemic or intratympanic administration of high doses of corticosteroids, associated to hyperbaric oxygen treatment in case of SLE, APS and TA [81, 145].

Other associated treatments include antioxidant compounds to avoid progression of SNHL [146], hearing aids to support the residual hearing function or cochlear implants in case of severe hearing loss [147, 148].

Tinnitus is commonly treated by psychologic support [149], antidepressant drugs when a psychological involvement is detected, and by oral supplements that combine antioxidants and vasoactive substances.

Vertigo can be treated with high doses of corticosteroids [150] associated to Betahistine, a strong antagonist of the histamine H3 receptor and a weak agonist of the histamine H1 receptor, that improves vascularization of the inner ear [149]. Additional therapeutic approaches include Metoclopramide and antidepressant drugs (inhibitor of D1 receptor) that act on central function by reducing the sensation of vertigo, nausea and gastrointestinal symptoms [150]. For chronic dizziness, specific rehabilitation treatments are used to favor central vestibular compensation and restore normal balance function [151].

Conclusion

Audio-vestibular symptoms may be found in a variety of autoimmune diseases and diagnosis is essential for the elevate chances of hearing restoration when specific therapy is promptly initiated. Inner ear involvement in autoimmune diseases is ascertained by the history, clinical findings, an immunologic evaluation of the patient's serum and response to immunosuppressive therapies, following exclusion of other known causes.

Audio-vestibular symptoms could play a role in the diagnostic process of autoimmune diseases as they may be an early-onset symptom - and in some cases the only symptom - of an autoimmune condition. Furthermore, they may be useful to monitor the progression of the systemic disease.

Systemic autoimmune diseases should always be considered in patients with audio-vestibular symptoms such as progressive/fluctuating SNHL with no other explainable cause. When a systemic autoimmune disease involving the inner ear is suspected, predisposing factors must be investigated,

such as noise exposure, ototoxic treatments, previous ear surgery, trauma, meningitis or family history of hearing loss. The exclusion of concomitant conditions may be challenging, especially in the case of presbycusis or noise-induced hearing loss. The low prevalence of these conditions, the heterogeneity of studies available in literature and the absence of randomized trials are the factors that limit the knowledge of inner ear involvement in systemic autoimmune diseases with underestimation of the problem and under-treatment.

References

1. Matsuoka, A.J. and J.P. Harris, *Autoimmune inner ear disease: a retrospective review of forty-seven patients.* Audiol Neurootol, 2013. **18**(4): p. 228-39.
2. Lehnhardt, E. *Sudden hearing disorders occurring simultaneously or successively on both sides.* Z Laryngol Rhinol Otol 1958. **37**: p. 1–16.
3. McCabe, B.F., *Autoimmune sensorineural hearing loss.* Ann Otol Rhinol Laryngol, 1979. **88**(5 Pt 1): p. 585-9.
4. O'Malley, J.T., J.B. Nadol, Jr., and M.J. McKenna, *Anti CD163+, Iba1+, and CD68+ Cells in the Adult Human Inner Ear: Normal Distribution of an Unappreciated Class of Macrophages/Microglia and Implications for Inflammatory Otopathology in Humans.* Otol Neurotol, 2016. **37**(1): p. 99-108.
5. Rossini, B.A.A., et al., *Sudden Sensorioneural Hearing Loss and Autoimmune Systemic Diseases.* Int Arch Otorhinolaryngol, 2017. **21**(3): p. 213-223.
6. Vambutas, A. and S. Pathak, *AAO: Autoimmune and Autoinflammatory (Disease) in Otology: What is New in Immune-Mediated Hearing Loss.* Laryngoscope Investig Otolaryngol, 2016. **1**(5): p. 110-115.
7. Malik, M.U., et al., *Spectrum of immune-mediated inner ear disease and cochlear implant results.* The Laryngoscope, 2012. **122**(11): p. 2557-2562.
8. Ruckenstein, M.J., *Autoimmune inner ear disease.* Curr Opin Otolaryngol Head Neck Surg, 2004. **12**(5): p. 426-30.
9. Mijovic, T., A. Zeitouni, and I. Colmegna, *Autoimmune sensorineural hearing loss: the otology-rheumatology interface.* Rheumatology (Oxford), 2013. **52**(5): p. 780-9.
10. Hervier, B., et al., *[Auto-immune sensorineural deafness: physiopathology and therapeutic approach].* Rev Med Interne, 2010. **31**(3): p. 222-8.

11. Greco, A., et al., *Idiopathic bilateral vestibulopathy: an autoimmune disease?* Autoimmun Rev, 2014. **13**(10): p. 1042-7.
12. Greco, A., et al., *Sudden sensorineural hearing loss: an autoimmune disease?* Autoimmun Rev, 2011. **10**(12): p. 756-61.
13. Jeffries, M.A. and A.H. Sawalha, *Autoimmune disease in the epigenetic era: how has epigenetics changed our understanding of disease and how can we expect the field to evolve?* Expert Rev Clin Immunol, 2015. **11**(1): p. 45-58.
14. Kanzaki, J., *Immune-mediated sensorineural hearing loss.* Acta Otolaryngol Suppl, 1994. **514**: p. 70-2.
15. Di Stadio, A. and M. Ralli, *Systemic Lupus Erythematosus and hearing disorders: Literature review and meta-analysis of clinical and temporal bone findings.* J Int Med Res, 2017. **45**(5): p. 1470-1480.
16. Abbasi, M., Z. Yazdi, and A. Kazemifar, *Hearing loss in patients with systemic lupus erythematosus.* Glob J Health Sci, 2013. **5***:*p. 102–106.
17. Ralli, M., et al., *The effect of the NMDA channel blocker memantine on salicylate-induced tinnitus in rats.* Acta Otorhinolaryngol Ital, 2014. **34**(3): p. 198-204.
18. Roverano, S., et al., *Asymptomatic sensorineural hearing loss in patients with systemic lupus erythematosus.* J Clin Rheumatol, 2006. **12**(5): p. 217-20.
19. Kariya, S., et al., *Histopathologic Findings in Peripheral Vestibular System From Patients With Systemic Lupus Erythematosus: A Human Temporal Bone Study.* Otol Neurotol, 2015. **36**(10): p. 1702-7.
20. Agrup, C. and L.M. Luxon, *Immune-mediated inner-ear disorders in neuro-otology.* Curr Opin Neurol, 2006. **19**(1): p. 26-32.
21. Hughes, G.B., et al., *Clinical diagnosis of immune inner-ear disease.* Laryngoscope, 1988. **98**(3): p. 251-3.
22. Lidar, M., et al., *Hearing loss as the presenting feature of systemic vasculitis.* Ann N Y Acad Sci, 2007. **1107**: p. 136-41.
23. Cohen, P.R. and R.P. Rapini, *Relapsing polychondritis.* Int J Dermatol, 1986. **25**(5): p. 280-5.
24. Raut, V.V., J. Cullen, and G. Cathers, *Hearing loss in rheumatoid arthritis.* J Otolaryngol, 2001. **30**(5): p. 289-94.
25. Roberts, L.E., et al., *Ringing ears: the neuroscience of tinnitus.* J Neurosci, 2010. **30**(45): p. 14972-9.
26. Eggermont, J.J. and L.E. Roberts, *The neuroscience of tinnitus.* Trends Neurosci, 2004. **27**(11): p. 676-82.

27. Sheppard, A., et al., *Review of salicylate-induced hearing loss, neurotoxicity, tinnitus and neuropathophysiology.* Acta Otorhinolaryngol Ital, 2014. **34**(2): p. 79-93.
28. Auerbach, B.D., P.V. Rodrigues, and R.J. Salvi, *Central gain control in tinnitus and hyperacusis.* Front Neurol, 2014. **5**: p. 206.
29. Lin C, L.S., Weng SF, , *Risk of sudden sensorineural hearing loss in patients with systemic lupus erythematosus: a population- based cohort study.* Audiol Neurootol, 2013. **18**: p. 95–100.
30. Maciaszczyk, K., et al., *Auditory function in patients with systemic lupus erythematosus.* Auris Nasus Larynx, 2011. **38**(1): p. 26-32.
31. Khalidi, N.A., R. Rebello, and D.D. Robertson, *Sensorineural hearing loss in systemic lupus erythematosus: case report and literature review.* J Laryngol Otol, 2008. **122**(12): p. 1371-6.
32. Sperling, N.M., et al., *Aural symptoms and hearing loss in patients with lupus.* Otolaryngol Head Neck Surg, 1998. **118**(6): p. 762-5.
33. Dayal, V.S. and M.H. Ellman, *Sensorineural hearing loss and lupus.* J Rheumatol, 1999. **26**(9): p. 2065.
34. Gomides, A.P., et al., *Sensorineural dysacusis in patients with systemic lupus erythematosus.* Lupus, 2007. **16**(12): p. 987-90.
35. Karatas, E., et al., *Audiovestibular disturbance in patients with systemic lupus erythematosus.* Otolaryngol Head Neck Surg, 2007. **136**(1): p. 82-6.
36. Batuecas-Caletrı´o A, d.P.-M.J., Cordero-Civantos C, , *Hearing and vestibular disorders in patients with systemic lupus erythematosus.* . Lupus 2013; . **22**: p. 437-442.
37. Gad, G.I. and H. Abdelateef, *Function of the audiovestibular system in children with systemic lupus erythematosus.* Curr Allergy Asthma Rep, 2014. **14**(7): p. 446.
38. Morgan RF, B.C., *Menier's disease complicated by recurrent interstitial keratitis.* . West J Surg 1934. **42**(628.).
39. D'Aguanno V, Ralli M, de Vincentiis M, Greco A., *Optimal management of Cogan's syndrome: a multidisciplinary approach.* J Multidiscip Healthc, 2017. **22**;11: p.1-11
40. Greco, A., et al., *Cogan's syndrome: an autoimmune inner ear disease.* Autoimmun Rev, 2013. **12**(3): p. 396-400.
41. Lunardi, C., et al., *Autoantibodies to inner ear and endothelial antigens in Cogan's syndrome.* Lancet, 2002. **360**(9337): p. 915-21.
42. Haynes, B.F., et al., *Cogan syndrome: studies in thirteen patients, long-term follow-up, and a review of the literature.* Medicine (Baltimore), 1980. **59**(6): p. 426-41.
43. Gluth, M.B., et al., *Cogan syndrome: a retrospective review of 60 patients throughout a half century.* Mayo Clin Proc, 2006. **81**(4): p. 483-8.

44. James DG, S.O., *Neurological complications of sarcoidosis.* Proc R Soc Med 1967;. **60**: p. 1169-70.
45. Joseph, F.G. and N.J. Scolding, *Neurosarcoidosis: a study of 30 new cases.* J Neurol Neurosurg Psychiatry, 2009. **80**(3): p. 297-304.
46. Colvin, I.B., *Audiovestibular manifestations of sarcoidosis: a review of the literature.* Laryngoscope, 2006. **116**(1): p. 75-82.
47. Babin RW, L.C., Aschenbrener C., *Histopathology of sensory deafness in neurosarcoidosis.* Ann Otol Rhinol Laryngol, 1984. **93**: p. 389-93.
48. Cama, E., et al., *Sudden hearing loss in sarcoidosis: otoneurological study and neuroradiological correlates.* Acta Otorhinolaryngol Ital, 2011. **31**(4): p. 235-8.
49. Takatsu, M., et al., *Ear involvement in patients with rheumatoid arthritis.* Otol Neurotol, 2005. **26**(4): p. 755-61.
50. Murdin, L., et al., *Hearing difficulties are common in patients with rheumatoid arthritis.* Clin Rheumatol, 2008. **27**(5): p. 637-40.
51. Rosenberg, J.N., et al., *Middle ear function in rheumatoid arthritis.* Ann Rheum Dis, 1978. **37**(6): p. 522-4.
52. Wilson, W.A., et al., *International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop.* Arthritis Rheum, 1999. **42**(7): p. 1309-11.
53. Naarendorp, M. and H. Spiera, *Sudden sensorineural hearing loss in patients with systemic lupus erythematosus or lupus-like syndromes and antiphospholipid antibodies.* J Rheumatol, 1998. **25**(3): p. 589-92.
54. Levine, J.S., D.W. Branch, and J. Rauch, *The antiphospholipid syndrome.* N Engl J Med, 2002. **346**(10): p. 752-63.
55. Toubi, E., et al., *Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus.* Am J Med, 1995. **99**(4): p. 397-401.
56. Toubi, E., et al., *Immune-mediated disorders associated with idiopathic sudden sensorineural hearing loss.* Ann Otol Rhinol Laryngol, 2004. **113**(6): p. 445-9.
57. Mouadeb, D.A. and M.J. Ruckenstein, *Antiphospholipid inner ear syndrome.* Laryngoscope, 2005. **115**(5): p. 879-83.
58. Jennette, J.C., et al., *2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.* Arthritis Rheum, 2013. **65**(1): p. 1-11.
59. De Virgilio, A., et al., *Polyarteritis nodosa: A contemporary overview.* Autoimmun Rev, 2016. **15**(6): p. 564-70.

60. Hernandez-Rodriguez, J., et al., *Diagnosis and classification of polyarteritis nodosa.* J Autoimmun, 2014. **48-49**: p. 84-9.
61. Adkins, W.Y. and P.H. Ward, *Temporal bone showing polyarteritis nodosa, otosclerosis, and occult neuroma.* Laryngoscope, 1986. **96**(6): p. 645-52.
62. Wolf M, K.J., Engelberg S, Leventon G. , *Rapidly progressive hearing loss as a symptom of polyarteritis nodosa.* . Am J Otolaryngol 1987;8:105-8, 1987. **8**: p. 105-8.
63. Bomholt, A., et al., *Profound sensorineural hearing loss in polyarteritis nodosa. An atypical case of Cogan's syndrome.* Arch Otorhinolaryngol, 1982. **236**(1): p. 53-8.
64. Rowe-Jones JM, M.D., Sorooshian M. . *Polyarteritis nodosa presenting as bilateral sudden onset cochleo-vestibular failure in a young woman.* J Laryngol Otol 1990. **104**: p. 562-4.
65. G., L.-B., *Polyarteritis nodosa presenting with bilateral nerve deafness.* J R Soc Med, 1978. **71**: p. 144-7.
66. Tsunoda, K., et al., *Sensorineural hearing loss as the initial manifestation of polyarteritis nodosa.* J Laryngol Otol, 2001. **115**(4): p. 311-2.
67. Peitersen E, C.B., *Hearing impairment as the initial sign of polyarteritis nodosa.* Acta Otolaryngol (Stockh), 1966. **61**: p. 189-95.
68. Evereklioglu, C., et al., *Audio-vestibular evaluation in patients with Behcet's syndrome.* J Laryngol Otol, 2001. **115**(9): p. 704-8.
69. Gemignani, G., et al., *Hearing and vestibular disturbances in Behcet's syndrome.* Ann Otol Rhinol Laryngol, 1991. **100**(6): p. 459-63.
70. Soylu, L., et al., *Hearing loss in Behcet's disease.* Ann Otol Rhinol Laryngol, 1995. **104**(11): p. 864-7.
71. Kulahli, I., et al., *Audio-vestibular disturbances in Behcet's patients: report of 62 cases.* Hear Res, 2005. **203**(1-2): p. 28-31.
72. Greco A., et al., *Behçet's disease: New insights into pathophysiology, clinical features and treatment options.* Autoimmun Rev, 2018. **17**(6): p.567-575.
73. Yesilot, N., et al., *Silent neurological involvement in Behcet's disease.* Clin Exp Rheumatol, 2006. **24**(5 Suppl 42): p. S65-70.
74. Alibaz-Oner, F., S.Z. Aydin, and H. Direskeneli, *Recent advances in Takayasu's arteritis.* Eur J Rheumatol, 2015. **2**(1): p. 24-30.
75. Keser, G., H. Direskeneli, and K. Aksu, *Management of Takayasu arteritis: a systematic review.* Rheumatology (Oxford), 2014. **53**(5): p. 793-801.
76. Maruyoshi, H., et al., *Sensorineural hearing loss combined with Takayasu's arteritis.* Intern Med, 2005. **44**(2): p. 124-8.

77. Noel, N., et al., *Small vessel involvement in Takayasu's arteritis.* Autoimmun Rev, 2013. **12**(3): p. 355-62.
78. Siglock, T.J. and K.H. Brookler, *Sensorineural hearing loss associated with Takayasu's disease.* Laryngoscope, 1987. **97**(7 Pt 1): p. 797-800.
79. Kunihiro, T., et al., *Steroid-responsive sensorineural hearing loss associated with aortitis syndrome.* ORL J Otorhinolaryngol Relat Spec, 1990. **52**(2): p. 86-95.
80. Yasui, T. and T. Yamasoba, *Acute sensorineural hearing loss associated with aortitis syndrome.* Acta Otolaryngol Suppl, 2007(559): p. 29-33.
81. Ralli, M., et al., *Recovery from Repeated Sudden Hearing Loss in a Patient with Takayasu's Arteritis Treated with Hyperbaric Oxygen Therapy: The First Report in the Literature.* Case Rep Otolaryngol, 2017. **2017**: p. 3281984.
82. Michet, C.J., Jr., et al., *Relapsing polychondritis. Survival and predictive role of early disease manifestations.* Ann Intern Med, 1986. **104**(1): p. 74-8.
83. Longo, L., et al., *Relapsing polychondritis: A clinical update.* Autoimmun Rev, 2016. **15**(6): p. 539-43.
84. McAdam LP, O.H.M., Bluestone R, Pearson CM *Relapsing polychondritis: prospective study of 23 patients and a review of the literature.* Medicine 1976. **55**: p. 193–215.
85. Shimizu, J., et al., *Cutaneous manifestations of patients with relapsing polychondritis: an association with extracutaneous complications.* Clin Rheumatol, 2016. **35**(3): p. 781-3.
86. Issing, W.J., D. Selover, and P. Schulz, *Anti-labyrinthine antibodies in a patient with relapsing polychondritis.* Eur Arch Otorhinolaryngol, 1999. **256**(4): p. 163-6.
87. Damiani, J.M. and H.L. Levine, *Relapsing polychondritis--report of ten cases.* Laryngoscope, 1979. **89**(6 Pt 1): p. 929-46.
88. Stone, J.H. and G. Wegener's Granulomatosis Etanercept Trial Research, *Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial.* Arthritis Rheum, 2003. **48**(8): p. 2299-309.
89. Takagi, D., et al., *Otologic manifestations of Wegener's granulomatosis.* Laryngoscope, 2002. **112**(9): p. 1684-90.
90. Kornblut, A.D., S.M. Wolff, and A.S. Fauci, *Ear disease in patients with Wegener's granulomatosis.* Laryngoscope, 1982. **92**(7 Pt 1): p. 713-7.
91. Bakthavachalam, S., et al., *Hearing loss in Wegener's granulomatosis.* Otol Neurotol, 2004. **25**(5): p. 833-7.
92. Susac, J.O., J.M. Hardman, and J.B. Selhorst, *Microangiopathy of the brain and retina.* Neurology, 1979. **29**(3): p. 313-6.

93. Greco, A., et al., *Susac's syndrome — Pathogenesis, clinical variants and treatment approaches.* Autoimmunity Reviews, 2014. **13**(8): p. 814-821.
94. Magro, C.M., et al., *The role of anti-endothelial cell antibody-mediated microvascular injury in the evolution of pulmonary fibrosis in the setting of collagen vascular disease.* Am J Clin Pathol, 2007. **127**(2): p. 237-47.
95. Dörr J, K.S., Wildemann B, Jarius S, Ringelstein M, Duning T, Aktas O, Ringelstein EB, Paul F, Kleffner I. , *Characteristics of Susac syndrome: a review of all reported cases.* . Nat Rev Neurol, 2013. **9**: p. 307–16.
96. Greco, A., et al., *Meniere's disease might be an autoimmune condition?* Autoimmun Rev, 2012. **11**(10): p. 731-8.
97. Greco, A., et al., *Susac's syndrome--pathogenesis, clinical variants and treatment approaches.* Autoimmun Rev, 2014. **13**(8): p. 814-21.
98. Tucci, M., C. Quatraro, and F. Silvestris, *Sjogren's syndrome: an autoimmune disorder with otolaryngological involvement.* Acta Otorhinolaryngol Ital, 2005. **25**(3): p. 139-44.
99. Boki, K.A., et al., *How significant is sensorineural hearing loss in primary Sjogren's syndrome? An individually matched case-control study.* J Rheumatol, 2001. **28**(4): p. 798-801.
100. Tumiati, B., P. Casoli, and A. Parmeggiani, *Hearing loss in the Sjogren syndrome.* Ann Intern Med, 1997. **126**(6): p. 450-3.
101. Ziavra, N., et al., *Hearing loss in Sjogren's syndrome patients. A comparative study.* Clin Exp Rheumatol, 2000. **18**(6): p. 725-8.
102. Kim, K.S. and H.S. Kim, *Successful treatment of sensorineural hearing loss in Sjogren's syndrome with corticosteroid.* Korean J Intern Med, 2016. **31**(3): p. 612-5.
103. Alexander, E.L., *Neurologic disease in Sjogren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update of immunopathogenesis.* Rheum Dis Clin North Am, 1993. **19**(4): p. 869-908.
104. Ralli, M., et al., *Relationship between hearing function and myasthenia gravis: A contemporary review.* J Int Med Res, 2017. **45**(5): p. 1459-1465.
105. Grob D, A.E., Brunner NG, , *The course of myasthenia gravis and therapies affecting outcome.* . Ann N Y Acad Sci, 1987. **505:** : p. 472–499.
106. Toth, L., et al., *Otoacoustic emission in myasthenia gravis patients and the role of efferent activation.* Hear Res, 1998. **126**(1-2): p. 123-5.
107. Hamed, S.A., A.M. Elattar, and E.A. Hamed, *Irreversible cochlear damage in myasthenia gravis -- otoacoustic emission analysis.* Acta Neurol Scand, 2006. **113**(1): p. 46-54.

108. Fetoni AR, G.M., Ralli M, , *The monitoring role of otoacoustic emissions and oxidative stress markers in the protective effects of antioxidant administration in noise-exposed subjects: A pilot study.* . Med Sci Monit, 2009; . **15**: p. 1–8.
109. Di Girolamo, S., et al., *Effects of contralateral white noise stimulation on distortion product otoacoustic emissions in myasthenic patients.* Hear Res, 2001. **162**(1-2): p. 80-4.
110. Moulin, A., L. Collet, and R. Duclaux, *Contralateral auditory stimulation alters acoustic distortion products in humans.* Hear Res, 1993. **65**(1-2): p. 193-210.
111. Williams, D.M. and A.M. Brown, *The effect of contralateral broad-band noise on acoustic distortion products from the human ear.* Hear Res, 1997. **104**(1-2): p. 127-46.
112. Ralli, M., et al., *Development of progressive hearing loss and tinnitus in a patient with myasthenia gravis: an overlooked comorbidity?* Hearing, Balance and Communication, 2017: p. 1-7.
113. Hamed SA, E.A.a.H.E., *Irreversible cochlear damage in myasthenia gravis – otoacoustic emission analysis.* Acta Neurol Scand, 2006. **113**: p. 46–54.
114. Stys, P.K., *Multiple sclerosis: autoimmune disease or autoimmune reaction?* Can J Neurol Sci, 2010. **37 Suppl 2**: p. S16-23.
115. Furst, M. and R.A. Levine, *Hearing disorders in multiple sclerosis.* Handb Clin Neurol, 2015. **129**: p. 649-65.
116 Di Stadio A, et al. *Sudden Hearing Loss as an early detector of Multiple Sclerosis. A systematic review.* Eur Rev Med Pharmacol Sci, 2018. In press.
117. Doty, R.L., et al., *Pure-tone auditory thresholds are not chronically elevated in multiple sclerosis.* Behav Neurosci, 2012. **126**(2): p. 314-24.
118. Ozunlu, A., N. Mus, and M. Gulhan, *Multiple sclerosis: a cause of sudden hearing loss.* Audiology, 1998. **37**(1): p. 52-8.
119. Matas, C.G., et al., *Auditory evoked potentials and multiple sclerosis.* Arq Neuropsiquiatr, 2010. **68**(4): p. 528-34.
120. Klugman, T.M. and E. Ross, *Perceptions of the impact of speech, language, swallowing, and hearing difficulties on quality of life of a group of South African persons with multiple sclerosis.* Folia Phoniatr Logop, 2002. **54**(4): p. 201-21.
121. Alpini, D., et al., *Vertigo and multiple sclerosis: aspects of differential diagnosis.* Neurol Sci, 2001. **22 Suppl 2**: p. S84-7.
122. Di Stadio, A. and M. Ralli, *Inner ear involvement in Multiple Sclerosis: an underestimated condition?*Autoimmunity Reviews, 2017.
123. Arduc, A., et al., *Evaluation of hearing functions in patients with euthyroid Hashimoto's thyroiditis.* Endocrine, 2015. **50**(3): p. 708-14.

124. Berrettini, S., et al., *Inner ear involvement in mixed cryoglobulinaemia patients.* Br J Rheumatol, 1995. **34**(4): p. 370-4.
125. Samson, M., et al., *Recent advances in our understanding of giant cell arteritis pathogenesis.* Autoimmun Rev, 2017. **16**(8): p. 833-44.
126. Amor-Dorado, J.C., et al., *Audiovestibular manifestations in giant cell arteritis: a prospective study.* Medicine (Baltimore), 2003. **82**(1): p. 13-26.
127. Loffredo, L., S. Parrotto, and F. Violi, *Giant cell arteritis, oculomotor nerve palsy, and acute hearing loss.* Scand J Rheumatol, 2004. **33**(4): p. 279-80.
128. Al Dousary, S., *Auditory and vestibular manifestations of Vogt-Koyanagi-Harada disease.* J Laryngol Otol, 2011. **125**(2): p. 138-41.
129. Casella, G., et al., *Symptomatic sensorineural hearing loss in patients with ulcerative colitis.* Tech Coloproctol, 2015. **19**(12): p. 729-31.
130. Sagit, M., et al., *Cochlear involvement in patients with ulcerative colitis.* J Laryngol Otol, 2016. **130**(2): p. 128-33.
131. Rossini BAA, Penido N de O, Munhoz MSL, Bogaz EA, Curi RS., *Sudden Sensorioneural Hearing Loss and Autoimmune Systemic Diseases*. Int Arch Otorhinolaryngol, 2017. **21**(3): p. 213-23.
132. Castro C, Gourley M., *Diagnostic Testing and Interpretation of Tests for Autoimmunity*. J Allergy Clin Immunol, 2010. **125**(2): p.238-47.
133. Bertsias G, Ioannidis JPA, Boletis J, et al., *EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics.* Ann Rheum Dis, 2008. **67**(2): p.195-205.
134. Singer O., *Cogan and Behcet syndromes*. Rheum Dis Clin North Am, 2015. **41**(1): p.75-91
135. Baughman RP, Lower EE., *Treatment of Sarcoidosis*. Clin Rev Allergy Immunol, 2015. **49**(1): p.79-92.
136. Davis JM 3rd, Matteson EL, American College of Rheumatology, European League Against Rheumatism., *My treatment approach to rheumatoid arthritis*. Mayo Clin Proc, 2012. **87**(7): p.659-73.
137. Forbess L, Bannykh S., *Polyarteritis nodosa.* Rheum Dis Clin North Am, 2015. **41**(1): p.33-46.
138. Keser G, Direskeneli H, Aksu K., *Management of Takayasu arteritis: a systematic review.* Rheumatology (Oxford), 2014. **53**(5): p.793-801.
139. Lekpa FK, Chevalier X., *Refractory relapsing polychondritis: challenges and solutions.* Open Access Rheumatol, 2018. **9**(10) p.:1-11.

140. Pagnoux C, Guillevin L., Tre*atment of granulomatosis with polyangiitis (Wegener's)*. Expert Rev Clin Immunol, 2015. **11**(3): p.339-48.
141. García-Carrasco M, Mendoza-Pinto C, Cervera R., *Diagnosis and classification of Susac syndrome.* Autoimmun Rev, 2014. **13**(4-5): p.347-50.
142. Mavragani CP, Nezos A, Moutsopoulos HM., *New advances in the classification, pathogenesis and treatment of Sjogren's syndrome*. Curr Opin Rheumatol, 2013. **25**(5): p.623-29.
143. Andersen JB, Owe JF, Engeland A, Gilhus NE., *Total drug treatment and comorbidity in myasthenia gravis: a population-based cohort study*. Eur J Neurol, 2014, **21**(7): p.948-55.
144. Derwenskus J, Lublin FD., *Future treatment approaches to multiple sclerosis*. Handb Clin Neurol, 2014. 122: p.563-77.
145. Ralli M, Greco A, De Vincentiis M., *Hearing Loss in Takayasu's Arteritis: A Role for Hyperbaric Oxygen Therapy?*. J Int Adv Otol, 2017. **13**(3): p.417-418.
146. Le Prell CG, Gagnon PM, Bennett DC, Ohlemiller KK., *Nutrient-enhanced diet reduces noise-induced damage to the inner ear and hearing loss*. Transl Res, 2011. **158**(1): p.38-53.
147. Quaranta N, Bartoli R, Giagnotti F, Di Cuonzo F, Quaranta A., *Cochlear implants in systemic autoimmune vasculitis syndromes*. Acta Otolaryngol Suppl, 2002. 548: p.44-8.
148. Mancini P, et al., Hearing loss in autoimmune disorders: Prevalence and therapeutic options. Autoimmun Rev, 2018. pii: S1568-9972(18)30103-4
149. Savage J, Waddell A., *Tinnitus*. BMJ Clin Evid, 2014. **20**. pii: 0506.
150. Strupp M, Brandt T., *Diagnosis and Treatment of Vertigo and Dizziness*. Deutsches Ärzteblatt International, 2008. **105**(10): p.173-80.
151. Cabrera Kang CM, Tusa RJ., *Vestibular rehabilitation: rationale and indications*. Semin Neurol, 2013. **33**(3): p.276-85.