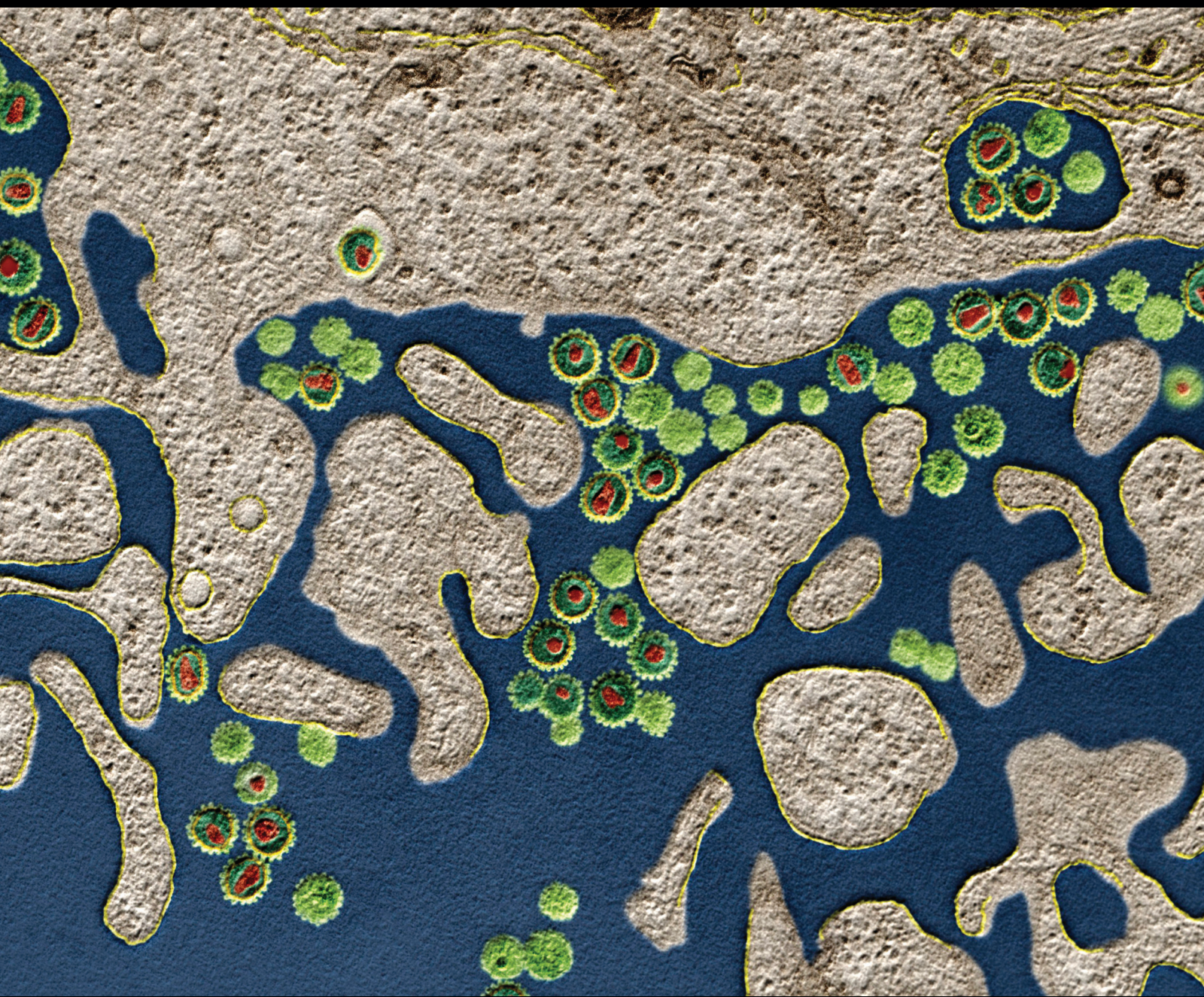
Journal of Immunology Research

Autoimmunity and Otolaryngology Diseases

Lead Guest Editor: Marco de Vincentiis
Guest Editors: Massimo Ralli, Arianna di Stadio, Armando de Virgilio, and Adelchi Croce



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Editorial Board

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Editorial

Autoimmunity and Otolaryngology Diseases

Massimo Ralli,[1] **Arianna Di Stadio**,[2] **Armando De Virgilio**,[3] **Adelchi Croce**,[4] **and Marco de Vincentiis**[5]

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

Correspondence should be addressed to Massimo Ralli; massimo.ralli@uniroma1.it

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1. Main Text

Many systemic autoimmune diseases have otolaryngology manifestations that could represent a diagnostic challenge for clinicians, as they often constitute an early sign of an otherwise asymptomatic autoimmune condition and may lead to delayed diagnosis and treatment. In other cases, otolaryngology manifestations can be overlooked in patients with previously diagnosed autoimmune diseases. The presence of concomitant conditions, the heterogeneity of studies available in the literature, and the lack of randomized trials are factors that may limit the prompt diagnosis of otolaryngology manifestations in systemic autoimmune diseases, with underestimation of the problem and undertreatment of the related condition.

Audio-vestibular symptoms may be found in a variety of autoimmune diseases, and early diagnosis is essential for the elevate chances of near-complete restoration when specific therapy is promptly initiated. Sensorineural hearing loss is the most common audiological symptom associated to systemic autoimmune diseases, although conductive hearing loss may also be present. Hearing loss may present in a sudden, slowly or rapidly progressive, or fluctuating form and is mainly bilateral and asymmetric. Current evidence shows a good response of hearing impairment to corticosteroid therapy that may lead to near-complete hearing restoration. Vestibular symptoms, tinnitus, and aural fullness often mimic Menière's disease in patients with systemic autoimmune conditions and mainly affect both ears simultaneously. Inner ear involvement in autoimmune diseases is suggested by the history, clinical findings, an immunologic evaluation of the patient's serum, and response to immunosuppressive therapies, following exclusion of other known causes. Hearing loss, vertigo, and tinnitus, as reported in the reviews by Ralli et al. and Girasoli et al., can be found in patients with Wegener's granulomatosis, systemic lupus erythematosus, Cogan's syndrome, relapsing polychondritis, polyarteritis nodosa, Sjögren's syndrome, myasthenia gravis, Behçet's disease, Takayasu's arteritis, rheumatoid arthritis, and other autoimmune conditions.

Oral manifestations, such as recurrent oral mucosal ulcerations, can be seen in patients with systemic lupus erythematosus, Sjögren's syndrome, pemphigus vulgaris, mucous membrane pemphigoid, and Behçet's disease, as described in the paper by Saccucci et al. In these cases, the dentist plays a central role to reach an early diagnosis and therefore improving the quality of treatment strategies as well as the quality of life in affected patients.

Salivary gland involvement may be found in patients with Sjögren's syndrome and sarcoidosis, two conditions that may also be associated to xerostomia, trigeminal nerve dysfunction, and peripheral facial nerve palsy. Furthermore, salivary glands can be affected in the rare IgG4-related disease; the article from Puxeddu et al. discusses new insights in the pathogenesis of IgG4-related disease with involvement of

the salivary glands, focusing on its clinical aspects and the tools that are currently available for a correct differential diagnosis with other conditions affecting the salivary glands.

Nose and paranasal sinuses can be affected in patients with Wegener's granulomatosis, Churg-Strauss syndrome, polychondritis, and sarcoidosis. Laryngeal involvement with cricoarytenoid joint alterations can be found in rheumatoid arthritis, ankylosing spondylitis, and gout. Dysphagia has been described in patients with dermatomyositis, systemic sclerosis, and systemic lupus erythematosus.

The aim of this special issue was to stimulate publication of research, both in the form of original articles and review papers, to describe the current state of the art of otolaryngology manifestations in systemic autoimmune diseases. Many manuscripts that focused on different topics within the field of this special issue were submitted, and after a thorough peer review process, seven papers were accepted for publication.

We hope that this special issue will provide valuable information to interested researchers and clinicians and will raise awareness on otolaryngology manifestations in autoimmune systemic disease to favor an early diagnosis and appropriate treatment of these conditions.

Conflicts of Interest

The authors report no conflict of interest.

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Massimo Ralli
Arianna Di Stadio
Armando De Virgilio
Adelchi Croce
Marco de Vincentiis

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Review Article

Update on Vertigo in Autoimmune Disorders, from Diagnosis to Treatment

Laura Girasoli,[1] **Diego Cazzador**,[1] **Roberto Padoan**,[2] **Ennio Nardello**,[1] **Mara Felicetti**,[2] **Elisabetta Zanoletti**,[1] **Franco Schiavon**,[2] **and Roberto Bovo**[1]

[1]*Department of Neurosciences, Otorhinolaryngology Unit, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy*
[2]*Department of Medicine DIMED, Operative Unit of Rheumatology, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy*

Correspondence should be addressed to Laura Girasoli; laura.girasoli@alice.it

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The prevalence of autoimmune diseases has been increasing over the last 20 years. The clinical presentation of this large and heterogeneous group of disorders depends on whether the involvement is organ-specific or non-organ-specific. Dizziness, vertigo, and disequilibrium are common symptoms reported by patients with vestibulocochlear involvement. The association of vertigo and autoimmune diseases has been largely documented, suggesting that autoimmune disorders could be overrepresented in patients with vertigo in comparison to the general population. The aim of this review is to present the recent literature findings in the field of autoimmune-mediated diseases with cochleovestibular involvement, focusing on the clinical presentation, diagnosis, and treatment of immune-mediated inner ear diseases including autoimmune inner ear disease (AIED), Meniere's disease, and bilateral vestibulopathy, as well as of systemic autoimmune diseases with audiovestibular disorders, namely, Behçet's disease, Cogan's syndrome, sarcoidosis, autoimmune thyroid disease, Vogt-Koyanagi-Harada syndrome, relapsing polychondritis, systemic lupus erythematosus, antiphospholipid syndrome, IgG4-related disease, and ANCA-associated vasculitides.

1. Introduction

The percentage of autoimmune disorders in western countries is around 8% of the total population, though many studies reported an increase in prevalence and incidence over the last 20 years. The cochlear-vestibular system might be affected by autoimmune diseases although the diagnosis of autoimmune vestibular disorders is probably overlooked due to an absence of a reliable test that could identify the specific inner ear antigen [1].

Both sensory organs of the inner ear can be involved in autoimmune disorders: cochlea for the hearing and vestibular system for the balance. These two organs share the same sensory receptor, the ciliated cell, a mechanoreceptor with spontaneous activity able to signal not only the intensity and duration of a stimulus but also the direction in which it is applied. The apical surface of a ciliated cell is the mechanically sensitive portion. The basolateral portion is able to activate the terminations of the afferent nerve fibers, by releasing a neurotransmitter (glutamate). The nerve fibers in contact with the basal pole of the ciliate cell then convert the chemical stimulus into a discharge of action potentials that is sent to the central nervous system.

The sensory organs of the vestibular system are represented by the utricle, the saccule, and the three semicircular canals; they can perceive the gravity vector, the position of the head, and the linear, torsional, and angular accelerations that the head undergoes.

Variations in the spontaneous activity of the labyrinthine organs therefore provoke problems of equilibrium, ranging from modest sensations of instability, up to severe attacks of vertigo. Clinical features include dizziness, generalized imbalance, ataxia, motion intolerance, positional vertigo, oscillopsia, and episodic vertigo.

The objective of the present study is to provide an update on autoimmune disorders and audiovestibular consequences, especially for balance.

The review was conducted searching the relevant literature in the PubMed database for vertigo in autoimmune disorders. Works not focused on aspects of interest in the vestibulocochlear system were excluded.

Autoimmune vestibular disorders can be classified into two main groups: isolated immune-mediated inner ear disorders and audiovestibular pathology associated with autoimmune systemic manifestations.

2. Immune-Mediated Inner Ear Diseases

2.1. Autoimmune Inner Ear Disease (AIED). Autoimmune disease of the inner ear is part of the large group of neurosensory hearing losses, of which it represents less than 1%. The disease is defined as a rapidly progressive, often fluctuating bilateral sensorineural hearing loss, which evolves over a period of weeks or months and which initially responds to immunosuppressive therapy [2]. Vestibular disorders coexist in 50% of patients and tinnitus in 25%, and clinical outcomes may be very similar to Menière's disease [3]. In 80% of cases, it is presented as bilateral, even if the involvement of the second ear can occur after months or years. Sensorineural hearing loss should be at least 30 dB, with evidence of progression in at least one ear in two successive audiograms performed over 3 months [4]. This is a rare condition with an incidence of about 5 cases per 100,000 people per year [5]. The prevalence in women and in the age group between 20 and 50 is higher. It may be associated in 15 to 30% of cases with a systemic autoimmune disease [6].

The concept of a role of immunity in idiopathic hypoacusia was introduced at the beginning of the century with the first experiments by Joannovic [7] and Masugi and Tomizuka [8] in the 1920s and 1930s. In 1958, Lehnhardt theorized the presence of "anticancer antibodies" as a cause of progressive bilateral hypacusia in 13 patients observed in his studies [9]. In analogy to sympathetic ophthalmopathy, Kikuchi hypothesized that the "sympathetic otitis," i.e., the sensorineural hearing loss following surgery in the contralateral ear, had an autoimmune origin [10]. The German researcher Beickert was among the first to create an animal model, immunizing guinea pigs against tissues of the inner ear, verifying the subsequent appearance of cochlear damage, but not the hearing loss [11]. McCabe gave the definition of AIED after the observation of the beneficial effects of cortisone therapy on a series of 18 patients: "AIED is a progressively bilateral sensorineural hearing loss, that responds to the administration of immunosuppressives" [2]. Hughes et al. subsequently completed the definition of McCabe and introduced the distinction between primary or secondary autoimmune hearing loss, i.e., associated with a systemic autoimmune disease [12].

It has been hypothesized that the pathogenesis of this disease is linked to self-aggression by T lymphocytes against specific antigens of the inner ear with the formation of circulating autoantibodies. However, the demonstration of autoantibodies against internal ear antigens has been very difficult in AIED for three main reasons: the lack of specificity of autoantibodies in affected patients, the very low percentage of circulating autoantibodies, and the impossibility of performing diagnostic biopsies of the tissues involved in human in vivo. Due to the impossibility of having direct evidence with the induction of disease in humans, according to the Witebsky postulates, the diagnosis of autoimmune disease in AIED is mainly based on indirect tests in animal models (autoantibodies and autoreactive T lymphocytes) and on circumstantial evidence, such as association with other autoimmune diseases, lymphocyte infiltration of the cochlea, genetic correlation, and response to immunosuppressive therapy. There are numerous autoantibodies studied in the pathophysiology of AIED, some of the ubiquitous type, for example, HSP70 and collagen type II, others specific for the antigens of the inner ear (cochlina, β-tectorin, connexin 26, etc). Cochlina is mainly located in the spiral ligament and is the major component of the extracellular matrix of the inner ear after collagen; β-tectorin is present in ciliated cells, in support cells, and in the tectoral membrane. Activated T lymphocytes can enter the cochlea, exercising immunological surveillance. The transfer within the cochlea of $CD4^+$ T lymphocytes activated with cochlina and β-tectorin antigens causes hypoacusia in the mouse model [13]. Immunohistochemical analysis with $CD45^+$ shows leukocyte infiltration at the level of the inferior spiral ligament (5 weeks after immunization with Coch 131–150); activated T lymphocytes (INF-γ producers), both $CD4^+$ and $CD8^+$, are involved in cochlina recognition [14]. The deposition of immune complexes in the vascular stria causes damage to the capillary epithelium with alterations in vascular permeability that can cause endolymphatic hydrops, destruction of hair cells, collapse of the Reissner membrane, and membrane tectoria distortion [15]. In the animal model, there is a progressive fusion of the capillaries of the vascular stria, with the presence of perivascular inclusion at the level of the cochlear modulus [16].

The inner ear has always been considered a privileged immunological site: both for the absence of lymphatic drainage [17] and for the presence of an effective hemato-labyrinthine barrier. The hemato-labyrinthine barrier in the vascular stria is a highly specialized network that controls the exchanges between blood and interstitial space in the cochlea, necessary to maintaining the ionic gradient and the endocochlear potential for the active processes of mechanical-electrical transduction of the ciliate cells. Endothelial cells are connected by tight junctions, which together with the basement membrane form a barrier to the passage of many substances; the barrier is also formed by pericitis and perivascular melanocytes (the latter are activated during exposure to noise). Local immunity is regulated by the endolymphatic sac, the main antigen-processing site; its destruction causes a reduction of the immune response of the inner ear [18]. Other studies have subsequently shown the presence of immunoreactive cells in other areas of the inner ear, even in the absence of pathology. The migration of cells of hematopoietic origin, in particular of macrophages, has been described at the level of the modulus, of the lateral wall of the cochlea, and of the spiral ligament [19]. The cytokine cascade also activates the macrophages residing in the cochlea.

The diagnosis of AIED is still problematic as there are no reliable specific tests: it is mainly based on clinical evaluation and experience and must be suspected whenever we are evaluating a patient with a rapidly progressive idiopathic sensorineural hearing loss. García-Berrocal et al. have proposed the following criteria, which confirm the diagnosis of AIED in the presence of at least 3 major criteria, or 2 major and 2 minors [20]. Among these criteria, there is the rate of auditory recovery after corticosteroid or immunosuppressive therapy, which should be calculated as (Initial audi tory threshold − final auditory threshold)/initial auditory thr eshold − auditory ear contralateral threshold) × 100(%).

Major criteria:

(i) Bilateral hearing loss

(ii) Autoimmune systemic disease

(iii) ANA title > 1 : 80

(iv) Reduction of T-naive lymphocytes (CD4RA)

(v) Auditory recovery with therapy > 80%

Minor criteria:

(i) Unilateral hearing loss

(ii) Young or middle-aged patients

(iii) Female sex

(iv) Auditory recovery with therapy < 80%

Otoscopy is generally normal, although lesions of the skin or cartilages of the outer ear may occur in relapsing polychondritis. Furthermore, lesions of the tympanic membrane, middle ear, and mastoid can be observed in Wegener's granulomatosis. Vestibular symptoms such as acute vertigo, disequilibrium, ataxia, and paroxysmal positional vertigo are present in 50% of patients. From 25 to 50% of patients also complain of tinnitus and auricular fullness. The differential diagnosis includes bilateral Menière disease, treatment with ototoxic drugs (gentamicin, cisplatin, etc.), enlarged vestibular aqueduct syndrome, Lyme disease, otosyphilis, toxoplasmosis, Charcot-Marie-Tooth disease, and intracranial hypertension [3].

Currently, no reliable diagnostic tests are available, although several studies have looked for a serological test applicable to patients with AIED [21]. In the mid-nineties, a 68 kDa protein was isolated from Western blot in the blood serum of some patients with AIED and Menière's disease, subsequently identified as an antibody to heat shock protein 70 (HSP70) [4]. The test was then marketed under the name of OTOblot, and its positivity as being predictive for a good response to steroid therapy was considered. Unfortunately, OTOblot proved to be a test with very low sensitivity and controversial specificity (Berrocal et al. [22]); subsequent studies have shown that the antibody binds the 68 kDa antigen of bovine cochlea, but not in humans, resulting in a ubiquitous, nonspecific ear protein. Probably the antigen target anti-68 kDa antibody is not HSP70 (as believed in the last 15 years) but choline transporter-like protein 2 (CTL2) [23]. For the possible correlation with systemic autoimmune diseases, a screening including antinucleus antibodies (ANA) was recommended; serum immunoglobulins IgG, IgA, and IgM; C3 and C4 complement factors; and immunophenotype of peripheral blood lymphocytes (PBL) [20].

Corticosteroid drugs remain the first-choice treatment for AIED, but immunosuppressive and immunomodulatory drugs can be used as adjuvant or second-choice treatments. Corticosteroids have an anti-inflammatory, immunosuppressive, and regulation mechanism in the electrolyte balance in the cochlea, thanks also to their mineralocorticoid action. The dosage and duration of therapy can be variable, and some protocols recommend 60 mg/day of prednisone (or 1 mg/kg/day) to be continued for at least 4 weeks; if a good hearing recovery is obtained, it is advised to continue with a maintenance dose for at least two months before a gradual reduction in dosages. On the other hand, if no auditory improvement is achieved after 4 weeks at full dosage, treatment is generally suspended. The response of patients with AIED, however, varies between 15 and 50%, and it is necessary to repeat a course of corticosteroids in case of relapses of hearing loss or vertigo [3]. Furthermore, the association of AIED with an autoimmune systemic disease generally requires the continuation of steroid therapy for at least 1 year. The limits of long-term high-dose steroid therapy are linked to the side effects of the drug.

The use of immunosuppressive drugs in AIED is described in the literature, including methotrexate, cyclophosphamide, and azathioprine. Methotrexate in the 1990s was used as a second-choice therapy in cases of poor hearing loss after steroid therapy; a multicentric randomized double-blind and case-control study published in 2003, however, showed that methotrexate is no more effective than placebo in hearing loss in these patients [24]. Cyclophosphamide remains an effective but limited therapeutic alternative with important side effects: pancytopenia, infections, hemorrhagic cystitis, bladder cancer, and infertility.

The advent of biologic drugs represented progress in AIED therapy: tumor necrosis factor (TNF) inhibitors showed good efficacy and little side effects. Their action effect is rapid (from hours to days) and is contraindicated only in the presence of active infections. Infliximab (Remicade) would have demonstrated a good effectiveness when applied in the forms of AIED associated with other organ diseases [25].

Etanercept (Enbrel) has been used in AIEDs with controversial results [26]. Several years' research is underway for the intracochlear administration of drugs or other substances, using different technologies. Micropumps with endocochlear catheters, nanoparticles, and viral vectors are being tested [27]. Recently, the use of vectors consisting of genetically modified monocytes/macrophages has been hypothesized. This hypothesis of gene therapy is based on the ability of circulating monocytes and macrophages to be recruited into the inner ear in a condition of inflammation. These "intracochlear drug delivery" techniques would allow a high and generally well-controlled concentration of the drug in the inner ear, reducing its systemic effects. On these topics, careful

in vivo experiments will be required before clinical use in the AIED [27]. There are also methods of intracochlear administration that take advantage of the permeability of the round window, that is, the intratympanic injection or insertion of drugs soaked in the fenestral region after the surgical lifting of the tympanic membrane under local anaesthesia. These methods have been described since the 40s of the last century, unfortunately with generally modest and contrasting results.

If AIED does not respond to immunosuppressive therapy, the evolution of hearing loss must be carefully monitored with the serious execution of an internal ear MRI. In fact, fibrosis and ossification of the cochlea can evolve rapidly even within a few weeks and only the loss of the hyperintensity of labyrinthine liquids in the sequences in T2, or the image of initial ossification to the CT, allows the timely recognition of these processes. In these cases, the application of a cochlear implant must absolutely take place before fibrosis prevents the insertion of the electrode cable into the cochlea. The correct timing of the cochlear implant is a delicate decision that requires close cooperation between the ear surgeon, rheumatologist, and radiologist. A delay in the recognition of cochlear fibrosis may permanently preclude the rehabilitation of deep deafness or cophosis [28].

2.2. Menière's Disease. Menière's disease (MD) is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops and characterized by a triad of fluctuating vertigo, tinnitus, and sensorineural hearing loss (with aural fullness). The Committee guidelines of 1995 consist of a diagnostic scale which includes diagnoses of "definite MD," "certain MD," "possible MD," and "probable MD."

The exact aetiology and pathogenesis mechanism of MD is still unclear, although several etiologies have been proposed, as autoimmune, allergic, genetic, traumatic, or infectious (viral). Menière's disease is a syndrome certainly caused by multiple factors; nonetheless, autoimmunity has a significant role in MD, thought to represent less than 20% (6% of unilateral and 16% of bilateral forms). The role of autoimmunity as aetiology is supported by: high prevalence of systemic autoimmune diseases in patients with MD than in the general population [29], bilateral presentation of the disease in 25–40% of patients, good efficacy of glucocorticoids and anti-inflammatory treatments, and possibility of experimentally inducing hydrops by injection of antigens or monoclonal antibodies.

Furthermore, some studies confirmed elevated levels of autoantibodies or circulating immune complexes and antigen-antibody reactions, in the serum of MD patients and in animal inner ear tissues [30]. They have recently been identified in protoarray analysis-specific antigens that caused immune reactions with patient's serum, which can be good candidates for diagnostic biomarkers of MD [31].

Although most cases are sporadic, a familial form of the disease has been described, from 2.6% to 23.5% [32]. Familial MD (FMD) should be considered if at least two family members (first or second degree) fulfill all the criteria of definite or probable MD. Most families described have an autosomal dominant pattern of inheritance, but, as FMD shows clinical heterogeneity, mitochondrial and recessive inheritance patterns are also observed in some families. Linkage studies in FMD have found candidate loci at 5q14–15 in a German family [33] and 12p12.3 in a large Swedish family [34], but the genes were not identified. By exome sequencing, Requena et al. [35] have identified mutations in DTNA and FAM136A genes in an autosomal dominant Spanish family with MD segregating the phenotype in three women in consecutive generations. DTNA encodes alpha-dystrobrevin, a dystrophin-associated protein which interacts with transmembrane proteins and actin in the basolateral membranes of epithelial cells, and it is associated with tight junction reorganization [36].

Genetic factors can be one of the causes of autoimmunity or increased immune reaction in Menière's disease. Recently, the first gene locus associated with sporadic Menière disease has been identified using a genotyping array; this locus (6p21.33), through the nuclear factor kB (NF-κB) and the TWEAK/Fn14 pathway, is involved in inflammation modulation of many autoimmune diseases. Potential sites of this inflammatory damage are the blood–brain barrier, the endolymphatic sac, the spiral ligament, and the reticular lamina in the neurosensory epithelium of the cochlea. Patients with this genotype have been shown to develop bilateral Menière disease through a mediated NF-κB inflammatory response [37].

Delayed endolymphatic hydrops (DEH) is a secondary endolymphatic hydrops that usually occurs suffering from longstanding hearing loss in one ear. The hearing loss can be caused by various causes: idiopathic, infectious, traumatic, etc. Its classification is still controversial in the international literature: DEH is considered in most cases as a secondary form of Menière, while for some Japanese and German authors, it is a pathology distinct from MD.

DEH mostly occurs in the ipsilateral ear, with episodic vertigo, or less frequently in the contralateral ear, with fluctuating hearing loss and recurrent vertigo. Symptoms, diagnosis and therapy are identical to those of Ménière's disease. In a few families, both unilateral hearing loss and DEH can have a genetic aetiology, showing autosomal dominant transmission with incomplete penetrance [38].

2.3. Bilateral Vestibulopathy (BVP). This disease was called in 1989 by Baloh as "idiopathic bilateral vestibulopathy" [39] and was recently defined in a consensus document by the Classification Committee of the Bárány Society [40]. The prevalence of BVP in adults is estimated to be 28/100,000 [41], and the mean age of onset is around 50–60 years; often, there is a diagnostic delay due to unclear symptoms and signs.

The BVP develops in most cases slowly and progressively; in the initial phase of the disease, patients can report recurrent short-term episodes of vertigo, with or without association of hearing loss. Both labyrinths and/or vestibular nerves can be affected, simultaneously or sequentially. The symptoms in BVP are caused by the sensory vestibular impairment leading to insufficent vestibulospinal reflexes. This disease has a negative impact on social and physical functions, with decay of the health-related quality of life in 90% of the patients.

The diagnosis is based on patient anamnesis (movement-dependent postural imbalance and unsteadiness of gait) and clinical finding (bilaterally reduced or absent function of

the VOR). Symptoms are exacerbated in darkness and on uneven ground, because they depend more on visual and somatosensory control, and they can disappear under static conditions; some patients can present movement-induced oscillopsia, for example, during rapid head turns.

Diagnostic criteria for bilateral vestibulopathy (BVP) have been defined by the Classification Committee of the Bárány Society [40]:

(a) Chronic vestibular syndrome with the following symptoms: unsteadiness when walking or standing plus at least one of 2 or 3; movement-induced blurred vision or oscillopsia during walking or quick head/body movements; and worsening of unsteadiness in darkness and/or on uneven ground

(b) No symptoms while sitting or lying down under static conditions

(c) Bilaterally reduced or absent angular VOR function documented by bilaterally pathological horizontal angular VOR gain <0.6, measured by the video-HIT or scleral-coil technique, and/or reduced caloric response, and/or reduced horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair and a phase lead >68 degrees

(d) Not better accounted for by another disease

The aetiology remained unknown in more than 70% of cases [42]. The most frequent causes of BVP include ototoxic drugs, bilateral Menière's disease, infections, autoimmune diseases, tumors, bilateral labyrinth contusion, and vascular abnormalities. A genetic cause can be identified as 15–25% of cases [43]. In 20% of patients, the BVP is associated with gangliopathy, described in 2011 as CANVAS (cerebellar ataxia, nonlength-dependent sensory neuropathy, vestibular areflexia) [44], while 50% of the idiopathic BVH patients present with migraine according the International Headache Society criteria [43]. In a recent paper, it was reported that 23.4% of patients with idiopathic BVP had autoimmune disorders in their medical history; autoimmune disorders might not always cause BVH directly, but it seems reasonable to admit that autoimmune response could have a modulating role in this disease.

Most patients presented with a mutation in their COCH gene. This mutation has been identified to cause autosomal dominant nonsyndromic hearing loss accompanied by vestibular disorders (DNFA9). Although a strong underlying familial character seems to be present in multiple vestibular disorders, genome-wide association studies remain very difficult to perform, partly due to the clinical heterogeneity of vestibular disorders [43].

3. Audiovestibular Pathology Associated with Systemic Autoimmune Diseases

3.1. Behçet's Disease. Behçet's disease (BD) is a rare systemic immune mediate disorder of unknown aetiology characterized by the presence of recurrent oral and genital ulcers, ocular inflammation, and skin lesions. The aetiology and pathogenesis of BD are unknown although epidemiological data suggest the involvement of both genetic and environmental factors. The presence of HLA-B 51 represents a significant predisposing genetic factor. BD can affect any age group, but its onset in early and advanced age is relatively rare, the most common age of presentation being around the third decade of life, with a balanced male/female ratio [45]. BD is a systemic leukocytoclastic vasculitis, and any part of the organism may be affected. The prevalence of vestibular lesions ranges from 15% to 47% in separate studies. Morales-Angulo et al. reported high-frequency sensorineural hearing loss, vertigo, and bilateral vestibular hypofunction, but also in one patient were symptoms compatible with vestibular neuritis as the first manifestation of central nervous system (CNS) involvement in the context of neuro-Behçet. Brama and Fainaru reported in a selected group of 17 patients with vestibular lesions the presence of dizziness (82%), spontaneous nystagmus (11%), abnormal saccades (5%), abnormal caloric test (29%), and alteration in the rotational tests (58%) [46, 47]. Kulahli et al. found that 47% of patients had audiovestibular symptoms, with 8% complaints of vertigo [48]. Endolymphatic hydrops, with a presentation similar to bilateral Menière disease (fluctuating hearing loss, severe hearing loss, and vertigo), has been also reported [49, 50].

Although a specific audiogram pattern of hearing loss does not exist, sensorineural high-frequency downward audiometric slopes are frequently reported in BD [51]. The diagnoses of BD can be delayed by years when audiovestibular impairment is the presenting symptom in the absence of classical signs and symptoms, as in the case of a 66-year-old man with peripheral bilateral vestibulopathy and severe sudden SNHL as disease onset, reported by White and colleagues [52]. BD enters in the differential diagnosis of acute vestibular syndromes accompanied by SNHL.

Vestibular function studies seem to identify a peripheral lesion more frequently than damage to the central vestibular tract, although other authors found also a higher prevalence of central vestibular syndrome [48, 53]. A possible relationship between age or the disease duration and inner ear involvement is still uncertain.

First defined in 1954, [54], central nervous system (CNS) involvement (neuro-Behçet) occurs in 5–10% of patients, more frequently in males, and it usually occurs around 5 years after the onset of the disease [55, 56].

Vertigo, sensorineural hearing loss, tinnitus, and imbalance may be the initial symptoms of the mild form of neuro-BD. Neuro-BD may be parenchymal (80% of patients), nonparenchymal, or mixed. Parenchymal brain disease affects the brain system and/or basal ganglia while nonparenchymal brain disease is characterized by cerebral venous thromboses, arterial vasculitis, and aseptic meningitis. Koçer et al. estimated that the pontobulbar region in NB is affected by focal lesions in 40% of cases and Lee et al. and Gan et al. reported clinical cases of relapsing vertigo due to multiple recurrent reversible occlusions of basilar artery and/or posteroinferior cerebellar artery (PICA) [57–59].

According to a recent review reporting 130 cases of neuro-Behçet's disease in the pediatric population, the

median age at presentation was 12 years with a male gender prevalence. Vertigo and/or hearing loss were present in 5.6% of the patients and only in the parenchymal form of the disease, with a prevalence of 21.4% among this subgroup of patients [60]. Treatment with immunosuppressive therapies or antitumor necrosis factor drugs revealed good prognosis with recovery or significant improvement of symptoms [60, 61].

To date, there are no diagnostic tests, therefore diagnosis is based on clinical symptoms. But it could be challenging when the symptoms are not concomitant or when BD is characterized by episodes of relapses and remission. The ICBD criteria included recurrent oral and genital aphthosis, eye lesions (anterior or posterior uveitis, cells in vitreous on slit lamp examination, and retinal vasculitis), skin lesions (erythema nodosum, pseudofollicolitis or papulopustular lesions, and acneiform nodules), neurological manifestation, vascular manifestation, and/or a positive pathergy test [62]. Increase in inflammatory markers, peripheral leukocytosis, and moderate anemia of chronic disease may be present but are not specific.

Multiple treatments have been proposed for BD. The European League Against Rheumatism (EULAR) proposed general treatment recommendations for the management of BD, not specifically for inner ear involvement. High doses of corticosteroid and immunosuppressive drugs (cyclophosphamide, azathioprine, and methotrexate) are recommended in case of parenchymal brain involvement [63]. Recently, anti TNF-alpha inhibitors have demonstrated to improve neurological symptoms and parenchymal lesions in 94% of 17 patients with neuro-BD and a complete response was achieved in one-third of cases. The onset of action was fast as the median time to achieve remission was of 3 months [64].

3.2. Cogan's Syndrome. Cogan's syndrome (CS) is a rare chronic inflammatory disease, characterized by nonsyphilitic ocular keratitis and Mèniére-like cochleovestibular dysfunction, with relapsing attacks of vertigo, sudden onset of tinnitus, vomiting, and progressive, mostly bilateral sensorineural hearing loss [65]. The hearing loss is generally bilateral and progresses over a period of 1 to 3 months to complete deafness in 60% of cases [66]. Haynes et al. proposed the definition of "typical" CS, with the ocular inflammation in addition to cochleovestibular symptoms, and "atypical" CS characterized by (a) ocular lesions other than interstitial keratitis (conjunctivitis, scleritis, iritis, choroiditis, subconjunctival, or retinal hemorrhage), (b) a delay of more than 2 years from the onset of ocular and cochleovestibular symptoms, and (c) systemic manifestations, including cardiovascular, neurological, and gastrointestinal symptoms [67]. Atypical disease is associated with systemic vasculitis in 20% of cases [68]. Furthermore, life-threatening aortic insufficiency develops in 10% of cases.

The etiopathogenesis of CS is currently unknown, but some evidences suggest that it might be the result of an autoimmune process. Antibodies against a peptide antigen—called Cogan peptide—are found in the serum of patients affected by CS. This peptide showed similarity with autoantigen SSA/Ro and with Reovirus III major core protein lambda and shared sequence homology with the cell density-enhanced protein tyrosine phosphatase-1 (DEP1/CD148), which is expressed on the sensory epithelia of the inner ear and on endothelial cells [69]. Traditional antibodies such as antinuclear antibodies and rheumatoid factor are not consistently found, but in 15–30% of cases, especially in the atypical form [70]. Recently, Jung et al. observed a lymphocytic, neutrophilic, and histiocytic infiltrate in both basal turns of the cochlea, vestibular system, and surrounding tissue, with thrombosis and necrosis of the small vessel wall. The organ of Corti and the stria vascularis were necrotic, the perilymphatic and endolymphatic spaces contained fibrotic material, and there was loss of inner and outer hair cells throughout the cochlea [71].

Treatment of CS traditionally consists of systemic corticosteroids, with ocular symptoms being more responsive than cochleovestibular symptoms. When a high dose of steroids is required, or relapsing symptoms are present, a second line of treatment with immunosuppressive agents is usually added. Nevertheless, from 43.5% to 52% of CS patients become deaf [72] and cochlear implantation represents a valuable rescue surgical strategy before cochlear partial obliteration or ossification, in both adult and pediatric patients [28, 73]. However, anecdotical cases of cochleovestibular function recovery are reported [74].

Recently, several studies described a treatment strategy with biotechnological drugs (biologic therapy), such as TNF-alpha inhibitors, anti-CD20 and anti-IL-6 receptors, for patients' refractory to the first- and second-line drugs. Infliximab appears to be the more frequently used biologic drug in the therapy of CS. In all cases but one, the treatment was able to lead to some improvement or stabilization of hearing loss and corticosteroid tapering. Durtette et al. confirmed that patients receiving infliximab experienced significant improvement in vestibuloauditory signs, different from patients with steroids alone or DMARDs, while systemic and ocular signs usually improve with steroids alone [75]. However, complete remission is rarely reported.

3.3. Sarcoidosis. Sarcoidosis is a granulomatous disease of unknown aetiology that can involve several organs. Its prevalence ranges from 10 to 40 per 100,000, with a mortality of 1% to 5% [76].

Environmental and genetic factors have been demonstrated in the pathogenesis of the disease. Environmental factors could include infections such as M. tuberculosis and P. acnes as well as other agents such as silica or metal dusts [77]. The Th1 response produces cytokines including interferon-gamma and IL 2, 6, and 12, recruiting additional phagocytes and T cells leading to the aggregation of phagocytes into epithelioid cells and giant cells. The hallmark of sarcoidosis is the noncaseating granuloma, consisting of activated macrophages and CD4-helper T lymphocytes. Granulomas are the source of ACE, which is found to be elevated in 60% of patients [78].

Neurologic involvement could occur in 5% of all sarcoidosis patients. It rarely occurs at disease onset, since about 40% of patients with neurosarcoidosis (NS) have previously diagnosed sarcoidosis in another organ, most commonly the chest or anterior uvea [79, 80].

Most commonly, patients present with cranial neuropathies, with facial nerve palsy being the most frequent. Otolaryngologic manifestations are found in 10% of patients [81]. Ear involvement and vertigo are also rarely described. They are observed in the presence of vestibulocochlear nerve involvement, presenting, therefore, with sensorineural hearing loss in association with vertigo and ataxia [82].

A review of cochleovestibular involvement in 50 cases of NS evidenced the presence of mostly bilateral, mild to profound sensorineural hearing loss in 94% of the patients, whose onset was mostly sudden (48%) or rapidly progressive (42%). Details of vestibular impairment were recorded in 64% of the patients, including vertigo, dizziness, and benign paroxysmal positional vertigo. The authors found a 96% rate of vestibular function loss in the tested cases, with a prevalence of bilateral impairment (67%) [83].

Cranial neuropathies in neurosarcoidosis are likely to be the result of a sarcoid basal meningitis affecting the exit of the lower cranial nerves. However, enhancing lesions within the internal acoustic canals (IACs) or in the CPA are reported on MRI, with the appearance of nerve meninges inflammation [83]. There are no randomized controlled trials in the treatment of NS, but general consensus suggests a rapid treatment with corticosteroids. High-dose systemic corticosteroids were administered either orally (prednisone 1 mg/kg/day) or through a short course of intravenous pulse (methylprednisolone 1000 mg per day, intravenously, during 3 days), followed by slow tapering, expecting a response within six to eight weeks [78]. For patients with refractory disease, immunosuppressants are usually considered. A specific DMARD is often chosen based on cost, availability, and side effect profile. Anti-TNFα agents have shown encouraging results in the treatment of ocular sarcoidosis, but further controlled studies are needed to elucidate their role [84].

3.4. Autoimmune Thyroid Disease. Autoimmune thyroid disease (AITD) is very common, affecting 1–5% of the entire population [85]. The most common are Graves' disease (GD) and chronic autoimmune thyroiditis also known as Hashimoto's thyroiditis (HT), with similar pathogenic mechanisms [86]. In both disorders, autoantibodies against thyroid antigens, including thyroglobulin, thyroid peroxidase, and thyroid-stimulating hormone receptor, can be detected. The clinical manifestations of thyroid dysfunction can range from hyperthyroidism as observed in Graves' disease, to symptomatic hypothyroidism, occurring in some HT patients.

A relationship between Meniere's disease (MD) and thyroid disease was firstly postulated in 1964 by Tamura, who hypothesized a role of hypothyroidism in the pathogenesis and progression of endolymphatic hydrops [87]. A second hypothesis was proposed in 1988 by Evans, who found positive anti-thyroid-microsome antibodies in 17% MD patients [88]. A recent study comparing MD patients to age- and sex-matched subjects suffering from non-Ménière acute unilateral peripheral vestibulopathy as well as healthy controls showed a significantly higher proportion of positive anti-thyroid autoantibody levels in MD patients (38%) than in both the control groups (7% and 12%, respectively) [89]. These findings confirmed a relationship between thyroid disease and MD, without clarifying the role of thyroid dysfunction. Santosh and Rao demonstrated a higher incidence of thyroid dysfunction in MD patients as well as the subjective remission of symptoms in all hypothyroid MD patients following 12 weeks of L-thyroxine replacement therapy [90].

The association between autoimmune disorders and vertigo has raised the hypothesis that autoimmune mechanisms might be also involved in the pathogenesis of benign paroxysmal positional vertigo (BPPV). In 2000, Modugno et al. [91] reported that 34/70 patients with BPPV had high levels of anti-thyroid autoantibodies, in the absence of other risk factors for BPPV. In a subsequent study, 200 euthyroid patients affected by HT were evaluated, showing that 18% of them had signs of BPPV and postulated a link between HT and the vestibular disease, possibly related to anti-thyroid autoantibodies, in particular a mechanical stimulation by immune complexes and the possible coexistence of a microangioitis in the inner ear, in the context of an autoimmune multiorgan disease [92].

HT is frequently associated to other organ-specific autoimmune disorders such as celiac disease, type 1 diabetes mellitus, Addison's disease, pernicious anemia, multiple sclerosis, vitiligo, and dermatitis herpetiformis [93]. Moreover, the increasing number of reports suggesting a possible "systemic" effect of thyroid autoimmunity on various tissues, including inner ear, open new perspectives on the interpretation of some clinical manifestations of HT [94]. Several reports have demonstrated a negative, direct effect of autoimmunity on connective tissue in various organs [95].

In a recent study, Chiarella et al., demonstrated that vestibular alterations were observed in 50% of HT patients and there was a significant correlation between vestibular alterations and serum anti-thyroid peroxidase antibodies but not with thyroid-stimulating hormone levels [96]. They postulated that the association between vestibular lesions and HT was mainly related to the autoimmune response against thyroid-specific antigens and was not influenced by the thyroid functional status. This concept would also imply a morbidity related to extra-thyroidal effects of thyroid autoimmunity, besides thyroid hormone insufficiency.

Nowadays, literature identifies patients with MD or BPPV as potential candidates to develop HT and vice versa, while it remains unclear whether anti-thyroid peroxidase and/or anti-thyroglobulin autoantibodies per se could promote thyroid dysfunction.

3.5. Vogt-Koyanagi-Harada Syndrome. Vogt-Koyanagi-Harada (VKH) syndrome is a systemic granulomatous autoimmune disease that affects melanocyte-rich tissues, such as the eye, inner ear, meninges, skin, and hair [97]. Most studies have found that women were affected more frequently than men and the disease onset was in the second to fifth decades of life [98]. Among all cases of uveitis, it was estimated to represent approximately 7% in Japan, 1–4% in the United States, and 3% in Brazil ([99]; Ohno 1977).

It is characterized by an acute onset of bilateral blurred vision with hyperemia (acute uveitis) preceded by flu-like symptoms. After the uveitic stage, vertigo with hearing loss,

alopecia or vitiligo, and signs of meningeal irritation, including severe headache, periocular pain headache, and pleocytosis in the cerebrospinal fluid may appear. Peripheral vestibular dysfunction, such as rotato-horizontal or horizontal nystagmus, were observed in the vast majority of these patients by Yoshimoto [100]. Furthermore, Tahara and Sekitani [101] reported that vestibular function tests resulted to be abnormal in 77% of the patients, while symptoms or signs of central nervous system involvement were rarely demonstrated. On the other hand, in a recent series of 24 patients described by Ondrey et al. [102], only one (4%) had vertigo; elevated pure-tone thresholds were prevalent in eight (33.3%) and two (8.3%) experienced tinnitus.

About 17–73% of patients may progress to recurrence or chronicity [103], often associated with rapid tapering of corticosteroids, and this could lead to more severe and frequent audiovestibular abnormalities.

The etiopathogenesis of VKH is currently unknown, but some evidences reported an autoimmune aggression against antigens associated with melanocytes in a genetically susceptible individual after a virus infection trigger. Sugita et al. described that T cells from peripheral blood and intraocular fluid from patients with VKHD cross-reacted with tyrosinase protein and with highly homologous cytomegalovirus-specific sequences [104]. As suggested by recent studies, the immune response is aimed at proteins associated with melanocytes, with involvement of a T cell-mediated immune process with a peptide-specific Th1 cytokine response [105]. Cellular and humoral autoimmunity against retinal components has also been demonstrated in patients with VKH, as well as anti-Ro/SSA reactivity, in a small percentage of patients [106].

The diagnosis of VKH is primarily based on clinical features. The cornerstone of treatment of VKH is prompt, high-dose systemic corticosteroids, administered either orally (prednisone 1–mg/kg per day) or through a short course of intravenous pulse (methylprednisolone 1000 mg per day, intravenously, for three days), followed by slow tapering of oral corticosteroids throughout a minimum of a 6-month period. When a high dose of steroids is required, or relapsing symptoms are present, a second line of treatment with immunosuppressive agents is usually added [107]. Case series demonstrating the efficacy of several other treatment modalities are found in the literature including biologics agents, such as infliximab and rituximab [108].

3.6. Relapsing Polychondritis. Relapsing polychondritis (RP) is a rare, multisystemic autoimmune disease characterized by recurrent episodes of inflammation of the cartilaginous structures. It involves predominantly ears, nose, joint, vessels, and the respiratory tract [109]. RP affects 1 in 1.4 million people per year in UK [110] with a peak of incidence in the fifth decade of life, but the disease has been described in children and very old people. The clinical course of RP is variable, ranging from minor symptoms to a rapidly progressive illness and can be potentially lethal [111]. Otology manifestation in RP is common, and the otolaryngologist evaluation is frequently requested for the first diagnosis. The most frequent otology presenting symptoms is auricular chondritis, which is specific of RP once a local disease or infection has been ruled out. Episodes of nasal chondritis can lead to a collapse of the nasal septum with saddle-nose deformity, and laryngo-tracheal involvement can cause hoarseness dyspnea and stridor and may lead to subglottic stenosis due to recurrent laryngeal inflammation and laryngomalacia [112]. Vestibular dysfunction is rare and documented unilaterally or bilaterally in 6–13% of patients, usually in combination with cochlear involvement [113, 114]. Vestibular symptoms and sensorineural involvement may be due to the result of vestibular structure inflammation associated with chondritis, destruction of the Eustachian tube, and endolymphatic hydrops or due to the vasculitic process in the vestibular or cochlear branch of the internal auditory artery [112, 115].

Aetiology and pathogenesis of RP are not known, but many evidences suggest an autoimmune response against a yet unknown cartilage immunogenic epitope of chondrocytes or extracellular cartilage matrix antigen. Autoantibodies against collagen type II are detected in 33% of RP patients but also against IX and XI or other cartilage proteins such as cartilage oligomeric matrix protein (COMP) and matrilin-1 [116]. The immune-mediated process is hypothetically induced by different noxae (trauma, toxin, or infectious agents) which lead to the exposure of connective tissue or cell membrane self-epitopes in genetically susceptible individuals. The subsequent inflammatory process determines cartilage matrix destruction by protease release from inflammatory cells and from chondrocytes undergoing apoptosis [117].

Diagnosis is usually challenging, since it is based on a set of clinical evidence and imaging studies, and presenting manifestations are highly variable. Although not validated, the McAdam's or the Michet's diagnostic criteria are useful in the clinical setting. The former considers audiovestibular damage as an item required for diagnosis [118]; the latter defines hearing loss and vestibular dysfunction as minor criteria [114].

Unfortunately, there are no laboratory features to establish the diagnosis of RP yet. Antinuclear antibodies can be detected in 5–20% of patients [119]. Both p-ANCA positivity and c-ANCA positivity sometimes without antibodies to myeloperoxidase (MPO) or proteinase 3 (PR3) have been described [120]. Also, rheumatoid factor and antiphospholipid antibodies have been reported in RP [121].

Because of lack of clinical trials, the treatment of RP remains empirical. Corticosteroids are the cornerstone of the therapy. In inner ear involvement, high doses are required although permanent sequelae are common. Once the disease has been controlled, corticosteroid therapy should be gradually reduced but there are no definitive guidelines indicating how long-maintenance therapy should be continued before attempting withdrawal. Immunosuppressive agents should be considered if a satisfactory clinical response to steroid is not achieved or if high dosages of steroids are required to keep the patient in stable clinical status. Cyclophosphamide, azathioprine cyclosporine, and methotrexate are the most commonly drugs used. There are several reports about the successful treatment with the TNF-alpha antagonist, while for other biological agents such as abatacept

(blocking of CD28 costimulation), rituximab (anti-CD20 antibody), and tocilizumab (anti-Il-6 receptor antibody), results are variable and the number of treated patients is too small to allow definitive conclusion [122].

3.7. Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multiorgan involvement and an incidence of 12.5–39.0 per 100,000 people, higher in women, and it is two to three times more prevalent in African people [123]. The most frequent age at onset is from 20 to 40 years.

SLE is a multifactorial disease with different aetiologies, including genetic alterations, inflammation, drugs, environmental factors, and interactions between the adaptive and innate immune systems. The hallmark of SLE is the production of autoantibodies that react with self-nuclear and cytoplasmic antigens and culminate in immunologic attacks, resulting in tissue inflammation and multiorgan damage [124]. T and B lymphocyte disorder plays a central role in this autoimmune dysfunction, with an intense polyclonal B cell activation, with a population shift towards immature B cells and defects of T cells in signalling, adhesion, costimulation, gene transcription, and alternative splicing [125]. Autoantibodies are directed toward antigens at the nuclear cell level (ANA); one of the most relevant antigens in SLE is double-stranded DNA. They are highly specific for SLE, being present in 70% of cases, whereas they appear in only 0.5% of people without SLE [126]. Other ANA that may occur in people with SLE are anti-U1 RNP (which also appears in systemic sclerosis and mixed connective tissue disease), SS-A (or anti-Ro), and SS-B (or anti-La, both of which are more common in Sjögren's syndrome).

As a systemic disease, SLE has protean clinical manifestations, involving different organs including the skin, kidney, neurologic system, and musculoskeletal system. The clinical course is highly variable among patients and may be characterized by periods of remissions and of chronic or acute relapses.

Recent studies have also shown involvement of the inner ear [127, 128]. At this level, there are several mechanisms that lead to damage to the inner ear: (1) humoral-type antibody attacks on inner ear antigens, (2) cell-mediated cytotoxic damage to cochlear and vestibular hair cells, and (3) immune-complex deposition in the microvessels of the inner ear [124].

The most common otologic symptom found in clinical studies in SLE patients is sensorineural hearing loss (SNHL) that may be either slowly progressive or acute, with a reported prevalence of 6% to 70% [129–131]. Other audiovestibular symptoms associated with SLE include tinnitus and vertigo. Tinnitus was associated with hearing loss and may have been a consequence of deafferentation. The vestibular system appears to be involved in SLE, although to a lesser extent; vertigo and dizziness have rarely been reported. Only few authors have described vertigo in patients with SLE, and, in all cases, this symptom was always associated with SNHL or tinnitus [132, 133].

In a recent meta-analysis, the most common pathological findings in temporal bone specimens of SLE patients were polymorphonuclear infiltration (31%) and vasculitis (27%), followed by fibro-osseous reaction (21%), new bone formation (17%), and granulation (4%). Stria vascularis atrophy (33%) and spiral ganglion degeneration (23%) were two other consistent findings [127].

Different treatments for SLE-related hearing disorders have been proposed, focusing on prevention, especially for slowly progressive hearing loss, and hearing restoration for cases of sudden hearing loss. Corticosteroid therapy is routinely used for sudden hearing loss and for the prevention of further worsening of progressive hearing loss in SLE patients. Other treatments reported in literature are plasmapheresis as reported by Kobayashi et al. [134], anticoagulant therapy in case of antiphospholipid antibodies [130], and cyclophosphamide for refractory patients [135].

3.8. Antiphospholipid Syndrome. Antiphospholipid syndrome (APS) is an acquired disorder characterized by the association of antiphospholipid antibodies with thrombosis and pregnancy morbidity and mortality. It can be divided into a primary or secondary antiphospholipid syndrome, depending on the absence or presence of other autoimmune diseases, in particular SLE [136]. The etiopathogenetic mechanism involves hypercoagulability, thus determining microthrombosis and subsequent clinical consequences related to the affected vessels.

There is an increasing interest in the literature in investigating the association between idiopathic sudden sensorineural hearing loss (SNHL) and the occurrence of elevated antiphospholipid antibodies title, but the investigation of an underlying APS is rarely contemplated. Moreover, to date, no strong associations are reported concerning vertigo and APS. In fact, only sparse case reports marginally described the occurrence of vertigo in patients suffering from SNHL, where elevated antiphospholipid antibody title was identified. The first report was the case of a 23-year-old primigravida diagnosed with pre-eclampsia and elevated IgG anticardiolipine antibody level, who presented profound bilateral SNHL and loss of balance, with bilaterally absent caloric response [137]. Vertigo was also reported in 47% of patients with progressive SNHL, where the rate of elevated anti-cardiolipin antibodies was 16% [138]. Finally, only one case describes transient vertigo in a patient with sudden unilateral hearing loss diagnosed with APS [139].

The concept of an antiphospholipid inner ear syndrome has been recently proposed, assessing an elevated title for anticardiolipin, anti-B2 glycoprotein, and lupus anticoagulant antibodies in 25% of patients with idiopathic progressive SNHL with or without vertigo. Unfortunately, specific results concerning vertigo are missing [140].

3.9. IgG4-Related Disease. IgG4-related disease (IgG4-RD) is an idiopathic chronic relapsing-remitting inflammatory condition characterized by sclerotic pseudotumor formation in multiple organs, including head and neck structures, such as orbit, salivary glands, and thyroid [141]. The disease generally occurs most commonly in middle-aged and older men, but the epidemiology data requires further definition [142].

IgG4-RD can present as a single organ or a multiorgan disease; therefore, clinical manifestations could be extremely different. Due to their infiltrative nature and nonspecific radiologic findings, pseudotumors are often confused with neoplasms or localized infection; therefore, the biopsy with immunostaining is mandatory [143]. The pathogenesis is not completely known; up to date, the hypothesis identifies a T-follicular helper cell response responsible for the development of germinal centers within lymph nodes and involved organs and the production of cytokines (e.g., IL-4) that drive the IgG4 class switch, culminating in the creation of IgG4-secreting plasmablasts and long-lived plasma cells. This continuous antigen presentation by B cells and plasmablasts sustains a clonally expanded population of $CD4^+$ cytotoxic T lymphocytes, which produces potentially important mediators of the fibrosis. [144].

Although the clinical presentation, diagnosis, and treatment for IgG4-RD involving head and neck have been described in the literature, there is a limited number of data regarding otologic manifestations and temporal bone involvement. There are few published case reports of unilateral temporal bone involvement causing single-sided progressive hearing loss and vestibular dysfunction [145, 146].

In a recent case series of 39 patients with confirmed diagnoses of IgG4-RD, 12.8% had otologic symptoms, namely, two cases of eosinophilic otitis media, two of otitis media with effusion, and one of SNHL were registered [147]. The latter case also developed vertigo at disease onset.

Vestibular impairment was described in other two cases of IgG4-RD with pseudotumor lesions of the temporal bone, in one case presenting bilaterally. Neuroimaging techniques are mandatory to defining the extent of the disease inside and outside the temporal bone. Bone erosion of the labyrinth was observed, as well as pachymeningeal enhancement of the posterior fossa [148, 149].

Moreover, there is also evidence of a case of IgG4-related hypertrophic pachymeningitis of the posterior cranial fossa in a 52-year-old man presenting with vertigo, moderate bilateral hearing loss, tinnitus, and blurred vision. Initial disease progression under corticosteroid and immunosuppressive drug improved only after rituximab, leading to tinnitus and vertigo improvement within 6 months [150].

The typical histopathologic finding is a lymphoplasmacytic infiltrate, eosinophils, storiform fibrosis, and obliterative phlebitis and by immunohistochemistry demonstrating IgG4-positive plasma cells >10 per HPF and a ratio of $IgG4/IgG^+$ cells >40% [151]. However, histological diagnosis is difficult using specimens from the middle ear and it is recommended that biopsy specimens should be taken from the paranasal sinus or nose. Serum IgG4 levels may be elevated; however, these are normal in 30% to 50% of patients with IgG4-RD [152].

Steroids are often used as induction therapy or as adjunctive therapy to surgery for symptomatic IgG4-RD. Most of the patients respond to steroids within several weeks, particularly in early stages of the disease. In refractory cases, immunosuppressive drugs should be considered. Rituximab, a monoclonal antibody against the short-lived $CD20^+$ B cells, has been demonstrated to be an effective treatment [153]. Surgical resection with adjunctive corticosteroids may be required for temporal bone IgG4-RD, which has been suggested to follow a more aggressive course. In all reported cases of unilateral temporal bone IgG4-RD, tumor size reduction and disease remission were achieved with a combination approach of mastoidectomy and medical management [148].

3.10. ANCA-Associated Vasculitides. The antineutrophil cytoplasm antibody- (ANCA-) associated vasculitides (AAV) are heterogeneous, multisystemic, autoimmune diseases of unknown aetiology characterized by necrotizing small and medium vessel vasculitis. AAV are associated with ANCA autoantibodies, mainly directed against anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) [154]. In the group of AAV are listed granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome).

GPA, MPA, and EGPA have respective annual incidence rates of 2.1–14.4, 2.4–10.1, and 0.5–3.7 per million in Europe, and they are slightly more common in men, typically those aged over 60 years [155].

MPO and PR3-specific ANCA can activate neutrophils and monocytes through their Fc receptors, which determines their adhesion to endothelial cells where degranulation occurs. This releases free oxygen radicals and lytic enzymes, resulting in damage to the endothelium via the induction of necrosis and apoptosis. Furthermore, neutrophils release chemoattractive signalling molecules that recruit more neutrophils to the endothelium, acting as a positive feedback loop [156]. In addition to this mechanism, the role of ANCA-reactive B cells has recently been proposed, which further leads to neutrophil degranulation and inflammation [157].

AAV may involve organs throughout the body, such as the eye, nose, ear, lung, and kidney, and the presentation could range from a skin rash to a fulminant multisystem disease [158]. Typical features of GPA include nasal crusting, discharge and epistaxis, uveitis, upper respiratory tract involvement, and often, when in the context of an active urinary sediment, renal involvement. Patients with MPA are typically older and present with more severe renal diseases than GPA together with rash and neuropathy. EGPA typically presents with a multisystem disease on a background of asthma, nasal polyposis, and peripheral blood eosinophilia.

It has been reported that 19 to 61% of systemic AAV patients show otologic symptoms such as otalgia, hearing loss, aural fullness, tinnitus, and vertigo during their clinical courses, and in turn, otologic symptoms are sometimes the initial manifestation of AAV [159, 160].

In GPA patients, Takagi et al. [161] described classification of otologic involvement into 5 distinct patterns: (1) serous otitis media, the most common (90%), resulting from Eustachian tube obstruction and nasopharyngeal involvement; (2) SNHL (43%) due to vasculitis of the cochlear vessels and the immunocomplex deposits in the cochlea; (3)

chronic otitis media (24%) caused by middle ear mucosa lesions; (4) vertigo resulting from central system involvement and immunocomplex deposits in the vestibular portion of the inner ear; and (5) facial nerve palsy (8%) usually associated with otitis media, secondary to compression of the nerve in the middle ear course, especially in the presence of dehiscence in the fallopian canal. In a recent paper, Morita et al. [162] noted that the bilateral or at least the unilateral vestibular periphery was affected in 84% of the GPA patients with otologic involvement. The authors described two types of vestibular symptoms: chronic dizziness accompanied by progression of hearing loss and acute vertigo attack with sudden hearing loss that mimics sudden deafness. In the latter case, vertigo may be caused by acute dysfunction of the vestibular periphery, and it would be difficult to make a correct diagnosis of this condition at the early stage. Temporal bone histopathological studies in GPA patients revealed hemorrhages in the stroma of the crista of semicircular canals, changes in vessel caliber, and lymphocytic infiltration [163].

The most typical otological manifestation of EGPA is chronic granulomatous otitis with chronic, thick aural discharge, which is responsible for conductive hearing loss [164]. Middle ear involvement is a self-sustaining disease, with no direct correlation with the nasal counterpart. The pathogenic mechanism of the otitis media is probably due to eosinophilic infiltration, thick secretions, and mucosal edema that may block the functioning of the Eustachian tube, and consequently middle ear ventilation. However, the complete etiopathogenesis of otologic manifestations in EGPA is still unknown and may be multifactorial. In patients with sensorineural hearing loss but no signs of middle ear involvement, the presence of a vasculitic process causing an eight-cranial-nerve neuropathy could be hypnotized [165]. It remains not clear why the vasculitic process apparently spares the vestibular system, as demonstrated by the lower percentage of vestibular disorders compared to audiological problems.

Management of the otological complications of AAV is challenging. Medical therapy is the main treatment and is based on a steroid regimen, both systemic and local. Surgical treatment is generally limited to the application of a ventilation tube, which significantly increases audiological performances and the patient's quality of life. Other surgical treatments, such as tympanoplasty, are reserved for complicated cases.

Although immunosuppressive therapy in addition to steroid treatment may be effective for preventing progression to intractable dizziness, other variables such as general health, lifestyle, other systemic diseases, and genetics might also influence the recovery rate. [162].

4. Conclusions

Autoimmune vestibular disorders are rare and probably underestimated diseases in the general population.

Currently, there are no specific diagnostic tests able to identify the presence of autoimmune or immune-mediated diseases in the inner ear. Therefore, classification systems and diagnostic criteria including the ENT involvement for systemic autoimmune diseases are of utmost importance.

Physicians should be aware of cochleovestibular symptoms every time he suspects an autoimmune disease, with specific oriented questions in the anamnesis in order to investigate the presence of hearing or balance problems. On the other hand, ENT specialists need to perform a complete clinical-instrumental evaluation every time he exams a patient with a certain or suspected history of autoimmune disease; the hearing test and the vestibular bedside examination are mandatory, and if the condition required further investigation, it is advisable to perform specific vestibular tests, such as electronystagmography, posturography, and VEMPs.

A close collaboration between rheumatologists, radiologists, and otolaryngologists is essential to recognizing patients with indication to systemic therapy.

Timely and adequate medical treatments allow recovery of audiovestibular damage in most cases. However, the evolution of hearing loss and vertigo must be carefully monitored because fibrosis and ossification of the inner ear can evolve rapidly even within a few weeks.

The introduction of new classifications could lead to the use of effective immunological therapies, such as biological drugs, even in those cases limited to the posterior vestibule. New molecules and the above "intracochlear drug delivery" methods currently being tested will allow a more effective, personalized therapy with fewer side effects in the future.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Audiovestibular Symptoms in Systemic Autoimmune Diseases

Massimo Ralli,[1] **Vittorio D'Aguanno**,[2] **Arianna Di Stadio**,[3] **Armando De Virgilio**,[4] **Adelchi Croce**,[5] **Lucia Longo**,[2] **Antonio Greco**,[2] **and Marco de Vincentiis**[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, Italy*
[5]*Department of Otolaryngology, University G. D'Annunzio of Chieti-Pescara, Chieti, Italy*

Correspondence should be addressed to Arianna Di Stadio; ariannadistadio@hotmail.com

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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 conditions. Sensorineural hearing loss is the most common audiovestibular symptom associated with systemic autoimmune diseases, although conductive hearing impairment may also be present. Hearing loss may present in a sudden, slowly, rapidly progressive or fluctuating form, and 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.

1. 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, O'Malley et al. identified cells with staining characteristics and morphology consistent with macrophages/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 proinflammatory cytokines and reactive oxygen species (ROS) induced by microglia [4].

There is growing interest for inner ear involvement in systemic autoimmune diseases [5, 6]; this condition should be considered in patients with audiovestibular dysfunction presenting a constellation of symptoms consistent with systemic autoimmunity or with a preexisting diagnosis of autoimmune disease [7, 8]. Inner ear involvement in systemic autoimmune diseases should be distinguished from primary autoimmune inner ear disease, a condition in which the immune response acts directly against the inner ear [6, 7].

Inner ear involvement in autoimmune diseases is estimated to account for less than 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 of the different clinical presentations of audiological and vestibular symptoms in systemic autoimmune diseases, although this is often only reported in the form of case reports due to the rarity of some of these conditions.

2. Inner Ear Involvement in Autoimmune Diseases

2.1. 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 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 the ROS level responsible for damage to 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].

2.2. Audiovestibular Symptoms in Systemic Autoimmune Diseases. Audiovestibular dysfunction in systemic autoimmune diseases may have different clinical presentations with high interindividual 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 high frequencies [8, 9], although low-frequency and mid-frequency hearing loss are common in cases 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 may be the presenting symptom in some cases [5, 20]. Despite hearing loss being 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 involvement of 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's disease [3, 21].

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

2.2.1. 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 audiovestibular symptoms that are 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 audiovestibular symptom in SLE, with a prevalence of 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 low and middle frequencies [15]. Maciaszczyk et al. [30] and Roverano et al. [18] described progressive, bilateral SNHL involving 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.

Table 1: Systemic autoimmune diseases associated to audiovestibular symptoms.

Autoimmune disease	Prevalence of audiovestibular involvement	Classification	Literature reference
Systemic lupus erythematosus	6–70%	Systemic autoimmune rheumatic disorders	[15, 16, 18]; [29–37]; [38]
Cogan syndrome	31–45%	Systemic vasculitis	[39–44]; [45]
Sarcoidosis	5–96%	Systemic granulomatous diseases	[46–50]; [51]
Rheumatoid arthritis	25–72%	Systemic autoimmune rheumatic disorders	[24]; [52–54]
Antiphospholipid syndrome	Case reports only	Autoimmune hypercoagulable condition	[55–60]
Polyarteritis nodosa	Case reports only	Systemic vasculitis	[61–70]; [71]
Behcet's disease	12–80%	Systemic vasculitis	[72–77]; [45]
Takayasu's arteritis	Case reports only	Systemic vasculitis	[78–85]; [79]; [86]
Relapsing polychondritis	40–54%	Autoimmune connective tissue disorder	[23]; [87–92]; [93]
Wegener's granulomatosis	8–65%	Systemic vasculitis	[94–97]
Susac's syndrome	Case reports only	Systemic vasculitis	[98–102]; [103]
Sjögren's syndrome	22–46%	Systemic autoimmune rheumatic disorders	[22]; [104–109]; [110]
Myasthenia gravis	22–34%	Autoimmune condition affecting neuromuscular junction	[111–119]; [120]
Multiple sclerosis	1–28%	Autoimmune inflammatory demyelinating disease	[4, 15]; [121–129]; [130]
Hashimoto thyroiditis	Case reports only	Autoimmune thyroid disease	[131]
Mixed cryoglobulinemia	22%	Systemic vasculitis	[132]
Giant cell arteritis	7–100%	Systemic vasculitis	[133–135]
Vogt-Koyanagi-Harada's disease	48–62%	Systemic granulomatous diseases	[136]
Ulcerative colitis	2–5%	Autoimmune inflammatory bowel disease	[137, 138]

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

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.

2.2.2. Cogan's Syndrome. Cogan's syndrome (CS), first described in 1934, is a rare autoimmune disorder characterized by ocular and audiovestibular symptoms [39]. CS develops in young adults, mostly during their first three decades of life [40, 41]. 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 [42].

CS includes a large spectrum of clinical manifestations. Haynes et al. [43] defined two types of CS, a typical and an atypical variant. Typical CS is defined by ocular symptoms, classically presenting as nonsyphilitic interstitial keratitis (IK), audiovestibular symptoms similar to those of Menière's disease (recurrent episodes of hearing loss, tinnitus, and vertigo), and an interval between the onsets of ocular and audiovestibular manifestations of less than 2 years. Atypical CS is characterized by different inflammatory ocular manifestations, with or without IK; audiovestibular symptoms (usually progressive hearing loss); and, most important, a delay of more than 2 years between the onset of ocular and audiovestibular 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 [41].

Inner ear involvement in CS has been reported with a prevalence of between 31% and 45% [40–44]. The most common audiovestibular manifestations in CS are hearing loss, vertigo, tinnitus, ataxia, and oscillopsia [41]. These symptoms can appear at any time during the course of the disease [44]. Hearing loss may be both unilateral and bilateral, often presenting 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 [44].

Tinnitus usually follows auditory deafferentation [41]. 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 show clinical symptoms of vestibulopathy that last for days or weeks from the time of onset without spontaneous resolution that frequently results to hospitalization [44].

2.2.3. Sarcoidosis. Sarcoidosis is an inflammatory multisystem disease with unknown origin. CNS involvement is reported in about 5–7% of patients with systemic sarcoidosis, called neurosarcoidosis (NS) [46].

A cranial nerve neuropathy affecting the facial and optic nerves is a common finding in up to 80% of NS patients [46, 47].

Audiovestibular involvement is common in sarcoidosis. In a review of 50 patients with NS [48], a high incidence of audiovestibular 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 and found abnormalities in 23 (96%). Of those, six (25%) had unilateral alterations, 16 (67%) had bilateral alterations, and one (8%) had a nonlocalizing dysfunction. In another review, Babin [49] reported SNHL in approximately 90% of reported cases, characterized 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 [49].

A recent study [50] 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.

2.2.4. Rheumatoid Arthritis. Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting nearly 0.6% of the general population [52]. Principal symptoms referred by patients are articular and periarticular, although RA can involve other organs including the heart, lung, skin, and eye [52].

Several events can lead to audiovestibular 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 [53]. SNHL is the most common type of hearing impairment in RA patients ranging from 25% to 72% [53]. Conductive hearing loss and mixed hearing loss have also been reported, although less frequently [53].

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 [54] was proposed although other authors [24] suggested increased stiffness of the ossicular system.

2.2.5. 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 association of specific antibodies, arterial or venous thrombosis, and/or pregnancy morbidity and mortality [55]. APS is associated with microthrombosis, causing cutaneous manifestations like purpuric eruptions, livedo reticularis, and skin ulcerations. The involvement of the retina may cause amaurosis fugax [56].

The involvement of the inner ear has been reported in APS and may be 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 [57].

The association of aCL or LAC antibodies and SNHL was firstly reported by Naarendorp and Spiera [56] in six patients with SLE or a lupus-like syndrome. Toubi et al. [58] studied sudden and progressive SNHL in 30 patients showing that in the 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 et al. [59] reported that 31% of patients with idiopathic SSNHL were positive for aCL, compared with only 6% of matched control subjects. A prospective study [60] had 168 patients with progressive SNHL who underwent 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.

2.2.6. Polyarteritis Nodosa. Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that mainly affects medium-sized arteries, although small arteries may also be involved [61]. 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 [62]. PAN affects men more frequently than women and occurs in all ethnic groups; the average age at onset is approximately 50 years [63].

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 [62].

Clinical manifestations of PAN include nonspecific 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 [62].

SNHL is often reported in PAN [64–66] and, in rare instances, may occur as the presenting symptom of the disease [67, 68]. Hearing loss is typically bilateral and symmetrical, with sudden onset [67, 69] or a rapidly progressive course [65, 70]. 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 [69]. Tinnitus, vertigo, and occasional nausea and vomiting may also be found in patients with PAN [67].

2.2.7. 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 [72].

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 [72, 73]. No relationship has been found between age or disease duration and inner ear involvement [73, 74]. A recent survey [75] of 65 BD patients reported that audiovestibular complaints were found in 47% of patients. The most common symptoms were tinnitus (11%), hearing loss (10%), and vertigo (8%); a case of unilateral SSNHL was also reported.

Nearly half of BD patients report orthostatic disequilibrium [72]. Studies of the vestibular function [73, 74] showed that BD mainly causes peripheral lesion rather than damage to the central vestibular tracts, although another study [76] 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 [75, 76]. Neural involvement in BD (neuro-Behcet) may appear with dizziness or vertigo as initial symptoms, mimicking a vestibular neuritis [77].

2.2.8. 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 [78, 79].

The aetiology of hearing impairment in TA remains unknown [79]; 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 arterial disease [80]. Although TA involves medium and large calibre arteries, Noel et al. reported that the occlusion of small retinal vessels is a possible microcirculatory complication in TA; common immunopathology mechanisms with hearing loss could be hypothesized [81]. Moreover, Maruyoshi et al. 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 [80].

Only a few cases in the literature reported an association of TA with SNHL [82–84]. 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 [80]. 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 of treatment with hyperbaric oxygen therapy associated to corticosteroids, with significant improvements in both ears [85, 86].

2.2.9. 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 [87]. 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 [88]. McAdam et al. [89] proposed diagnostic criteria for RP when three or more of the six clinical features are present: recurrent chondritis of both auricles; nonerosive, seronegative inflammatory polyarthritis; chondritis of the nasal cartilages; ocular inflammation (conjunctivitis, keratitis, scleritis, and uveitis); respiratory tract chondritis affecting laryngeal and tracheal cartilages; and cochlear and/or vestibular dysfunction (SNHL, tinnitus, and vertigo).

Auricular chondritis 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 [90]. One or both ears can be affected. The ear 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.

Audiovestibular impairment is reported in 40–54% of all patients with RP [91]. 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 [89]. 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 [92] or due to autoantibodies against the cochlea and vestibular organ [91]. This could explain the near-complete hearing recovery in patients after treatment with corticosteroids.

2.2.10. 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% to 65% of patients with WG, mainly auditory symptoms with SNHL [94, 95] or CHL in cases of WG involving the middle ear [96]. 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 [96]. Hearing impairment may also present as SSNHL; Bakthavachalam et al. [97] identified that hearing loss was present in 56% of patients suffering from WG and SSNHL was the most common form, occurring in 47% of cases.

Hearing loss may also be a presenting symptom of WG. SNHL in WG is believed to be largely irreversible, therefore potentially adding to the patient's cumulative disability [96]. SNHL evaluation and monitoring are 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 [94, 95].

2.2.11. Susac's Syndrome. Susac's syndrome (SS) is a rare immune disease characterized by encephalopathy, branch retinal artery occlusion, and SNHL [98]. SS has a higher prevalence in females, with a male: female ratio of 1 : 3.5 [99].

The pathophysiology of SS is not entirely clear. Antiendothelial cell antibodies (AECAs) in SS have been recently documented [99]. Potential targeted antigens suggested in 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 [100].

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 trial of central nervous system (CNS) dysfunction [101]. 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 [101].

Hearing loss can be a dramatic and severely debilitating feature of SS; it may be mild and insidious or may be fluctuating, mimicking Menière's disease [102]. A loss of low or middle frequencies is typical, suggesting a vulnerability of the cochlear apex to microinfarction; loss of high frequencies can also occur [99]. Hearing loss often occurs overnight and may affect both ears. Dörr et al. refer to this clinical behaviour as the "bang-bang hearing loss" [101]. 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 [99]. 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.

2.2.12. 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 the 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 [104]. 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 [104].

Audiovestibular involvement in patients with pSS has been reported in the literature with a prevalence ranging from 22% to 46%. Boki et al. [105] reported in a pSS patient the presence of SNHL affecting preferentially high frequencies. Tumiati et al. [106] reported SNHL in 46% (14/30) of patients with pSS. Ziavra et al. [107] 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 [108].

The high prevalence of cranial neuropathies is a known condition in pSS, mainly with trigeminal and facial nerve involvement [109].

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 [106]. However, the prevalence of audiovestibular symptoms in pSS might be underestimated, suggesting that their association with pSS was not previously made because it had not been actively sought [106].

2.2.13. Myasthenia Gravis. Myasthenia gravis (MG) is the most common autoimmune disorder affecting the neuromuscular junction, characterized by muscle weakness and fatigue [111]. Weakness, the typical clinical symptom of MG, affects facial, ocular, bulbar, respiratory, or limb muscles and worsens after muscular activity [112].

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 postsynaptic membrane of OHC [113].

In patients with MG, autoantibodies against AChRs were reported to bind with AChRs on OHCs, inducing a progressive loss of AChRs that decreases OHC electromotility [114]. This cascade of events induces apoptosis in all three rows of OHCs, evolving into a clinically evident SNHL in rare cases [115]. The efferent auditory system has been investigated using contralateral acoustic stimulation (CAS) [116]. CAS produces physiological suppression of otoacoustic emissions [117] protecting the hair cells from noise of moderate to high intensity [118]. 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 [114, 116].

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 [115, 119]. 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) [114]. Therefore, OAE should always be performed in MG patients because they can early detect the MG-related effects on the ACh-innervated auditory system [111].

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 [112].

2.2.14. 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 [121]. 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 [122].

The evidence of a clear presence of macrophages in the human temporal bone of patients affected by autoimmune diseases [15] support the hypothesis that in MS, the autoimmunity mechanisms also affect the structures of the inner ear; hair cells and 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 the 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 pathways [123]; however, in some case, MS lesions involving the auditory pathways may not determine a clinically evident hearing impairment [124]. 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 [125].

MS patients typically report a difficulty in speech perception, especially in noise [126]. This alteration is due to an abnormal auditory processing, such as problems with dichotic listening tasks and auditory temporal processing [126]. 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 [127].

Furthermore, studies have shown that 40% to 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 [127].

Disequilibrium in MS is often related to internuclear ophthalmoplegia, and multiple nystagmus constitutes the most typical vestibular signs of MS, although peripheral equilibrium may coexist [128]. 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 [128].

Audiovestibular 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 tests to exclude peripheral incipient MS [129].

2.2.15. Other Autoimmune Conditions. Other autoimmune diseases associated to audiovestibular 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 [131].

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 [132].

Hearing loss has been reported with a prevalence ranging from 7% to 100% in several case series of patients with GCA, a multisystemic vasculitis mainly involving large- and medium-sized blood vessels [133]. In a series of 44 patients with GCA, PTA at the time of diagnosis showed auditory dysfunction in all patients [134]. In some patients, hearing loss was progressive and appeared as an initial manifestation [135].

Bilateral rapidly progressive SNHL and tinnitus and vestibular manifestations have been observed in 48% to 62% of patients with Vogt-Koyanagi-Harada's disease [136].

In a retrospective study, SNHL was found in about 2% of patients with ulcerative colitis [137]. In these patients, OAE play a central role as they may indicate a cochlear involvement even when normal hearing thresholds are present [138].

2.3. Audiovestibular Diagnostic Workup in Systemic Autoimmune Diseases. The audiovestibular 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].

The current literature agrees that SNHL is the most common auditory symptom of systemic autoimmune diseases [5], 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, audiovestibular symptoms found in autoimmune conditions are also common to other conditions such as diabetes and hypertension. For these reasons, a correct differential diagnosis of the cause of the audiovestibular involvement is of utmost importance.

The diagnostic process in patients presenting with a variety of audiovestibular symptoms should begin with individual medical history and family history followed by traditional audiovestibular tests. The most important audiological test battery in all cases should include PTA possibly extended to the high-frequency region, TEOAE and DPOAE, and ABR [5, 129]. Vestibular testing should include a basic vestibular exam integrated with caloric test, video head impulse test, and VEMPs [129]. The aforementioned test batteries should be performed at the onset of the audiovestibular symptom and during follow-up to monitor the course of the disease. Audiovestibular examination should be integrated, when an autoimmune condition is suspected, with specific blood tests as summarized in Table 2 [139].

2.4. Treatment Approaches to Audiovestibular Symptoms in Systemic Autoimmune Diseases. The treatment of audiovestibular symptoms should first aim at preserving the function, such as hearing preservation and/or restoration in patients with SNHL, and then at solving 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 audiovestibular symptoms, may have an effect on the underlying autoimmune systemic disease and delays its diagnosis.

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

The most common treatment for SSNHL is systemic or intratympanic administration of high doses of corticosteroids, associated with hyperbaric oxygen treatment in cases of SLE, APS, and TA [85, 86]. Other associated treatments include antioxidant compounds to avoid progression of SNHL [142], hearing aids to support the residual hearing function, or cochlear implants in case of severe and profound SNHL [143, 144].

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

Test	Classification
Red and white cell counts	General blood test
Coagulation test (aPTT, PT)	General blood test
Creatine 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
Antiextractable nuclear antigen (anti-ENA)	Antibody
Antisignal recognition particle (anti-SRP)	Antibody
Anti-Mi2	Antibody
Antineutrophil cytoplasmic antibody (ANCA)	Antibody
Lupus anticoagulant (LAC)	Antibody
Antiphospholipid autoantibodies (aPL)	Antibody
Anticardiolipin (aCL)	Antibody
Complement (C3, C4, and B)	Complement
Cryoglobulins	Immunoglobulin

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

Table 3: Common treatment for systemic autoimmune diseases with audiovestibular 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 nonresponsive patients, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate should also be considered	[38]
Cogan's syndrome (CS)	Prednisone 1 mg/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	[45]
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 treatment of refractory neurosarcoidosis; in addition, methotrexate, azathioprine, and TNF-alpha antagonists	[51]
Rheumatoid arthritis (RA)	Methotrexate at disease onset (10–15 mg/week) and then 20 mg/week for 4–8 weeks; it is possible to use prednisolone at high dosage (40–60 mg) and tapering to 7.5 mg at week 6 for a total of 12 weeks	[140]
Antiphospholipid syndrome (APS)	Chronic treatment with low dose of acetylsalicylic acid	[57]
Polyarteritis nodosa (PAN)	PAN without viral syndrome: prednisone 1 mg/kg/day and then tapering when remission is reached	[71]
Behcet's disease (BD)	Steroid treatment with azathioprine; for resistant cases, azathioprine + interferon + TNF-α antagonists	[45]
Takayasu's arteritis (TA)	Prednisone 1 mg/kg/day; additionally, it is possible to use immunosuppressants such as methotrexate, azathioprine, mycophenolate mofetil, leflunomide, tacrolimus, and TNF-alpha antagonists	[79]
Relapsing polychondritis (RP)	Corticosteroid treatment at high dosages; in addition, colchicine, methotrexate, azathioprine, intravenous immunoglobulins, minocycline, and leflunomide	[93]
Wegener granulomatosis (WG)	Prednisone or equivalent 1 mg/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	[141]
Susac syndrome (SS)	High-dosage corticosteroids; additionally, intravenous immunoglobulin, plasma exchange azathioprine, mycophenolate mofetil, methotrexate, cytochrome P450 enzymes, and cyclosporine A	[103]
Sjögren's syndrome (pSS)	Cyclosporine A for local treatment of eye disease; colchicine and steroid treatment are used; controversial use of rituximab	[110]
Myasthenia gravis (MG)	Immunosuppressant therapy; in addition, treatment with insulin,thyroid hormones, and pyridostigmine	[120]
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	[130]

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

Tinnitus is commonly treated with approaches aimed to restore hearing function, with antidepressant drugs when a psychological involvement is detected, and using oral supplements that combine antioxidants and vasoactive substances [145].

Vertigo can be treated with high doses of corticosteroids [146] 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 [145]. 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 [146]. For chronic dizziness, specific rehabilitation treatments can be used to favor central vestibular compensation and restore normal balance function [147].

3. Conclusion

Audiovestibular symptoms may be found in a variety of autoimmune diseases, and diagnosis is essential to increase the chances of 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.

Audiovestibular 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 audiovestibular 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 along with underestimation of the problem and consequent undertreatment.

Conflicts of Interest

The authors report no conflict of interest.

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Review Article

MicroRNA in Sjögren's Syndrome: Their Potential Roles in Pathogenesis and Diagnosis

M. Reale,[1] **C. D'Angelo**,[1] **E. Costantini**,[1] **M. Laus**,[2] **A. Moretti**,[2] **and A. Croce**[2]

[1]*Department of Medical, Oral and Biotechnological Sciences, Unit of Immunodiagnostic and Molecular Pathology, "G. d'Annunzio" University, Via Dei Vestini 31, 66100 Chieti, Italy*
[2]*Department of Medical, Oral and Biotechnological Sciences, Otorhinolaryngology Clinic, Clinical Hospital SS. Annunziata, "G. d'Annunzio" University, Via Dei Vestini 31, 66100 Chieti, Italy*

Correspondence should be addressed to M. Reale; mreale@unich.it

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Sjögren's syndrome (SS) or sicca syndrome was described by Swedish ophthalmologist Sjögren in the year 1933 for the first time. The etiology of the SS is multifunctional and includes a combination of genetic predisposition and environmental as well as epigenetic factors. It is an autoimmune disease characterized by features of systemic autoimmunity, dysfunction, and inflammation in the exocrine glands (mainly salivary and lacrimal glands) and lymphocytic infiltration of exocrine glands. In fact, the involvement of lacrimal and salivary glands results in the typical features of dry eye and salivary dysfunction (xerostomia). Only in one-third of the patients also present systemic extraglandular manifestations. T cells were originally considered to play the initiating role in the autoimmune process, while B cells were restricted to autoantibody production. In recent years, it is understood that the roles of B cells are multiple. Moreover, autoantibodies and blood B cell analysis are major contributors to a clinical diagnosis of Sjögren's syndrome. Recently, there has been rising interest in microRNA implication in autoimmunity. Unfortunately, to date, there are only a few studies that have investigated their participation in SS etiopathogenesis. The purpose of this work is to gather the data present in the literature to clarify this complex topic.

1. Introduction

1.1. Sjögren's Syndrome. Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of salivary and lacrimal glands that results in eye and mouth dryness [1]. The SS prevalence is approximately 3% of the worldwide adults and has been reported to rarely affect children [2]. However, epidemiological studies underline the marked predilection for female, with a ratio of 9 : 1 to male, with age between 20 and 50 years [3]. The disorder was described by Mikulicz in 1892, but only in 1933, Dr. Henrik Sjögren published an article on a cluster of women presenting keratoconjunctivitis sicca, lymphoid infiltrations of the conjunctiva, cornea, lacrimal and parotid glands, a history of arthritis, and swelling of the salivary glands, in order to distinguish the SS from xerophthalmia [4].

SS is a multifactorial syndrome, involving environmental factors, genetic predisposition, and hormonal factors in the presence of the innate and acquired immune system costimulation [2, 5]. Although the pathogenesis of SS remains largely unknown, the autoimmunity is considered to be the key player in the syndrome development.

SS may occur alone as the primary SS (pSS) or as the secondary SS (sSS), in association with other autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) [1]. The pSS is characterized by xerophthalmia, xerostomia, xerosis, and systemic extraglandular organ involvement [6]. The prognosis for pSS is not favorable because the disease is linked to the onset of respiratory or kidney failure. The sSS is characterized by keratoconjunctivitis and xerostomia associated with other autoimmune disorders. The course of sSS depends strictly on the primary autoimmune pathology with an increase in tiredness and arthralgia [7].

Cytokine production, T lymphocytes, B-cell activating factor (BAFF), and autoantibodies secreted by B lymphocytes

were found in the target tissue of SS and the salivary and lacrimal glands [8]. The histological analysis of glandular tissue reveals the presence of mononuclear lymphoid cell infiltration, replacing the glandular epithelium and causing epithelial destruction [2]. Glandular tissue destruction is observed in the minor salivary glands (MSG) with the massive presence of T and B cells [9]. Mononuclear cell infiltration is useful to classify SS severity. In mild lesions, CD4+ T cells are predominant, whereas in severe lesions B cells constitute the main population. The prevalence of CD4+ T cells decreases with lesion severity, whereas the prevalence of CD8+ T cells remains unchanged [9, 10]. More recently, the involvement of Th17 lymphocytes was detected, with a key role in inflammation, autoimmunity, and glandular tissue damage in SS [11]. Th17 cells, in association with Th1 and Th2 cells, are responsible for increased inflammatory cytokine production, such as IL-21 and IL-22 [12] which have been found in high concentration in the serum and salivary glands of SS patients [13, 14] with high relation to clinical symptoms. Moreover, matrix (interleukin) IL-17, transforming growth factor β (TGF-β), IL-6, and metalloproteinase (MMP) [11] are also expressed hypothesizing their involvement in the development and the onset of SS through the modulation of target tissue homeostasis and biological activities [13]. In mononuclear cells, infiltration has found also natural killer (NK) cells and professional antigen-presenting cells, such as macrophages and dendritic cells, and a small, but considerable, portion of the infiltrating mononuclear cells, and their percentage correlates with the grade of the lesions [9, 15, 16]. T regulatory cells (Tregs) also point out in MSG lesions, with increased expression in intermediate lesions. Treg cells were identified in an experimental animal model. Treg subset is important for their involvement in immune homeostasis [17], suppressive activity towards autoreactive lymphocytes, and release soluble mediators including IL-10 and TGF-β [18]. The lower number of Foxp3$^+$ Tregs in SS lesions is in a relationship with the ineffective regulation of the inflammatory status that result in the loss of immune control and worsening of the state of illness [17].

B lymphocytes have the central role in the pathogenesis of SS; they stimulate the immune response against self- and nonself-antigens [19] through their overproduction. The affected exocrine glands are the major site of autoantibody formation [20, 21] for the local overexpression of B cells and BAFF [22, 23].

Several studies show the alteration in B cell subset in SS patients [19, 23, 24]; however, the mechanisms are still debated for the involvement of genetic, epigenetic, and environmental triggers promoting B cell activation. Recently, a genetic cohort study was conducted to evaluate new regions associated with SS, showing a correlation with the (major histocompatibility complex) MHC region and the presence of innate immune system pathway activation, the interferon regulatory factor 5 (IRF5), T cell activation (HLA and MHC associations, STAT4, IL12, KLRG1, SH2D2A, and NFAT5), and NF-κB activation (TNIP1 and TNFAIP3) [24, 25]. Evidence on the environmental involvement in SS induction are supported by multiple factors, including ultraviolet light, smoking, or chemical exposure, that determine epigenetic change-associated SS. One of the principal alterations is the DNA demethylation with defective satellites and retrotransposons, splicing mutations, polymorphisms, and miRNA overexpression [26]. B cells' role in the pathogenesis of autoimmune diseases could be resumed in three key mechanisms: the production of inflammatory cytokines, autoantibody, and antigen-presenting cells. The autoantibody production represents the most important mechanism with the involvement of many different types of antibodies [24]. Elevated IgA level is a common finding and is strongly associated with abnormal salivary gland biopsy [27, 28], while IgG can be detected in half of the pSS patients, especially in those with extraglandular manifestations [28]. According to Tzioufas et al., these antibodies possess three different abilities: serving as disease markers, indicating the association with other autoimmune diseases, and exhibiting a possible pathogenetic role [29]. Some of these autoantibodies are against Ro/SSA (Sjögren's syndrome A) or La/SSB (Sjögren's syndrome B) ribonucleoprotein complexes. Anti-Ro/SSA antibodies represent two distinct entities of autoantibodies that react with two nonhomologous proteins, Ro52/TRIM21 and Ro60/TROVE2, respectively, a cytoplasmatic nuclear protein [30]. Ro52/TRIM21 contains a protein that acts as an intracellular Fc-Receptor, and it is implicated in the regulation of cell proliferation and activation, which induce cell death, as well as the regulation of TLR signaling and subsequent IFN [31]. Ro60/TROVE2 protein is a ring-shaped RNA-binding protein that participates in the quality control of nascent transcripts, including the recognition and leading of misfolded defective RNAs to degradation [32, 33]. The La/SSB autoantibodies are directed to a 47-kD protein that exists abundantly in both the nucleus and the cytoplasm. La protein is involved in RNA processing and metabolism. Detection of Ro/SSA and La/SSB autoantibodies occurs in 50–70% of patients [34]. Interestingly, the presence of anti-Ro/SSA is independent of anti-La/SSB; however, the coexpression is useful to identify SS patients [35]. The presence of these autoantibodies is related to a specific SS diagnosis, in particular in young patients with severe dysfunction in exocrine glands [35, 36]. Others autoantibodies with high prevalence in SS patients are rheumatoid factor, cryoglobulins, anticentromere antibodies (ACA), autoantibodies against cyclic citrullinated peptides (anti-CCP), calreticulin, antimitochondrial antibodies (AMA), antibodies to muscarinic receptors, autoantibodies targeting carbonic anhydrase II (anti-CAII), anti-smooth muscle antibodies (ASMA) [37], and antinuclear antibodies (ANA) are present in the sera of 59–85% of patients [38]. Other autoantibodies have been claimed to be specific for pSS diagnosis, such as antibodies to alpha-fodrin [39], muscarinic receptors [40], or Golgi [41], but their clinical relevance is still debated [30]. More recently, another set of autoantibodies has been detected in interleukin 14 alpha transgenic mouse (IL14αTG), an animal model for SS [42]. Antisalivary gland protein 1 (anti-SP1), anticarbonic anhydrase 6 (anti-CA6), and antiparotid secretory protein (anti-PSP) autoantibodies

are found in SS patients also in the presence of Ro/SSA and La/SSB autoantibodies. SP-1, CA6, and PSP are considered early stage markers for SS [1] than anti-Ro and anti-La. Diagnosing SS resulted to be difficult for a wide range of the clinical spectrum of nonspecific symptoms and the most evidence related to other autoimmune diseases. For a definitive diagnosis of SS, the establishment of specific criteria is required. The main diagnostic criteria of SS are defined by the American College of Rheumatology-European League against Rheumatism in 2016 that has published a set [43, 44]. Dry mouth, dry eyes, circulating autoantibodies to Ro/SS-A and La/SS-B, and lymphocytic infiltration of salivary glands are the most common criteria for SS [1]. Detection of circulating antinuclear autoantibodies are identified in the sera of patients [45]. Studies in animal models and humans with SS demonstrate that SP-1, CA6, and PSP autoantibodies are expressed earlier in patients with lower scores in MGS biopsies [46–48]. These autoantibodies concentration became higher at the time of diagnosis [45, 49]. The identification of prediagnostic autoantibodies is related to an unfavorable diagnosis [49]. A correlation between novel autoantibodies and diagnosis has been demonstrated by Everett et al., in a specific cohort of SS patients with "idiopathic dry eyes." The immune-mediated damage of lacrimal glands corresponds to anti-SP1, anti-CA6, and anti-PSP high presence in serum and represent markers for early Sjögren's syndrome diagnosis [47] Some authors showed that classical autoantibodies like ANAs, RF, anti-Ro/SSA, and anti La/SSB have a prognostic value for clinical diagnosis [45]. However other evidence is related to no association between these autoantibodies and the clinical and biological SS severity [48]. These data are supported by studies that define the MSG biopsy as the gold standard method for the detection of SS, also in 22-23% of seronegative patients [50, 51]. Further studies will be necessary to understand the role as well as the usefulness of antibodies and MSG biopsy in the diagnosis of SS.

During the last decade, genetic and epigenetic studies have been widely investigated in relation to SS and with the pathogenesis of other autoimmune disorders. In particular, the RNA interference system is a conserved biological response that regulates the expression of protein-coding genes. This mechanism represents an evolutionary system in experimental biology and may be important for comprehension in genomic and therapeutic interventions. This system involves microRNAs (miRNAs), molecules implicated in the control of several biologic processes, and autoimmune disease development [52, 53].

1.2. miRNA. miRNAs are 18 to 23 base pair (bp) noncoding RNAs that govern numerous biological processes regulating gene expression at the posttranscriptional level by degradation and translational repression of their targeted miRNAs.

It is estimated that human genome encodes up to one thousand miRNAs which are either transcribed as independent genes or embedded in the intronic region of other genes. The genes encoding miRNAs comprise 1 e 5% of all genes, making miRNAs the most abundant class of regulators that may control the expression of 30% of protein-coding genes. [54]. The inhibition of protein translation is achieved by a variety of mechanisms including direct cleavage of mRNAs or translational initiation repression and premature translation termination [55].

Beginning in the nucleus and ending in the cytoplasm, miRNA biogenesis is a complex process, which involves many steps. miRNAs are transcribed in the nucleus by RNA polymerase II as a longer preliminary transcript and are then generated by sequential processing by two RNase III enzymes, Drosha and Dicer. In the nucleus, the primary miRNA (pri-miRNA) transcripts are cleaved by Drosha into a 70-nucleotide stem-loop precursor referred as pre-miRNAs [56]. The pre-miRNA hairpin is exported by Exportin 5 to the cytoplasm and is further processed by Dicer into a double-stranded RNA, 19–24-nucleotide long, with one strand loaded in the RNA-induced silencing complex (RISC). At the core of the RISC ribonucleoprotein complex, duplex separation into single strands occurs, generating miRNAs. RISC consists in RNA helicase A and proteins such as argonaute 2 and TRBP that will facilitate the binding of miRNA to its mRNA target [57, 58]. For degradation or translational repression, mature miRNAs bind the 3′ untranslated region (UTR) of specific target miRNA with their so-called "seed" region. The seed is a sequence of nucleotides from position 2 to position 7 or 8 in the 5′ UTR region of the miRNA, responsible for the recognition and binding of the miRNA target [59]. For the subsequent regulatory action, if the complementary base pairing is perfect or near perfect, miRNA cleavage and degradation are induced. With incomplete base pairing, the resulting double-stranded RNAs lead to translational repression [60]. One-third of the transcriptome is suspected to posttranslational regulation by the 800–1000 human miRNAs since one miRNA can alter the expression of hundreds of miRNAs. miRNAs regulate different cellular processes such as embryonic development, cell differentiation, cell cycle and proliferation, apoptosis, immune cell development and immune responses, immune cell lineage commitment, and immune homeostasis [61, 62].

1.3. miRNA and Autoimmune Disease. To date, evidence from experimental animal models and clinical studies in humans have shown the involvement of miRNAs in the regulation of immune homeostasis [63–65]. Several miRNAs are reported to play a key role in immune cell development and differentiation of B and T cells from hematopoietic stem cells, for example, miR-155, miR-146, miR-132, and miR-181a and the cluster miR17–92 [64, 66].

It is understandable how a dysregulation in miRNA expression can be related to immune tolerance breakdown leading to autoimmune disease (AID) development. AID is a pathological condition in which autoantigens and inflammation affect one or more target organs, with cellular and tissue destruction [65, 67]. AIDs affect more than 3% and 80% of the worldwide population, with prevalence in female [68]. Dysregulation in miRNA expression can be found in several AIDs, for example, in rheumatoid arthritis (RA), type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), psoriasis (PS), primary biliary

cirrhosis (PBC), and idiopathic thrombocytopenic purpura (ITP) [62, 67, 68]. MicroRNA expression profile has become widely studied as a potential biomarker of various autoimmune diseases like MS, RA, and SLE. Tregs of systemic lupus erythematosus mice exhibit altered regulatory phenotype and reduced suppressive capacity and Dicer expression, together with a distinct miRNA profile. miR-26a has been found decreased in experimental autoimmune encephalomyelitis mice and in multiple sclerosis patients acts as a regulator of the Th17/Treg cell balance, promoting the generation of Tregs and inhibiting the generation of Th17 [69]. miRNAs such as miR-15a, miR-15b, miR-181c, and miR-328 were downregulated in MS; contrarily, miR-15a, miR-19a, miR-22, miR-210, and miR-223 were upregulated in both regulatory T cells (Tregs) and other samples such as plasma, blood cells, PBMCs, and brain white matter tissues from MS patients.

Nevertheless, the miRNA translational silencing mechanism is highly complicated, since each miRNA is considered to target the suppression of several hundreds of mRNAs, whereas a single mRNA can be regulated by several distinct miRNAs that act cooperatively.

The exact mechanism by which miRNA expression can be altered is not completely understood, as well as their involvement in the AID pathogenesis.

Moreover, there are still a great number of contradictions concerning the interpretation of the obtained findings on the over- or underexpression of various miRNAs, considering also that miRNAs are unlikely to be unique to a particular disease process.

2. miRNA in Sjögren's Syndrome

In recent years, extensive research has been performed to characterize miRNAs and their regulation of immune responses and immune cell development.

An ever-increasing number of studies have reported that miRNAs are associated with SS salivary gland tissue inflammation and are shown to be deregulated in the SS salivary gland and also in long-term cultured salivary gland-derived epithelial cells and peripheral blood mononuclear cells from SS patients (Table 1).

In one of the first researches conducted to evaluate the possible presence of deregulated miRNA directly in the salivary glands of patients with SS, Alevizos et al. reported a reduced expression of miR-17-92 cluster [70]. miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1 are members of the miR-17-92 cluster that is important in the cell cycle, proliferation, apoptosis, and other pivotal processes and is often deregulated in cardiovascular, immune, and neurodegenerative diseases [71]. The decrease of the mir-17-92 cluster was associated with accumulation of mature B cells and pro-B cells with a marked reduction of pre-B events that have been linked to lymphoproliferative disease and autoimmunity [64, 66, 70].

Considering the research results available to date, miR-146a and miR-155 seem to be two miRNAs upregulated in response to the adaptative immune response in multiple cell types. miR-146a can be considered a key gene regulator for proinflammatory signaling; activated by NF-κB, it acts as a negative feedback regulator of the immune response by targeting two genes TRAF6 (TNF receptor-associated factor 6) and IRAK1 (IL-1 receptor-associated kinase 1). Targeting the TNF receptor-associated factor 6 (TRAF6) and the IL-1 receptor-associated kinase (IRAK1), miR-146a controls the TLR/IFN pathway, the signal transducer and activator of transcription 1 (STAT1), and the interferon regulatory factor 5 (IRF5) [72, 73]. The posttranslational effect driven by miR-146a is the inhibition of IRAK1 and TRAF6 expression, impairing NF-κB activity and reducing expression of NF-κB target genes such as IL-6, IL-8, IL-1β, and TNFα proinflammatory cytokines. miR-146a has been found upregulated in PBMCs from patients affected by SS [74–77], even though this increased expression appeared correlated with IRAK1 underexpression and a contradictory overexpression of TRAF6 genes, from Zilahi et al. in 2011 [74]. miRNA-146a (miR-146a) is supposed to negatively regulate adaptative immunity, inflammatory response, and antiviral pathway, but it has to be stressed that the expression rate and suppressive effects of miR-146a, and of all types of miRNAs taken into consideration, could be different and varied depending on the specific tissue and disease.

Wang-Renault et al. in a recent study evaluated miRNA profile in purified T and B lymphocytes detecting increased expression levels of both miR-146a and miR-155 in T lymphocytes [78].

Examination of miR-155 targets reveals an effect on the response of Toll-like receptors and interleukin-1 receptors (TIRs) that are suspected to affect the immune response. Interestingly, the FoxP3 transcription factor, which is overexpressed in T cells infiltrating SS salivary glands, has been shown to induce miR-155 expression.

Two fold-increased level of miR-155 has been found also in cultured salivary gland epithelial cells from SS than controls [26].

miRNA expression is necessary for the development of Treg cells in the thymus and the efficient induction of Foxp3 by TGF-β in a cell-autonomous fashion. Foxp3 may directly activate several miRNAs such as miR-155, which is indispensable for Treg cells to normally respond to growth factor and largely dispensable for Treg cell suppressor function [79].

In PBMCs, Shi et al. confirm the overexpression of miR-146a level in patients with SS founding also a positive correlation with the score for parotid swelling and dry eyes [76]. However, the miR-155 expression level was significantly decreased in PBMCs from patients affected by SS, with a positive correlation with the score for dry eyes. Evidence shows the overactivation of B cells and T cells with the increased expression of miR-155 [64, 76, 80].

Williams et al., considering that monocytes and their derivatives of macrophages and DCs have abnormalities in autoimmune diseases such as SLE, RA, and SS, selected this cell subset in order to profile miRNAs in SS patients, focusing also on predicting their potential roles in SS pathogenesis. After the detection of deregulated miR-300, miR-609, miR-3162-3p, and miR-4701-5p, in SS patients compared to healthy donors, they pursued the pathways possibly influenced by these miRNAs, founding evidence on the targeting

Table 1: miRNA expression profiling in SS patients.

miRNA	*miRNA source*	Expression	Reference
miR-300, miR-609, miR-3162-3p, miR-4701-5p	Monocytes	Upregulated	(Williams et al. [81])
miR-181a	SG	Upregulated	(Kapsogeorgou et al. [53])
miR-200b	SGEC		
miR-223	PBMCs		
let-7b	SGEC	Downregulated	
miR-146a/b	PBMCs	Upregulated	(Zilahi et al. [74])
miR-17-92	MSG	Downregulated	(Alevizos and Illei [70])
miR-144-5p, miR-34a-5p, miR-425-3p/-5p, miR-145-5p, miR-21-3p, miR-18a-5p, miR-769-5p, miR-190a, miR-15a-5p, miR-106a-5p, miR-424-3p, miR-20b-5p, miR-16-1-3p, let-7e-5p, let-7d-5p, miR-126-3p/-5p, miR-186-5p, miR-20a-5p, miR-146a-5p, miR-484, miR-191-5p, miR-26a-5p, miR-222-3p	PBMCs	Upregulated	(Chen et al. [75])
miR-150-5p	T lymphocytes	Downregulated	(Wang-Renault et al. [78])
miR-155-5p, miR-222-3p, miR-146a-5p, miR-28-5p		Upregulated	
let-7d-3p, miR-30c-5p, miR-378a-3p		Downregulated	
miR-222-3p	B lymphocytes	Upregulated	
miR-378a-3p, miR-26a-5p, miR-30b-5p, miR-19b-3p		Downregulated	
miR-181a, miR-16	SG	Downregulated	(Wang et al. [82])
miR-146a	PBMCs	Upregulated	(Shi et al. [76])
miR-155		Downregulated	
miR-146a, miR-155	PBMCs	Upregulated	(Pauley et al. [77])
miR-181a	PBMCs	Upregulated	(Peng et al. [83])
miR-155, miR-181a	SGEC	Upregulated	(Le Dantec et al. [26])

SG: salivary glands; SGEC: cultured salivary glands epithelial cells; PBMCs: peripheral blood mononuclear cells; MSG: minor salivary glands.

of TGFβ signaling pathway. Also, MAPK, JNK, and p38 MAPK signaling pathways together with JAK-STAT signaling cascades, important for cytokine signaling, may be affected by SS-associated miRNAs. Therefore, proinflammatory cytokines and NF-κB signaling pathways are presumed to be well maintained; SS-associated miRNAs seem to slope regulatory TGFβ signaling responses, in SS monocytes [81].

miR-181a and miR-16, identified to be associated with Ro/SSA and La/SSB in patients with SS, were detected in labial salivary gland tissues showing a significant downregulation in patients with SS compared with the controls. A statistical correlation of miR-181a and miR-16 expression levels with SGPF scores revealed a higher level of miR-181a and miR-16 in patients with SS and high-grade inflammation SGPF scores, when compared with those patients exhibiting lower SGPF scores, suggesting that miR-181a and miR-16 may serve a role in the pathogenesis of SS [82]. Peng et al. reported that miR181a expression was elevated in PBMCs of patients with SS, with a positive correlation between miR-181a levels and ANA titer. Measurement of miR-181a levels in isolated B cells and T cells indicated that B cell population contribute in the major part to miR-181a expression probably explaining their compromised antigen sensitivity and then the dysfunction of exocrine glands in pSS [83]. miR-181a reduction also enhances the sensitivity of T cell response to antigens with high self-reactivity of the TCR [62].

Despite the uncertainty of the interpretation of the obtained results, in reviewing previous studies in this paper, the presence of deregulated miRNA in the SS appears clear. However, the mechanisms that regulate miRNA overexpression/underexpression and the understanding of its role in SS pathogenesis are still unknown. Larger SS patient cohorts need to be examined to determine if there could be a true and unique correlation between increased/decreased miRNA expression, the presence of SSA/SSB autoantibody reactivity, salivary gland inflammation, and biopsy focal score typical of SS.

3. Conclusions

The complexities of the miRNA network pathways, as well as the multiple targets of each miRNA, hinder the delineation of their role in SS disease phenomena. Of course, other miRNAs, epigenetic factors, as well as viral elements (including viral miRNAs) that possibly harbor in the affected tissues, might participate in the pathogenesis of this disease. To date, according to the SS criteria for diagnosis, labial salivary gland biopsy has the main importance, although this is an invasive procedure. Recently, with the increasing number of studies, revealing miRNA deregulation in PBMCs, sera, and saliva in SS, the identification of serum miRNA to mirror activation state of lymphocytic subsets may become an innovative tool

to provide pivotal information about the nature of the immune responses occurring in autoimmune disease. However, the fact that serum miRNAs circulating in different compartments might provide an advantage, but since miRNAs may be released by all cells in the body and most of the blood miRNAs are released by organs and dividing cells, their specificity as diagnostic biomarkers is impacted by high background. Saliva is undoubtedly a conspicuous source of biomarkers in SS since it is the direct product of the affected target organ. Larger studies are necessary to validate salivary microRNAs as diagnostic markers in SS, but the ultimate goal would be to replace the invasive biopsies with less invasive methods. Moreover, novel diagnostic approaches may lead to a prompt diagnosis.

Abbreviations

SS: Sjögren's syndrome
miRNAs: MicroRNAs
ON: Optic neuritis
ANA: Antinuclear antibodies
ACA: Anticentromere antibodies
anti-CCP: Autoantibodies against cyclic citrullinated peptides
AMA: Antimitochondrial antibodies
anti-CAII: Antibodies to muscarinic receptor autoantibodies targeting carbonic anhydrase II
ASMA: Antismooth muscle antibodies
MSG: Minor salivary gland
SGB: Salivary gland biopsy
SGEC: Salivary gland epithelial cells.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Autoimmune Diseases and Their Manifestations on Oral Cavity: Diagnosis and Clinical Management

Matteo Saccucci, Gabriele Di Carlo, Maurizio Bossù, Francesca Giovarruscio, Alessandro Salucci, and Antonella Polimeni

Department of Oral and Maxillo-Facial Sciences, Sapienza University of Rome, Viale Regina Elena 287a, 00161 Rome, Italy

Correspondence should be addressed to Matteo Saccucci; matteo.saccucci@uniroma1.it

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Oral signs are frequently the first manifestation of autoimmune diseases. For this reason, dentists play an important role in the detection of emerging autoimmune pathologies. Indeed, an early diagnosis can play a decisive role in improving the quality of treatment strategies as well as quality of life. This can be obtained thanks to specific knowledge of oral manifestations of autoimmune diseases. This review is aimed at describing oral presentations, diagnosis, and treatment strategies for systemic lupus erythematosus, Sjögren syndrome, pemphigus vulgaris, mucous membrane pemphigoid, and Behcet disease.

1. Introduction

Increasing evidence is emerging for a steady rise of autoimmune diseases in the last decades [1]. Indeed, the growth in autoimmune diseases equals the surge in allergic and cancer pathology; on the other hand, infections are shown to be less frequent in the Western societies [2]. Oral manifestations of autoimmune disease are frequently the primary sign of autoimmune diseases [3]. The dentists can therefore play a pivotal role in the detection and during the following multidisciplinary treatment. Precise and early diagnosis increases the efficiency and efficacy of treatment strategy [4–6]. Therefore, the goal of our review is to present the most common autoimmune diseases that show the first oral clinical signs and symptoms which are a manifestation of the general clinical disease. Our review is presenting details over systemic lupus erythematosus, Sjögren syndrome, pemphigus vulgaris, mucous membrane pemphigoid, and Behcet disease. Every single paragraph reviews the general conditions, and in the second part, we discuss the diagnosis and treatment strategies.

2. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a severe and chronic autoimmune inflammatory disease of unknown etiopathogenesis and various clinical presentations. SLE mainly affects women 8 times more likely than men. The worldwide prevalence of SLE ranges between 12 and 50 per 100,000, depending on location and ethnicity [7].

SLE is usually a chronic and progressive disease whose dormancy and progress are fairly regular and in sequence. There are cellular and cell-mediated processes involved in the SLE, even though it has been speculated that the primary involvement is mainly due to cell-mediated immunity and consequential humoral involvement [8]. The immune complex deposits in different organs triggering an inflammatory reaction that leads to organ functional impairment typical of the disease. In the pathogenesis of SLE, the activation of type I IFN pathways, B and T cell dysfunction, and presence of antinuclear antibodies were demonstrated [9]. Anti-DNA antibodies (deoxyribonucleic acid, antinuclear antibodies) are found in the patients' serum. The prolifer-

ation of these antibodies is supported by oestrogens. In some cases, there have been signs of antilymphocyte antibodies. The etiopathogenesis of SLE takes also into account genetic factors [8, 9].

Skin damage is the typical clinical sign of SLE, and it has been recorded in 85% of the cases [8]. Symptoms can vary from simple circular skin lesions to multiorgan impairment, potentially fatal. The most recurrent skin lesion is severe erythema on the surface of the skin exposed to light; also, oral discoid lesions are one of the more prevalent presentations of the disease. The so-called malar rash (or butterfly rush) is located on the nose and cheeks, and the erythema is found also on the finger tips. The healing process of these lesions which present a central scar and area around shows recrudescence very often. In SLE, we have involvement of joints, skin, muscles, eyes, lungs, central nervous system, and kidneys. At the joint level, arthralgia and arthritis are frequently associated with the advancement of SLE. The arthralgia has an asymmetric presentation and migratory behaviour [7]. The topography of joint manifestations is very wide. Indeed, it can interest any articular surface mimicking the rheumatoid arthritis. Deformities are generated by the inflammatory process of the tendons rather than degeneration [7]. At the skin level, purpuric manifestations and vitiligo can also be observed [8]. Lesions of retinae, as vasculitis, may injury the nerve fibres causing impairment or loss of vision. Renal disease or lupus nephritis is a grave complication of SLE that affects 30% of patients [10, 11]. The classical clinical manifestation is represented by a regular round or slightly red irregular area. This can be characterized by atrophy or the presence of ulceration. The red area is characterized by typical white radiating striae and telangiectasia. These signs may resemble those of lichen planus, despite the lack of symmetry. Although the oral condition is not major, petechial lesion and gingival bleeding such as desquamative gingivitis, marginal gingivitis, or erosive mucosal lesions have been reported in up to 40% of patients and may indicate serious thrombocytopenia. Many SLE patients may present at the same time Sjögren syndrome [8, 9, 12, 13].

2.1. Diagnosis. SLE diagnosis is based on a multiple-organ condition and the study of antinuclear antibodies at a serum level. The so-called LE cells can be detected in the blood stream. LE cells are mature neutrophils that have swallowed spherical inclusions produced by nuclear components and other cellular elements [8]. Lupus lesions can be confused with erythema multiforme lesions, lichen planus, and vesiculobullous lesions [7]. Moreover, the differential diagnosis has to include lichenoid reactions to dental fillings, traumatic or smoker's keratosis, and verrucous carcinoma [13]. The demonstration of intact adjacent tissues towards given lesions through histological and immunohistochemical confirmation is still the standard criterion for a definitive diagnosis [8, 12–14].

2.2. Treatment and Prognosis. SLE management is based on prevention, maintenance of states of remission and alleviation of symptoms, and reversal of inflammation [7, 8, 15, 16]. Salicylates and FANS are used in the less severe cases. There are other drugs used, such as hydroxychloroquine (an antimalarial), cortisones, and other immunosuppressants such as azathioprine and cyclophosphamide [8]. High- and medium-potency corticosteroids and calcineurin inhibitors are used as topical therapies for cutaneous manifestation [17]. Protection from sunlight is part of the strategy in order to avoid flare-ups of skin manifestations [7]. The prognosis is often good when the course of the disease is of an intermediate type and only few organs are involved. The disease can also be fatal in the case of kidney conditions with hypertension and rapid evolution towards kidney failure that leads to the patient's death [8, 18–20].

3. Sjögren Syndrome

Sjögren syndrome is an autoimmune disease affecting salivary and lacrimal glands and causing a reduction of the secretion activity due by lymphocytic infiltration and consequent destruction of the exocrine glands [8]. The lower production of saliva (hyposalivation) causes dryness in the mouth (xerostomia); the deficiency of tears causes xerophthalmia. Although the etiopathology of the Sjögren syndrome is still unknown, humoral- and cell-mediated immunity phenomena are involved in the process; as a matter of fact, increased activation of B cells followed by immune complex formation and autoantibody production plays important roles [21]. Genetic and environmental factors can also be part in the pathogenesis of the syndrome [13].

Sjögren syndrome affects 0.5–3% of the entire population and is predominant in women compared to men (9 : 1 ratio). Typically, Sjögren syndrome is detected around 50 years of age. It is important to underline that there are two characteristic surges: just after the menarche and after the menopause [13, 22, 23].

Some patients show clinical signs only confined to the mouth and eyes, while others present a more substantial autoimmune damage. 50% of the cases also have a different autoimmune condition, such as rheumatoid arthritis or systemic lupus erythematosus [8]. Damage to the glands without the evidence of other autoimmune issues is defined as primary Sjögren syndrome. The addition of an autoimmune disease is referred to as secondary Sjögren syndrome [13, 24]. The main signs of the syndrome are related to the oral cavity [8]. The xerostomia is responsible for creating different manifestations of SS at the level of oral cavity. Lack of saliva predisposes patients to develop tooth cavities. The lack of saliva facilitates the accumulation of plaque and their clearance. Edema and inflammations of the gingiva are frequent clinical signs. Moreover, a salivary flow decrease can develop opportunistic infections. *Candida* is often detected because the lack of lysozyme and immunoglobulins facilitates its development. Radfar et al. and Bayetto and Logan showed an association between *Candida* and the decreased stimulated salivary flow rate [25, 26]. The Sjögren syndrome affects both major and minor salivary glands. 50% of the cases show an increase in volume, symmetrical on both sides, of the parotid glands. The histological appearance of the hypertrophic glands is characterized by the replacement of the gland tissue by

the lymphocytes and the presence of epimyoepithelial islands [24].

In addition to oral symptoms, patients also present irritation and dryness of the eyes, caused by xerophthalmia, as well as by photophobia. Nearly 20% of the patients affected by Sjögren syndrome show signs of the Raynaud phenomenon, a condition that affects fingers and toes [8]. Finally, patients affected by this disease may have arthralgia, myalgia, and asthenia.

The conclusions of different epidemiological studies claim, although newer studies are required to confirm this, that genetical as well as environmental factors play a role in the pathogenesis of the diseases [27, 28]. The syndrome is often accompanied by lab data alteration. 90% of the patients result positive to the rheumatoid factor, an anti-IgG antibody in the patient's serum. There are also other autoantibodies such as anti-Sjögren A and anti-Sjögren B that can be found in these patients [8].

3.1. Diagnosis. The diagnosis of Sjögren syndrome is basically clinical, supported by oral presentation and laboratory investigations. During recent decades, many classification criteria have been elaborated with the purpose to provide useful guidance for diagnosis by clinicians. The classification made by Shiboski et al. is generally utilized and also endorsed by the American College of Rheumatology [29, 30].

The diagnosis of the syndrome can be confirmed when two out of three of the following conditions are identified: xerostomia, keratoconjunctivitis sicca, and rheumatoid arthritis or another autoimmune disease [8]. Measuring the salivary flow and carrying out a biopsy of the minor salivary glands are two basic diagnostic investigation tests to detect the syndrome [24]. Very often, the xerostomia generates secondary symptoms that can help the clinician to orientate the diagnosis. Indeed, difficulties to speech and metallic sensation in the mouth are characteristic of xerostomia, as well as burning sensation of the oral mucosae [24, 31].

The ophthalmologic test is necessary to detect keratoconjunctivitis sicca. The lacrimal flow is measured by means of special absorbing pads [8]. Damage to the corneas, instead, requires further specific analysis. In most cases, the disease has a chronic and benign progress; however, these patients are exposed to a high risk to develop more serious clinical autoimmune issues: lymphoma and Waldenström macroglobulinemia. Periodical check-ups are mandatory in order to control and prevent the risks [8, 32, 33].

3.2. Treatment and Prognosis. The treatment for the Sjögren syndrome is mainly clinical. The use of FANS has a beneficial effect on arthritis. In major cases, corticosteroid and immunosuppressive drugs may be needed. Xerostomia can be regulated by using saliva substitutes such as sprays/gel or by installing an air humidifier. Sugar-free chewing gums may be useful to alleviate the feeling of dryness in the oral cavity, as well as hyperstimulate the salivary production. Methylcellulose artificial tears can alleviate xerophthalmia. Very often, Sjögren syndrome is accompanied by candidiasis produced by *Candida albicans*. This will require antimycotic treatment [13, 33]. Salivary secretion can be increased by taking pilocarpine. At a dental level, teeth and gums must be protected from the collateral damage caused by xerostomia [8]. Intensive domiciliary as well as professional oral hygiene care is mandatory to avoid complications due to teeth decay or root canal inflammation [34].

4. Pemphigus Vulgaris

Pemphigus vulgaris is a chronic immunomediated disorder. This disease affects the skin and mucosa. Patients affected by pemphigus have immune globulin G autoantibody against desmosomal components like desmoglein-1 and desmoglein-3 [35]. This alters the properties of adhesion cell molecules, producing intraepithelial blisters between the Malpighian epitheliocytes. This phenomenon is called *acantolysis of suprabasilar cheratynocites* [8, 35].

Although epidemiologically there is no evidence of gender predilection, some studies reported a slight prevalence in women [13]. All ages can be affected, though the highest number of cases is observed in patients in their 40s and 50s [8, 13].

The etiology would seem to be linked to genetic and ethnic factors. The lesions seem to be triggered by different inputs like physical agents, viruses, hormones, drugs, and stress [8, 13].

In over 50% of cases, the first signs of the disease arise in the oral mucosa. Although there is no area predilection, the lesions could be located at the buccal mucosae, soft palate, lower lip, and tongue and, less frequently, at the gingiva [36]. Oral lesions can range from fairly superficial ulcers to small vesicles or blisters. In the oral cavity, the bubbles rapidly break, leaving a painful erosion producing burning sensation [13]. The size of the ulcers is extremely variable. It can be noticed that a detachment of a large area of the surface with the formation of blisters can occur by exerting a slight pressure on the epithelium of these patients. This phenomenon is referred to as the Nikolsky phenomenon [8].

Pemphigus skin lesions are subsequent to oral manifestations. They can arise as simple rashes to erosions, vesicles, blisters, or ulcers. Microscopic examination highlights superficial epithelial damage with the intact basal layer adhering to the basal membranes [8]

4.1. Diagnosis. The pemphigus can be easily confused with other disorders that present lesions like aphthae, lichen planus, candidiasis, and pemphigoid. Often, pemphigus is associated with other autoimmune clinical situations such as the Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus [37, 38]. As a matter of fact, clinical, histopathological, and, in particular, direct and indirect immunofluorescence is mandatory to perform an efficient differential diagnosis. Direct immunofluorescence is performed on the tissue and highlights the local cellular damage (visualization takes place through a special microscope that highlights the fluorescence inside the spinous layer). In the indirect type, the antibodies are detected in the patient's serum [8, 39].

4.2. Treatment and Prognosis. The pemphigus is a pathology that involves primarily dermatologists although dentists can

play an important role in the early diagnosis of the disease as well as in the management of oral manifestations. The treatment involves the administration of high-dose corticosteroids. In addition to these, immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine, and methotrexate are sometimes used. Recently, the use of rituximab has been proposed showing promising results [40, 41]. The titration of circulating antibodies is carried out to evaluate the progress of the disease. In fact, high antibody rates correspond to the most destructive phases of the disease. Their evaluation is also used to check the effectiveness of the treatment [8].

5. Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a group of immune-mediated chronic blistering conditions. The oral mucosa is targeted as well as genital, conjunctival, and skin mucous membranes [8]. The autoantibodies mostly IgA and IgG are located, together with the C3 complement, on the mucosae as well as on epithelial basal membranes [35].

The most affected area is the gingiva, almost 94% of the cases [35], where the pemphigoid lesions give rise to a clinical condition called *desquamative gingivitis*. It has been said that desquamative gingivitis is not, per se, diagnostic. The lesions show as simple erythema or true ulcerations affecting both the fixed gingiva and the adherent gingiva. Very often, this lesion is confounded with periodontal disease.

However, lesions can also occur in other areas of the oral cavity including the palate, buccal mucosae, lips, tongue, and pharynx.

The symptoms associated with these conditions go from burning sensation and bleeding to masticatory impairment [35]. Pemphigoid blisters are less brittle than those seen in pemphigus and can remain intact in the oral cavity for up to 48 hours [8, 42].

5.1. Diagnosis. The diagnosis of mucous membrane pemphigoid is based on clinical and histological samples. The histologic examination shows the detachment of the epithelium from the underlying connective tissue. Direct immunofluorescence is diriment when there are doubtful histological samples showing a linear involvement at the level of the basal membrane. The immunofluorescence is particularly useful in the differential diagnosis with pemphigus and lichen as well as with periodontal disease and SLE. Epithelial degeneration is not observed; the connective tissue appears pervaded by an intense inflammatory infiltrate mainly consisting of plasma cells and eosinophils [8].

5.2. Treatment and Prognosis. The mucous membrane pemphigoid is a chronic disease that requires a continuous treatment strategy although the prognosis is benign. Sometimes, the lesions can only be localized to the gums; in other cases, the oral condition is wider. In less severe cases, the lesions can be treated by topical corticosteroid gel application although in some selected cases, it is coupled with dapsone (diaminodiphenyl sulfone). In the most severe forms, the treatment must be carried out systemically. Often, the pathology can be difficult to resolve, tending to respond rather late to therapy. It is crucial to monitor the presence of eye lesions to prevent ocular damage, such as injury to the cornea, conjunctiva, or eyelids [13, 35].

6. Behcet Disease

Behcet syndrome is an autoimmune, multisystemic disease of unknown etiology. It is typically characterized by at least two of the three key typical factors: oral ulcers, genital ulcers, and eye inflammation. Although its original definition is linked to dermatologic pathology, Behcet disease is often characterized by neurological and vascular involvement. It usually affects individuals in their 30s and shows no evidence of gender predilection. The greatest incidence of the disease is observed in Mediterranean and Asian populations with a marked prevalence in Turkey. The demonstration of an autoimmune genesis is given by the presence of antimucous autoantibodies, together with the association of the disease with the HLA configurations B5 and B51 [8, 43].

The mucocutaneous lesions are very often the first sign of the presence of Behcet syndrome. Their recognition is a key factor for early diagnosis, and they permit a more favourable prognosis [44]. The oral lesions are ulcers of the oral mucosae indistinguishable from the conventional aphthae of the oral mucosa. They are painful and characterized by cyclic presentation. They are localized at the lips, buccal mucosa, soft palate, and tongue. At the beginning, the lesion shows as an erythematous lesion, followed by an evolution in ulcers. Their dimensions can vary from few millimeters to centimeters [8, 44].

The genital ulcers are smaller and are located at the level of the scrotum, on the base of the penis, or on the labia majora.

Ocular lesions are present in 30–70% of the cases [43]. They show up as an initial form of photophobia, followed by uveitis and conjunctivitis. In some cases, they were found to be associated with glaucoma and cataract [43].

The skin lesions have a papular or pustular appearance and are mainly localized to the trunk or limbs.

6.1. Diagnosis. It has been said that there are not pathognomonic laboratory findings [43]. In order to diagnose the Behcet syndrome, according to the ISG criteria [45], at least two of the main features (oral, genital, or ocular lesions) must be present when another clinical explanation is excluded. Indeed, the differential diagnosis is a challenge considering that oral aphthous lesions are very common in the general population. Moreover, aphthous lesions are linked to HIV, Crohn's disease, sarcoidosis, and SLE, given that the dual-site-specific ulcerations seem to be the unique sign used to differentiate the Behcet syndrome from different pathologies cited above [43].

6.2. Treatment and Prognosis. The treatment of Behcet syndrome is based on the use of local and systemic cortisones per se or coupled with immunosuppressant drugs. The use of immunosuppressive drugs is justified by the lack of prevention of relapses due to the monocorticosteroid treatment

strategy [43]. The main objective of Behcet syndrome patient care is to treat in time the oral mucocutaneous lesions in order to hinder the progression of the disease and to prevent the irreversible organ involvement in particular during the active phase [44]. Behcet syndrome could be fatal especially in the case of vascular involvement: aneurism rupture and thrombosis are the main causes of death.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Autoimmune Inner Ear Disease: Immune Biomarkers, Audiovestibular Aspects, and Therapeutic Modalities of Cogan's Syndrome

Oded Shamriz,[1] Yuval Tal,[2,3] and Menachem Gross[4]

[1]*Pediatric Division, Hadassah Hebrew-University Medical Center, Jerusalem, Israel*
[2]*Internal Medicine Division, Hadassah Hebrew-University Medical Center, Jerusalem, Israel*
[3]*Allergy and Clinical Immunology Unit, Hadassah Hebrew-University Medical Center, Jerusalem, Israel*
[4]*Department of Otolaryngology-Head and Neck Surgery, Hadassah Hebrew-University Medical Center, Jerusalem, Israel*

Correspondence should be addressed to Menachem Gross; drgrossm@hotmail.com

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Cogan's syndrome (CS) is a rare autoimmune disorder characterized by audiovestibular dysfunction and ocular inflammation. Currently, there is no specific serum autoantibody used in the diagnostic workup of CS. Treatment is based on immunosuppressive agents, mainly corticosteroids as first-line choice. Recently, novel therapeutic modalities in CS have emerged. These include tumor necrosis factor-α inhibitors and other biologicals. Despite medical treatment, hearing loss may progress to irreversible bilateral profound SNHL in approximately half of CS patients resulting in candidacy for cochlear implantation (CI). Due to the inflammatory nature of the disease that is causing endosteal reaction with partial obliteration or complete neoossification of the intracochlear ducts, early CI is recommended. CI provides excellent and stable hearing rehabilitation with high score of word and sentence recognition. In this review, we will discuss different aspects of CS including clinical presentation, diagnosis, treatment, and future directives.

1. Introduction

Classical definition of autoimmune inner ear disease (AIED) has been suggested as a disorder with bilateral sensorineural hearing loss (SNHL) progressing over a period of 3 to 90 days, which showed response to steroid treatment [1]. Suggested mechanisms include humoral, as well as cellular-mediated responses with upregulation and expression of different cytokines, such as interleukin- (IL-) 1β and interstitial cell adhesion molecule-1 (ICAM-1) [2]. Many systemic autoimmune diseases may be associated with bilateral rapidly progressive SNHL and vestibular symptoms that clinically resemble AIED.

Within the group of AIED, Cogan's syndrome (CS) is of special interest. Typical CS is characterized by inflammation of the eyes and inner ears, manifesting as interstitial keratitis (IK) and audiovestibulary dysfunction (AVD), respectively [3]. Association with systemic vasculitis is well described [4]. CS is believed to have an autoimmune aetiology, although many questions regarding aetiopathogenesis remain unanswered.

As current understanding of possible causes, disease course, and available biologic treatments is limited, a comprehensive review of the existing literature concerning CS is needed. In this review, we will uncover different clinical audiovestibular aspects, immune mechanisms, and therapeutic modalities and try to shed some light on this rare autoimmune disease.

2. Epidemiology of Cogan's Syndrome

CS is a rare disorder with approximately 250 cases reported so far [5]. It affects mainly young Caucasian adults in their third decade of life [6], although cases of CS were reported in children and in the elderly. In one study that analysed data from a cohort of 78 CS patients, median age of disease onset was 25 years and ranged between 5 and 63 years [7]. In

large cohorts published, there is no specific gender predominance [8].

3. The Clinical Spectrum of Cogan's Syndrome

Mandatory diagnostic criteria of CS consist of SNHL, inflammatory ocular symptoms, and ruling out any other causes of inflammation or infection, such as tuberculosis and syphilis [6].

CS is classified as having a "typical" and an "atypical" presentation. Typical CS, as it was first described in 1945, consists of IK and AVD including Meniere-like episodes and SNHL [9]. In typical CS, inner ear symptoms occur within a time period of 2 years from ocular symptoms [3]. Atypical CS manifests with non-IK inflammatory ocular symptoms. These comprise glaucoma, conjunctivitis, and episcleritis [10]. Uveitis is another ocular manifestation of atypical CS and was reported even in children [11], alerting physicians to be aware of the association between uveitis and SNHL in the context of atypical CS.

Systemic manifestations are more common in atypical CS [3]. Fever, headaches, polyarthralgia and arthritis, myalgia, anorexia, and gastrointestinal (GI) symptoms were previously described in CS patients [12]. Systemic vasculitis is seen in 15–21% of the patients [6]. Aortic root vasculitis, which is reported in 10% of CS patients, can result in life-threatening complications, such as aortic aneurysms, dissection, and insufficiency [13–15]. Mitral insufficiency was also reported [16]. Other organs, such as the kidneys and brain, may be affected by systemic vasculitis in CS [17], and CS patients with stroke have been reported [18].

Interestingly, review of the literature reveals a coexistence between CS and other autoimmune diseases. This includes the presence of atypical CS with granulomatosis with polyangiitis (Wegener's granulomatosis) [19], rheumatoid arthritis [20], and tubulointerstitial nephritis and uveitis (TINU syndrome) [21]. One study reported of 4 inflammatory bowel disease (IBD) patients presenting with CS symptoms, including SNHL and ocular inflammation, following GI symptoms [22]. Another large international multicenter study supported these findings and described 22 CS-IBD patients; 50% of them had GI symptoms before CS onset [23]. This coexistence of CS with other autoimmune diseases constitutes a clue for its autoimmune pathogenesis.

4. Autoantibodies and Serological Markers in Cogan's Syndrome

Currently, no specific serological biomarker is available in the routine diagnostic workup of CS. Moreover, the absence of serum autoantibodies does not rule out CS diagnosis [5].

However, several autoantibodies have previously been associated with CS (Table 1). In 2003, researchers from Italy identified autoantibodies produced in CS patients against a "Cogan peptide," which shared homology with laminin, connexin 26, cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), SSA/Ro, and reovirus III major core protein lambda 1. Injection of these autoantibodies into mice resulted in vasculitis and ocular symptoms. Furthermore, administering the Cogan peptide into rabbits has resulted in the development of SNHL [24].

As autoimmune aetiology of CS became more likely, a search for other autoantibodies was conducted. Anti-heat shock protein- (HSP-) 70 was suggested to be a strong candidate. Antibodies to both HSP-70 and inner ear 68 kDa antigen were isolated from an experimental autoimmune SNHL model of guinea pigs and patients with progressive SNHL and were suggested to be a marker for AIED [25]. In 2007, another study tested 14 CS patients for anti-HSP-70 serum titers and found that 50% of them were positive, as compared to only 4% in the control group [26]. A cohort of 38 CS patients, 55 autoimmune SNHL patients, and 19 control subjects found that positivity of anti-HSP-70 was highest among typical CS patients (92.9%), followed by ASNHL (52.7%), atypical CS (16.6%), and control (5.2%) groups [27].

Finally, one should also mention general autoimmune markers. These include anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), and rheumatoid factor (RF). ANCA are directed against myeloperoxidase (C-ANCA) and proteinase-3 (P-ANCA). Their association with numerous autoimmune diseases, including ulcerative colitis and vasculitides, is well established [28, 29]. Regarding CS, review of the literature yields several case reports of ANCA-associated CS, especially in the context of glomerulonephritis and renal vasculitis [30–33]. ANA and RF were also identified in sporadic CS cases [34]. However, positivity of ANCA, RF, and ANA among CS patients in large studies was found to be low [26], as well as with other general autoimmune markers, such as circulating anticoagulant antibodies, anticardiolipin antibodies, and cryoglobulins [35].

It appears that the sensitivity and specificity of serum biomarkers of CS are still not sufficient, and thus the search for a routine laboratory test that will support CS diagnosis is still not completed.

5. Biological Therapy in Cogan's Syndrome

Treatment of CS is challenging and particularly concerns AVD. Data regarding immunosuppressive treatment of CS is scarce and mainly relies on case reports and case series [6]. First-line therapy in order to achieve remission in CS remains high-dosage corticosteroids. Treatment failure may necessitate the addition of other immunosuppressive agents, such as methotrexate, cyclophosphamide, azathioprine, and cyclosporine A, which were shown to have a favourable outcome than corticosteroid monotherapy [36, 37]. In a systematic review, the use of methotrexate in CS was most common, as a nonsteroidal immunosuppressive agent [38].

However, there are increasing reports of CS patients treated successfully with different biological drugs (Table 2). Tumor necrosis factor (TNF-α) inhibitory agents are increasingly being used in autoimmune diseases, such as IBD. Among that group, data regarding treatment with infliximab, a chimeric anti-TNF-α monoclonal antibody, seems to be the most extensive. Review of the literature reveals 12 CS patients treated with infliximab [6, 39–45], of which one patient failed to achieve clinical remission [39]. Data

Table 1: Autoantibodies associated with Cogan's syndrome.

Autoantibody	Antigen location	Antigen function	References Human studies: number of CS patients/study design/country of publication	Animal models
Anti-HSP-70	Not specific	Protein folding and ubiquitin-mediated degradation; protection from cell stress	38/case control/Italy [27] 14/case control/Italy [26] 8/case control/USA [71]	—
ANCA	Neutrophils	Proteolysis (PR3) Production of oxidative free radicals (MPO)	5/case reports/France [72]; Japan [32, 73]; USA [30]; the Netherlands [33]	—
Anti-Cogan peptide	Endothelial cells in the inner ear, lymphocytes, and kidney	Contact inhibition of cell growth; homolog with laminin, connexin 26, SSA/Ro, reovirus III major core protein lambda1, and cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148)	8/case control/Italy [24]	Rabbits and mice [24]

HSP-70: heat shock protein-70; CS: Cogan's syndrome; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase-3; MPO: myeloperoxidase.

regarding age and gender of patients was available in 11 patients. Five males and 6 females with a mean age of 39.2 (range: 16 to 67) years were reported. AVD was noted in 8 patients, five of which also suffered from IK. Three patients presented with a non-IK ocular manifestation (two patients with scleritis and one with branch retinal arterial occlusion, glaucoma, and anterior uveitis). Infliximab doses were described in 8 patients and included a regimen of 3 mg/kg in most cases. These encouraging reports of infliximab use in CS correspond with a French nationwide study, and systematic review of the literature found that infliximab was more effective achieving AVD remission than corticosteroids or DMARDS alone. Moreover, the use of infliximab was found to predict AVD response [44]. Tayer-Shifman et al. suggested that considering treatment with infliximab after treatment with corticosteroids showed lack of response to corticosteroids within 2-3 weeks, steroid dependency of 10 mg/day, or contraindication for the continuation of corticosteroids. First-line therapy with infliximab was recommended by the authors in cases of severe ocular inflammation, rapid hearing loss, bilateral ear involvement, and systemic manifestations or if contraindicated for starting corticosteroid treatment [6].

There are only few reports of the use of other types of TNF-α inhibitors in CS. Etanercept, a TNF-α receptor fusion protein, was also shown to improve hearing loss in 2 out of 3 CS patients in a multicenter study [46]. Two other reports described failure to achieve clinical response by using adalimumab, an anti-TNF-α monoclonal antibody, in a 69-year-old man [47] and a 25-year-old woman with CS [48].

We found 3 case reports, in which rituximab, a chimeric anti-CD20 antibody, was used in CS. Among them, improvement in hearing loss was noted in only one patient [48]. Lack of efficacy was noted in a patient with atypical CS and non-Hodgkin's lymphoma [45] and in a patient with steroids and azathioprine-refractory CS [49].

Finally, one can find only two case reports describing treatment of adult CS patients with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody. Both patients presented with SNHL and uveitis [47, 50]. One patient suffered from a systemic disease including aortitis, meningitis, panniculitis, and seronegative arthritis and achieved clinical remission with tocilizumab after failed treatment with high dosage of prednisone, methotrexate, cyclosporine, azathioprine, and adalimumab [50]. Another CS patient was treated with tocilizumab but developed bilateral patchy acute lung injury [47].

6. Hearing Prognosis and Otologic Surgical Interventions

CS has a poor prognosis when eye, ear, and cardiovascular complications occur. Most of the untreated patients have moderate, severe, or profound hearing loss at 5-year follow-up [7]. In a literature review of 111 cases by Grasland et al., 54% and 37% of cases with typical and atypical Cogan syndrome remained deaf in both ears despite treatment [35]. Gluth et al. reported profound hearing loss in 52% of CS patients despite immunosuppressive therapy [51].

In patients with bilateral profound SNHL in whom no benefits are obtained from conventional hearing aids, cochlear implantation (CI) is a highly effective hearing rehabilitation modality. However, some clinical reports of patients with CS who have undergone CI describe major surgical issues. CI in CS patients may be technically challenged due to inflammatory endosteal reaction leading to partial obliteration or complete neoossification of the intracochlear ducts [52–55]. Due to this tendency, early cochlear implantation should be recommended in patients with bilateral profound SNHL. Postoperative wound healing problems have been also described in CS patients who have undergone CI [56–58]. Skin atrophy from long-term corticosteroid and immunosuppressant therapy and ischemia caused by vasculitis may be risk factors that contributed to the wound healing complication.

Short-term post-CI hearing outcomes in postlingual CS patients have been described in few clinical reports. Although deterioration of auditory performance after CI has been described by Bovo et al., presumably secondary to apposition or progression of new bone formation in the cochlea, which in turn increases the distance of the

Table 2: Evidence for treatment of Cogan's syndrome with biological agents.

Biological agent	Immune mechanism	Number of CS patients reported to be treated with biotherapy	Age (years)/gender/ clinical presentation	Biologic dosage and regimen	Number of CS patients that responded to biotherapy	Study design	Country of publication	Ref
Infliximab	Chimeric anti-TNF-α monoclonal antibody	2	33/M/AVD, IK	300 mg × 1/month	2	CR	Switzerland	[42]
			49/M/SNHL	300 mg × 6/week				
		3	30/F/AVD, IK	3 mg/Kg at weeks 0, 2, 6, 8, and then every 8 weeks	3	CR	Italy	[40]
			29/M/AVD, IK	NA*				
			35/M/SNHL, scleritis	NA				
		2	37/F/AVD, IK	3 mg/kg at 0, 2, and 6 weeks	1	CR	USA	[39]
			36/F/AVD, IK	3 mg/kg for 4 months				
		1	16/M/TINU, SNHL, BRAO, glaucoma, and uveitis	900 mg at 0, 3, and 5 weeks	1	CR	USA	[41]
		1	48/F/AVD	3 mg/kg at 0 and 3 weeks and then every 8 weeks	1	CR	Spain	[43]
		1	51/F/SNHL	3 mg/kg every 8 weeks for 3 years**	1	CR	Israel	[6]
		1	NA/NA/AVD, scleritis	NA	1	CR	Switzerland	[74]
		1	67/F/AVD	NA	1	CR	Greece	[45]
Etanercept	TNF-α receptor fusion protein	3	NA	25 mg × 2/week for 24 weeks	2	CR	USA	[46]
Adalimumab	Anti-TNF-α monoclonal antibody	1	69/M/SNHL, iritis, aortitis, meningitis, panniculitis, and seronegative arthritis	40 mg × 1/week for 2 weeks	0	CR	Japan	[50]
		1	25/F/AVD, conjunctivitis, IK	40 mg × 1/week for 6 months	0	CR	Italy	[48]
Rituximab	Anti-CD20 monoclonal antibody	1	25/F/AVD, conjunctivitis, IK	500 mg × 1/week for 4 weeks	1	CR	Italy	[48]
		1	67/F/AVD	NA	0	CR	Greece	[45]
		1	43/F/AVD, IK	375 mg/m^2 × 1/week for 4 weeks	0	CR	USA	[49]
Tocilizumab	Humanized anti-IL-6 receptor monoclonal antibody	1	69/M/SNHL, iritis, aortitis, meningitis, panniculitis, and seronegative arthritis	8 mg/kg × 1/month	1	CR	Japan	[50]
		1	59/M/SNHL, anterior uveitis	162 mg × 1/week for 2 weeks	0	CR	USA	[47]

CS: Cogan's syndrome; Ref: references; M: male; F: female; AVD: audiovestibulary dysfunction; SNHL: sensorineural hearing loss; IK: interstitial keratitis; TNF-α: tumor necrosis factor-α; CD: cluster of differentiation; IL: interleukin; CR: case report; NA: data is not available; TINU: tubulointerstitial nephritis and uveitis syndrome; BRAO: branch retinal artery occlusion. *Dosage is noted as given according to "international protocol." **Unpublished data.

CI electrode array from neural structures, most authors agree to the fact that prognosis of cochlear implantation with regard to hearing results is excellent [58–61].

There are only two studies on long-term post-CI hearing outcomes in postlingual CS patients. Kontorinis et al. reported the long-term outcomes of four patients with CS

(average follow-up of 9.25 years) providing evidence of hearing outcome's persistence [57].

These four patients achieved mean scores of 78.7 and 92.4% on word and sentence recognition tests, respectively. At their last evaluation, the mean word score was 80%, whereas the mean sentence score was 96.6%. Long-term study on 12 CS patients over 5 years of CI use by Bacciu et al. revealed that CI is safe in the long term and provides excellent and stable hearing results, with group means for word and sentence recognition tests 94 and 96.3%, respectively [62]. The data from these two long-term follow-up studies demonstrated that patients with CS receive significant open-set speech recognition benefits from a CI that remain stable in the long term.

7. Future Perspective

Human adipose-derived mesenchymal stem cells (hAdMSC) are known to have immunomodulatory properties. Their use in allograft transplantations was previously reported [63]. Interestingly, several animal models have shown promising results using hAdMSC in various autoimmune diseases. This includes murine models of rheumatoid arthritis [64], experimental autoimmune encephalomyelitis (EAE; animal model of multiple sclerosis) [65], and systemic lupus erythematosus [66]. Reduction of proinflammatory cytokines, such as TNF-α, IL-1, and IL-6 [67], and induced production of the anti-inflammatory cytokine IL-10 [66] by hAdMSC constitute a possible immune mechanism.

Several animal models have studied the use of hAdMSC in autoimmune SNHL. Experimental SNHL mice were treated with hAdMSC and demonstrated improvement in hearing parameters, increase in regulatory CD25+ FOXP3+ T cells and IL-10, and decrease in T helper (Th)1/Th17 cellular response [68]. These results were supported by another murine model of autoimmune SNHL, with restoration of hearing loss and similar findings in the modulation of the immune cellular components of Th1/Th17 and regulatory CD25+ FOXP3+ T cells, as well as in induction of IL-10 [69].

Clinical trials regarding hAdMSC use in autoimmune SNHL are scarce. One study examined 10 patients with autoimmune diseases, among them a 19-year-old woman with progressive AIED, in which treatment with hAdMSC demonstrated hearing improvement with a follow-up period of 11 months [70]. However, reviewing the literature, we found no reports of studies regarding hAdMSC use in CS. Applying current data from animal models of autoimmune diseases, including autoimmune SNHL, on CS necessitates further studies that will evaluate efficacy and safety of this novel therapeutic modality.

8. Conclusions

CS pathogenesis is still not fully understood; however, an autoimmune underlying mechanism is probably responsible for disease onset. Diagnosis must rely on clinical findings, as laboratory markers are not fully accepted and routinely used. The use of steroids, with or without a combination with another immunosuppressive agent, is needed to achieve initial remission. As biological treatments and hAdMSC therapy develop, their increasing use in autoimmune diseases shows encouraging results, and thus new therapeutic modalities in CS are introduced. Early CI should be recommended in patients with bilateral profound SNHL because of the tendency for partial obliteration or complete neoossification of the cochlea. CI provides excellent and stable hearing rehabilitation with long-term follow-up in most patients.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Oded Shamriz and Yuval Tal contributed equally in the preparation of this manuscript and should both be considered as first authors.

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Review Article

Salivary Gland Pathology in IgG4-Related Disease: A Comprehensive Review

Ilaria Puxeddu,[1] **Riccardo Capecchi**,[1] **Filippo Carta**,[2] **Antonio Gaetano Tavoni**,[1] **Paola Migliorini**,[1] **and Roberto Puxeddu**[2]

[1]*Clinical Immunology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[2]*Otorhinolaryngology Unit, Department of Surgery, Azienda Ospedaliero-Universitaria di Cagliari, University of Cagliari, Cagliari, Italy*

Correspondence should be addressed to Ilaria Puxeddu; ilarip@yahoo.it

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IgG4-related disease (IgG4-RD) is a rare fibroinflammatory condition that can affect almost any organ, characterized by swollen lesions and often by eosinophilia and elevated serum IgG4 concentrations. The diagnosis of IgG4-RD is a challenging task: in fact, single or multiple organs can be affected and clinical, serological, and histological findings can be heterogeneous. In IgG4-RD, the involvement of salivary glands is observed in 27% to 53% of patients. Several organ-specific conditions, now recognized as different manifestations of IgG4-related sialadenitis (IgG4-RS), were viewed in the past as individual disease entities. The study of salivary glands may sometimes be complex, because of the number of pathological conditions that may affect them, often with overlapping clinical pictures. Integration of different imaging techniques is often required in the case of swelling of salivary glands, even though biopsy remains the gold standard for a definite diagnosis of IgG4-RS. Thus, in this review, we discuss new insights in the pathogenesis of IgG4-RD, focusing on its clinical aspects and the tools that are currently available for a correct differential diagnosis when the salivary glands are involved.

1. Introduction

IgG4-related disease (IgG4-RD) is a rare fibroinflammatory condition that can affect almost any organ [1, 2], including the salivary glands, orbital and periorbital tissues, pancreas, retroperitoneum, and lymph nodes [3]. IgG4-RD is characterized by swollen lesions across organs and often by elevated serum IgG4 concentrations. Diagnosis of IgG4-RD is based on a set of clinical, serological, and pathological criteria [4], and the histological picture is critical for diagnosis. In fact, the hallmark features of the disease are tissue fibrosis with a storiform pattern, a diffuse lymphoplasmacytic infiltrate, obliterative phlebitis, abundance of $IgG4^+$ plasma cells, and mild to moderate tissue eosinophilia [5]. Presently, the pathophysiological mechanisms underlying IgG4-RD have not yet been fully established. The increase of IgG4 itself appears to be a reactive phenomenon rather than the primary disease driver. It is likely that in IgG4-RD, the interactions between cells of B cell lineage and a novel $CD4^+$ $SLAMF7^+$ cytotoxic T cells (CTLs) are involved in the processes leading to tissue inflammation and fibrosis [6–8]. These recent evidences have allowed to identify novel and more specific therapeutical approaches in IgG4-RD, such as targeting the B cell lineage, that have so far given promising results.

1.1. Pathophysiology of IgG4-RD. In the last decade, several pathophysiological mechanisms, potentially responsible for the development of IgG4-RD, have been described. B cells and plasmablasts seem to play an important role in IgG4-RD, secreting autoantibodies or acting as antigen presenting cells in the expansion of pathogenic T cells [8, 9]. Oligoclonal IgG4-producing plasmablasts are detected in the peripheral blood of IgG4-RD patients [10, 11], and this population of somatically hypermutated B cells has been proposed as disease biomarker. Furthermore, plasmablasts are reduced by immunosuppressive treatment and reemerge during relapse,

thus performing as disease activity marker as well [12, 13]. Recent evidences suggest that in addition to B cells, T cells also play a key role in IgG4-RD pathogenesis [6]. $CD4^+$ T cells are the most abundant cells in IgG4-RD lesions; given the eosinophil infiltrate and the levels of IgG4 and IgE, a prominent role of T helper cells type 2 (Th2) cells has been proposed. However, Mattoo et al. [10] demonstrated that relative increases in circulating Th2 were only observed in a subset of patients with IgG4-RD who had a history of atopic disease, while nonatopic IgG4-RD subjects did not exhibit any expansions of circulating Th2 cells. In a more recent study, they also showed clonal expansions of $CD4^+$ CTLs in the blood of patients with IgG4-RD [7]. By using multicolor immunofluorescence staining of affected organs, they demonstrated that these $CD4^+$ CTLs infiltrated tissue lesions and were the dominant $CD4^+$ T cells at disease sites, while $CD4^+GATA3^+$ Th2 cells were sparse [7]. This clonally expanded population of $CD4^+$ CTLs, detected in both peripheral blood and fibrotic lesions of IgG4-RD patients, seems to actively contribute to the disease process, particularly to tissue injury and fibrosis. $CD4^+$ CTLs, bearing SLAMF7 on their surface, might be actively involved in the fibrotic processes in IgG4-RD, releasing profibrotic mediators such as IL-1β, TGF-β, and INF-γ [7, 11]. To a certain degree, B cell depletion has the potential to attenuate fibrosis associated with IgG4-RD by reducing collagen deposition and myofibroblast activation [14]. In addition, the blood concentration of the $CD4^+SLAMF7^+$ CTLs slowly declines following B cell depletion in IgG4-RD patients, suggesting a direct link between B cells lineage and $CD4^+SLAMF7^+$ CTLs in the pathogenetic mechanisms of IgG4-RD. However, these cells do not express CD20 on their surface and thus are not a target of anti-CD20 treatment, suggesting that $CD4^+$ CTLs are sustained by B cells and plasmablasts.

Recently, a role of T follicular helper (Tfh) cells in IgG4-RD pathogenesis has also been proposed [15–17]. Higher proportions of T regulatory and Tfh cells have been detected in IgG4-RD patients compared to healthy controls, correlated with plasmablasts and serum IgG levels [17]. In support to these findings, an increased number and frequency of circulating PD-1^{high} Tfh cells have been detected in peripheral blood of patients, functionally effective in driving IgG4 production from autologous B cells and responsive to steroid treatment [15, 16]. A diffuse infiltrate of Tfh expressing PD-1, ICOS, and BCL6 at high density has been described in tissue lesions [16]. On the whole, these data suggest the possibility to use also circulating Tfh cells as biomarker of disease activity.

Moreover, these new data on T cell subpopulations suggest novel pathogenetic mechanisms and innovative therapeutic approaches to IgG4-RD.

1.2. General Clinical Aspects of IgG4-RD. IgG4-RD mainly involves middle-aged to elderly males, unlike classic autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome (SSj) that mostly affect females. IgG4-RD occurs in a subacute form in most patients, without the rapid onset of general symptoms such as fever. A minority of patients have weight loss, dramatic elevations of acute phase markers, and other manifestations of systemic inflammation. IgG4-RD typically comes to medical attention because of single-organ involvement, but more widespread disease is often observed following an accurate work-up [18]. Involvement of different organs can occur either simultaneously or metachronously, with the emergence of one newly affected organ following another. IgG4-RD can affect almost any organ, more frequently the salivary glands and pancreas, then the lacrimal glands, lymph nodes, biliary tract and gallbladder, retroperitoneum, thyroid, kidney, lung, periorbital tissues, aorta, and liver [3]. Other organs can also be involved, even if with lower frequency, such as the pituitary gland, meninges, prostate, breast, skin, pericardium, aortic valve, upper airways, ear, pleura, mediastinum, paranasal sinuses, and peripheral nerves.

Table 1: Diagnostic criteria for IgG4-related disease (modified after Umehara et al. [4]).

Diagnosis	Criteria
Definitive	Diffuse or local swelling or multiple organs Serum IgG4 levels ≥ 135 mg/dL Histology: (1) Lymphoplasmacytic infiltrate and fibrosis (2) $IgG4^+$ plasma cells: ratio of $IgG4^+/IgG^+$ cells > 40%, and >10 $IgG4^+$ plasma cells/high-power field
Probable	Diffuse or local swelling or multiple organs Histology: (1) Lymphoplasmacytic infiltrate and fibrosis (2) $IgG4^+$ plasma cells: ratio of $IgG4^+/IgG^+$ cells > 40%, and >10 $IgG4^+$ plasma cells/high-power field
Possible	Diffuse or local swelling or multiple organs Serum IgG4 levels ≥ 135 mg/dL

1.3. Diagnosis of IgG4-RD. The diagnosis of IgG4-RD is a challenging task: in fact, single or multiple organs can be affected and clinical, serological, and histological findings can be heterogeneous. IgG4-RD can be suspected in the presence of swollen lesions or diffuse/localized swelling in one or more organs. The diagnostic work-up involves laboratory investigations and imaging such as ultrasonography, computerized tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET). Histopathology is mandatory for diagnostic purposes and also to exclude neoplastic or other inflammatory disorders [19]. Criteria for the diagnosis of IgG4-RD have been proposed by Umehara et al. [4], as summarized in Table 1. A definite diagnosis is made only when three criteria are met: evidence of diffuse/localized swelling or mass lesions in one or more organs, elevated serum IgG4 concentrations, and a marked lymphoplasmacytic infiltration and fibrosis with $IgG4^+$ plasma cells at histology. When serological criteria (e.g., increased serum IgG4 levels) are not fulfilled, the disease is considered "probable" and "possible" when only the clinical and serological criteria are met. Less stringent criteria are used in the case of type I autoimmune

pancreatitis (AIP) and Mikulicz's disease (MD): in these localizations, histological data are not essential [4]. Differential diagnosis encompasses benign and malignant tumors, especially lymphomas, and disorders with a similar clinical picture: SSj, Castleman disease, sarcoidosis, granulomatous polyangiitis, primary sclerosing cholangitis, retroperitoneal fibrosis, and eosinophilic granulomatosis with poliangiitis. Differential diagnosis from a neoplastic disorder is particularly difficult when the disease affects a single organ or represents an accidental finding of a radiological or histological test. On the other hand, when IgG4-RD is multiorgan, lymphoma or a metastatic disease should be excluded; the clinical picture is often confusing, as both weight loss and lymphadenopathy can be present in all these conditions. Serology can be more helpful, if eosinophilia and hypergammaglobulinemia with increased serum levels of IgE and especially of IgG4 are detected. An increased number of $IgG4^+$ plasma cells in tissues are a more specific finding, but not exclusive of IgG4-RD. It is in fact observed in ANCA-associated vasculitis and urticarial vasculitis, in hematological malignancies, in pancreatic or lung cancer and sarcoma, in tumor of salivary glands and lymphoma, in infections, in inflammatory bowel diseases and diverticulitis, and in rheumatoid arthritis and histiocytosis. However, the other typical hystopathological findings of the disease are not present in any of these disorders. Therefore, histology remains, up to now, mandatory for differential diagnosis; clinicopathological correlation is also essential.

1.4. Therapy of IgG4-RD. In a few cases, spontaneous remission of the disease has been reported and "watchful waiting" represents an option in case of involvement limited to submandibular glands and lymph nodes. When vital organs are affected, or the disease has an aggressive course, treatment is necessary to prevent organ dysfunction. IgG4-RD has a significant response to treatment with immunosuppressants. Steroids represent the cornerstone of treatment. It has been shown that steroid treatment improves the function of affected organs, prevents organ damage, and decreases the rate of recurrence [20]. Response to treatment is observed within 2 weeks, with disappearance of symptoms, decrease of serum IgG4 levels, and improvement of organ function. Prednisolone is usually employed, at the initial dose of 0.6 mg/kg for 2–4 weeks, with gradual tapering (5 mg every week/2 weeks) [1]. Steroid treatment can be interrupted in 3–6 months, or a low dosage (2.5–5 mg/day) can be maintained for 3 years, as suggested by Japanese authors.

Steroid-sparing agents are often employed, as in other autoimmune disorders, to maintain disease control with lower steroid dosage or without steroids. Azathioprine, methotrexate, and mycophenolate mofetil have all been used, and less often 6-mercaptopurine and cyclophosphamide [21].

In patients with recurrent or refractory disease, the monoclonal anti-CD20 Rituximab has been proven to be effective, inducing a decrease in serum IgG4 levels and a rapid clinical response. The parallel decrease in $CD20^+$ B cells and serum IgG4 levels suggests that IgG4 are mainly produced by short-lived plasmablasts and plasma cells, rapidly depleted by a treatment affecting mature B cells. Rituximab therapy reduces inflammatory infiltrate and also, albeit partially, fibrosis [21].

1.5. Salivary Gland Involvement in IgG4-RD: General Aspects. In IgG4-RD, the involvement of salivary glands is observed in 27% to 53% of the patients [22]. Several organ-specific conditions, now recognized as different manifestations of IgG4-related sialadenitis (IgG4-RS) [23], were viewed in the past as individual disease entities. For example, MD, a dramatic bilateral painless swelling of parotid, lacrimal, and submandibular glands, was previously linked and not clearly distinguished from SSj until 2005, because of their similar glandular histological aspects [24]. Similarly, the Kuttner's tumor or chronic sclerosing sialadenitis, characterized by severe swelling of the submandibular glands, was initially considered as an individual disease entity, frequently associated with sclerosing cholangitis and retroperitoneum involvement.

1.5.1. Salivary Gland Involvement in IgG4-RD: Clinical Presentation. In IgG4-RS, the swelling of lacrimal and salivary glands is mostly, but not exclusively, bilateral and painless and persists generally for more than 3 months [25]. Submandibular glands are more frequently affected, but parotid, sublingual, and labial salivary glands are also involved. Usually, salivary secretion is normal or slightly reduced and xerostomia is present in 30% of the patients, less frequently than in SSj. The secretory impairment, when present, is more severe in submandibular glands [23] and improves with an early steroid treatment. It has been reported that in 40% of patients affected by type I autoimmune pancreatitis (AIP), IgG4-RS is also present. IgG4-RD patients with salivary involvement can experience more frequently AIP, sclerosing cholangitis, and asthma compared to those with SSj [23, 26]. Along with the salivary and lacrimal glands, other otorhinolaryngological sites may be involved in IgG4-RD, such as the nose, paranasal sinuses, and ears, with a frequency higher than 50% [27]. Furthermore, cervical lymphadenopathy can be found in 70% of IgG4-RS patients, raising the suspicion of an underlying IgG4-RS in subjects with enlarged salivary glands [23].

In our cohort of 20 IgG4-RD patients (M : F ratio 9 : 11, mean age 59, range 18–81), salivary gland involvement was observed in 3 cases. Diagnosis of IgG4-RD, according to the above described criteria [4], was definitive in all 3 patients. One patient was affected by MD with dacryoadenitis and parotid involvement with cervical lymphoadenopathy; symptoms were xerostomia, swelling, and oedema of parotid glands. Serological (elevated serum IgG4, 388 mg/dL) and histological data (biopsy of parotid with storiform fibrosis, lymphomonocytic infiltrate with high quote of $IgG4^+$ plasmablasts) led to the diagnosis.

The other two patients were affected by both MD and Kuttner's tumor, with AIP and retroperitoneal fibrosis. Their clinical picture was characterized by longer disease duration (17 and 35 years, resp.), higher serum IgG4 titer (1870 mg/dL and 304 mg/dL at the diagnosis), and more frequent relapses of the disease. In one patient, an

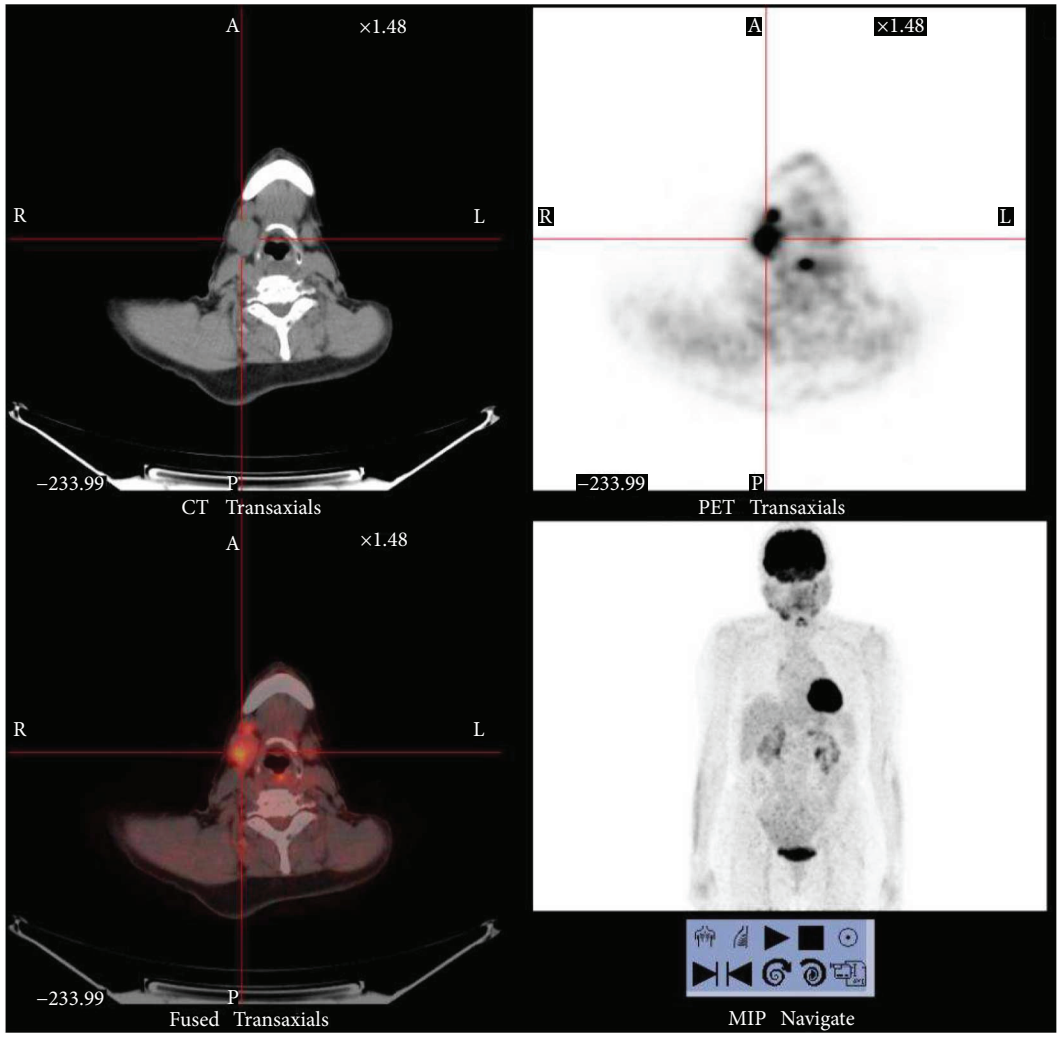

Figure 1: Positron emission tomography (PET) in an IgG4-RD patient with dacryoadenitis and sialoadenitis. PET analysis was performed during relapse of the disease before starting new therapy. In the right submandibulary region and pretracheal lymph nodes, the PET analysis shows an enlargement of the parotid gland with an increase concentration of 18-FDG and glucidic hypermetabolism.

enlargement of the parotid was detected by PET analysis (Figure 1); in the other one, the submandibular gland involvement was recognized retrospectively after gallium-67 scintigraphy in the absence of any local symptom, such as xerostomy.

1.5.2. Salivary Gland Involvement in IgG4-RD: Differential Diagnosis. In the presence of a mass lesion of salivary glands, the key point is to exclude a tumor. Differential diagnosis involves salivary gland neoplasms and other malignancies such as lymphoma or metastatic tumors. As an IgG4-producing marginal zone B cell lymphoma was described, to exclude a lymphoma may not always be easy [28]. Other entities that can mimic an IgG4-RS include SSj, Castleman disease, eosinophilic granulomatosis with polianGiitis, sarcoidosis, and the Heerfordt syndrome, characterized by extrapulmonary manifestations, in which salivary glands and cervical lymph nodes are involved, and uveitis and facial nerve palsy can be present. Among the various diseases to be taken into account for a differential diagnosis with IgG4-RD, SSj can often be challenging. These two diseases often share common clinical and laboratory aspects, such as glandular enlargement, sometimes sicca symptoms, arthralgias, hypergammaglobulinemia, hypocomplementemia, and the presence of antinuclear antibodies (ANA). However, there are features that distinguish the two entities, for example, the presence of anti-Ro/SSA and anti-La/SSB antibodies in the vast majority of SSj patients, the $IgG4^+$ plasma cells infiltration, and the response to steroids in IgG4-RD. However, in a few cases, the two disorders can coexist. Nakashima et al. [29] described a case in which the diagnostic criteria of both IgG4-RD and SSj were met. Furthermore, Baer et al. [30] reported that only one out of 2594 patients in a research registry for SSj presented histopathological findings consistent with the diagnosis of IgG4-RD. In a study including 133 patients with primary SSj, Mavragani et al. [31] described circulating IgG4 levels higher than 135 mg/dL in 10 patients and a marked infiltration of $IgG4^+$ plasma cells in the minor salivary glands of 3 patients. On the other

hand, Yamamoto et al. [32] described 7 patients out of 160 affected by MD that were positive for anti-Ro/SSA antibodies and met the American College Rheumatology criteria and the American European consensus criteria for SSj. However, the use of low stringency diagnostic criteria for MD, criteria that are presently under revision, suggests a potential misdiagnosis in some of these patients. In conclusion, coexistence of the two disorders can be suspected in a very limited number of patients, but an "IgG4-RD/SSj overlap" has not so far been proposed.

1.5.3. Salivary Gland Involvement in IgG4-RD: Imaging and Diagnostic Techniques. The study of salivary glands may sometimes be complex, because of the number of pathological conditions that may affect them, often with overlapping clinical pictures. Integration of different imaging techniques is often required in the case of swelling of salivary glands, even though biopsy remains the gold standard for a definite diagnosis of IgG4-RS. Among the different methods of imaging useful for the study of salivary glands, ultrasonography represents the most widely used technique. This is mainly due to its noninvasiveness and high tolerability for the patient, as well as for the low cost. Even if some ultrasonography features can be shared by IgG4-RS and SSj [33], the recent introduction of the color Doppler has allowed to reveal typical features of IgG4-RS in salivary glands, such as increased color Doppler signaling ratios [34]. Intraductally applied contrast-enhanced ultrasound (IA-CEUS) shows also promising results to depict the changes of the parenchyma of the gland due to incomplete contrast filling resulting from numerous small cysts [35].

PET is an emerging diagnostic option in the context of IgG4-RD, since organ lesions accumulate 18F-fludeoxyglucose at high concentration. Although this technology does not allow a specific distinction between inflammatory and cancerous lesions, it can be very useful in the identification of organ involvement beyond the salivary glands, such as the pancreas, retroperitoneum, and periaortic tissue, that can be affected by IgG4-RD, even if clinically silent. Moreover, this technique could be a tool for targeting specific biopsy sites, monitoring disease activity, and also evaluating response to treatment [36]. However, PET is an expensive diagnostic tool and its use must always be targeted.

Even if CT scan and MRI are useful techniques in the diagnosis of salivary glands swelling, they have some limitations in IgG4-RS diagnosis. Recently, Shimizu et al. [33] have conducted a study on the effectiveness of various imaging modalities in the screening of IgG4-RS, focusing on the differences with SSj and on the detection of typical features. They conclude that the nodal changes in IgG4-RS detected by ultrasonography were not clearly observed on CT scan or MRI and that ultrasonography, but not CT scan and MRI, is an effective imaging modality to differentiate IgG4-RS from SSj. IgG4-RS may have characteristics similar not only to SSj but also to chronic obstructive submandibular sialadenitis, one of the most common disorders of submandibular glands, characterized by the obstruction of the ductal system by various causes. Yamamoto et al. [37], comparing the three conditions, observed that sialography was effective to differentiate IgG4-RS from SSj, but not from chronic obstructive submandibular sialadenitis. A rising interest is on the potential role of sialendoscopy in salivary gland pathology that allows a precise evaluation of the duct system avoiding sialography. Sialendoscopy represents a promising gland-preserving tool in the management of nonstone disorders of major salivary glands [38].

Biopsy remains mandatory for establishing a diagnosis and should be analyzed as described above. However, slight differences in the histological pattern can be seen in tissue sample from labial salivary glands, parotid glands, or submandibular glands. For example, an intense tissue fibrosis seems to be a common feature of biopsies obtained from submandibular glands [39, 40], and obliterative phlebitis is present in almost one-third of patients with submandibular involvement. Conversely, both characteristics are rare in tissue samples from labial salivary glands. Labial salivary gland biopsy is relatively easy to obtain, but its sensitivity for the diagnosis of IgG4-RD is very low [40, 41]. Involvement of parotid and submandibular glands, on the other hand, leads to more destructive surgical interventions. Deshpande et al. [5] introduced the following diagnostic cut-off in the sample biopsies, more than 30–50 $IgG4^+$ plasmacytes per high-power field and a ratio of $IgG4^+$ to IgG^+ cells greater than 40%. However, a tissue-specific cut-off for tissue $IgG4^+$ plasma cells in IgG4-RD has not yet been validated. Ectopic germinative centers and occasional eosinophilic infiltration in the affected tissue are common findings. Given the recent description of a case of marginal zone B cell lymphoma that produced IgG4, Takano et al. [42] recommend to perform Western blot analysis of immunoglobulin heavy-chain gene rearrangement. Furthermore, they also propose to perform biopsy of submandibular glands as a "surrogate biopsy" for the diagnosis of AIP. They describe 10 patients with AIP and submandibular biopsies diagnostic for IgG4-RD, but only in 4 patients the biopsy of minor labial glands fulfilled the diagnostic criteria for IgG4-RD [43]. In line with these results, we observed that in 3 IgG4-RD patients with pancreatic involvement, the labial salivary gland biopsy was not diagnostic for IgG4-RD, confirming that this procedure has an insufficient diagnostic sensitivity.

1.6. Conclusion and Perspectives. IgG4-RD is a multisystem disease that can sometimes involve single organs such as the lacrimal and salivary glands. When the disease is suspected, the two key points are as follows: (1) the differential diagnosis from solid tumors and lymphomas (especially in the presence of mass lesions) and (2) the study of multiple organ localizations (by means of imaging techniques). Biopsy of affected organs remains so far the gold standard for diagnosis. Therapy is presently based on the use of steroids and immunosuppressants, but recent insights into pathogenic mechanisms forecast new more disease-tailored therapeutic approaches.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Management of Patients with Graves' Disease and Orbital Involvement: Role of Spectral Domain Optical Coherence Tomography

Alice Bruscolini, Maurizio La Cava, Magda Gharbiya, Marta Sacchetti, Lucia Restivo, Chiara Nardella, Marco Marenco, and Alessandro Lambiase

Department of Sense Organs, University Sapienza, Rome, Italy

Correspondence should be addressed to Alessandro Lambiase; alessandro.lambiase@uniroma1.it

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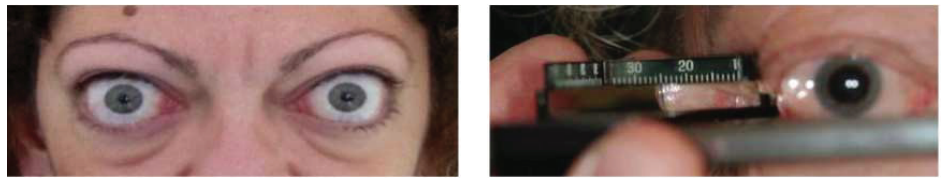
Purpose. To investigate the role of choroidal thickness evaluation with spectral domain optical coherence tomography (SDOCT) and enhanced depth imaging (EDI) technique in the management of patients with Graves' disease and orbitopathy (GO). *Methods*. Thirty-six eyes of 18 patients with GO and 36 eyes of 18 age-matched control subjects were included in this retrospective observational study. All the subjects underwent a complete ophthalmological evaluation, including clinical activity score (CAS) and exophthalmometry. The SDOCT images of the choroid were obtained by EDI modality. *Results*. Choroidal thickness was significantly increased in GO than in control eyes ($p < 0.01$). A significant correlation was found between choroidal thickness and CAS, proptosis, and the duration of disease ($p < 0.05$). *Conclusion*. This study shows that choroidal thickness, evaluated with EDI-OCT, is significantly increased in patients with GO and correlates with the activity of the disease, proptosis, and duration of the disease. The choroidal thickening may reflect the ocular hemodynamic changes, and enhanced depth imaging optical coherence tomography may be a useful tool for the evaluation of orbital congestion and management of patients with Graves' disease and orbital involvement.

1. Introduction

Graves' disease represents the most common cause of hyperthyroidism in adults. Orbital involvement is known as Graves' orbitopathy (GO) [1, 2]. The pathogenetic mechanisms of GO have not yet been fully resolved [3]. It is known that antibodies against the thyroid-stimulating hormone (TSH) receptors play an important role. TSH receptors can not only be found in the thyroid but also in the extraocular eye muscles and retrobulbar fat tissues. It is thought that circulating TSH receptor autoantibodies (TRAbs) trigger inflammation and activation of orbital fibroblasts leading to intraorbital swelling in an early active stage and, subsequently, to fibrosis at a later stage [4–6]. Active GO is characterized by an inflammatory response which may involve the ocular surface, extraocular muscles, and other orbital tissue. Depending on the site of inflammation, the disease may cause dry eye symptoms or conjunctival chemosis, while the increased orbital volume may cause proptosis and eye movement disorders [2, 7].

The pathogenesis of the acute inflammatory stage has been attributed to autoimmunity, but a number of clinical and experimental studies suggest that superior orbital vein congestion also plays an important role in the disease inflammatory staging and contributes to the development of clinical signs and symptoms (e.g., proptosis, muscle restriction, periorbital swelling, and chemosis) during the active stage of the disease [8–10]. These hemodynamic changes in orbital vessels can be observed by the orbital color Doppler examination; however, it is rarely performed, due to its poor reproducibility and repeatability [8–11]. As a consequence, novel diagnostic techniques able to assess orbital congestion are highly sought after. A prompt diagnosis and staging of disease activity and severity are mandatory to drive therapeutic approach and standardized management of GO. Recent evidence suggests that spectral domain optical coherence



(a) (b)

Figure 1: Patient with Graves' disease and orbitopathy showing a severe proptosis (a) as assessed by Hertel exophthalmometry (b).

tomography (SDOCT) examination may represent a useful, safe, and rapid diagnostic tool to evaluate GO activity [12, 13]. SDOCT has been recently developed to assess retinal and optic nerve morphology and to quantify thickness of choroidal vascularization by using the enhanced depth imaging (EDI) method [14]. The choroid is primarily a vascular structure that supplies oxygen and nutrients to the outer retina. The choroidal veins drain in the ophthalmic veins and are devoid of the valve; therefore, systemic conditions that affect blood flow in the ophthalmic veins may influence the choroidal thickening [15]. Several evidence showed changes of choroidal thickness during physiological variations and in a wide range of systemic conditions including inflammatory and vascular diseases such as Vogt Koyanagi Harada, Behçet syndrome, sarcoidosis, and migraine [16, 17].

The aim of this study is to evaluate changes of choroidal thickness in patients with Graves' disease and orbitopathy and their relationship with clinical features and activity of the disease.

2. Patients and Methods

2.1. Study Design. Eighteen consecutive patients with diagnosis of Graves' disease and orbitopathy were included in this retrospective study at the Department of Sense Organs of the University Sapienza of Rome. Eighteen healthy, age-matched volunteers were enrolled among the unaffected companions of patients attending the outpatients' service of the Eye Clinic of the University of Rome "Sapienza". Informed consent was obtained from all subjects involved in the study and the Local Ethics Committee approved the experimental protocol. The research followed the tenets of the Declaration of Helsinki.

All subjects were previously examined by an endocrinologist, and the laboratory diagnosis of Graves' disease was based on the finding of undetectable serum TSH and high blood thyroid hormone associated with the presence of circulating antibodies (TRAb). Clinical history was collected, and all patients underwent a complete eye examination including (i) exophthalmometry with Hertel instrument (Figure 1), (ii) measurement of eyelid aperture, (iii) assessment of subjective diplopia using Gorman score (0: no diplopia, 1: intermittent diplopia, 2: inconstant diplopia, and 3: constant diplopia) [7], (iv) measurement of visual acuity, (v) assessment of corneal status, (vi) fundus examination, (vii) ocular biometry (IOL Master, Carl Zeiss Meditec, Dublin, CA), and (viii) OCT.

Patients were included if they met the following criteria: (i) age 18 years or more, (ii) diagnosis of Graves' disease in the last 12 months, (iii) euthyroid in treatment with antithyroid drugs, and (iv) first episode of GO. All patients and controls included in this study did not use systemic steroids. To ensure reliable choroidal thickness assessment by SDOCT-EDI, all women were evaluated in the first week after menstruation and all patients with conditions associated with choroidal changes were excluded including refractive error $> \pm 3$ spherical equivalent; axial length $<$ 22 mm and $>$26 mm; intraocular pressure $>$ 18 mmHg, cup/disc ratio $>$ 0.5; any other systemic disease; any other ocular disease, such as glaucoma, uveitis, or central serous chorioretinopathy; history of uveitis or central serous chorioretinopathy; previous intraocular surgery; use of topical medication or systemic therapy with known interference on choroidal thickness such as steroids and diuretics; and low quality ($<$20 units) OCT images.

The activity of GO was assessed through the clinical activity score (CAS), [18, 19]. According to the EUGOGO (European Group of Graves' Orbitopathy) guidelines, patients were divided into nonactive GO (CAS $<$ 3) and active GO (CAS $\geq$ 3). The severity of GO was also assessed based on these guidelines and rated as mild, moderate to severe, and sight threatening (very severe).

2.2. Optical Coherence Tomography. Included patients and controls underwent optical coherence tomography (OCT) examination using the Heidelberg Spectralis (Spectralis Family Acquisition Module, V 5.1.6.0; Heidelberg Engineering, Heidelberg, Germany) with Heidelberg Eye Explorer (V 1.7.1.0; Heidelberg). The SDOCT images of the choroid were obtained by enhanced depth imaging modality, following a standardized protocol described elsewhere [20]. In brief, two high-quality 30° horizontal and vertical line scans through the fovea with 90 to 100 frames averaged for each scan were obtained for each eye and the image with the best visualization of the border between the choroid and sclera was used. Choroidal thickness was measured using the manual caliper tool provided with the software of the OCT device. The choroid was defined as the layer between the base of the RPE and the hyperreflective line or margin corresponding to the chorioscleral interface (Figure 2).

The subfoveal choroidal thickness from the horizontal and vertical line scans was measured by 2 physicians (Magda Gharbiya and Lucia Restivo) who were masked to the subjects' diagnosis, and values were averaged.

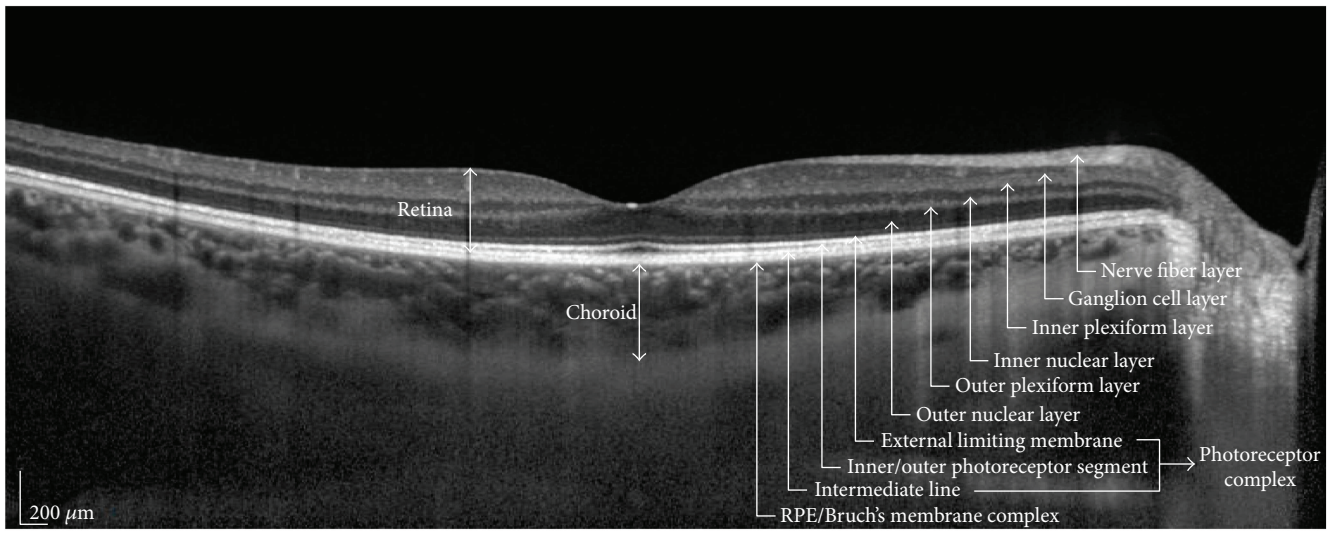


Figure 2: Optical coherence tomography scan showing the retinal layers and the macular choroidal thickness in a normal eye.

Table 1: GO patients versus controls: demographics and baseline clinical characteristics.

Variable	GO patients	Controls	p value
Age (years)	44.1 ± 9.8	44.2 ± 10.7	1.0*
Gender (male/female)	8/10	7/11	1.0§
Axial length (mm)	23.9 ± 0.8	24.0 ± 1.4	0.7*
Spherical equivalent (diopters)	−0.6 ± 1.3	−0.4 ± 1.7	0.5°
Intraocular pressure (mmHg)	14.0 ± 1.9	13.4 ± 1.6	0.2°
BCVA (number of ETDRS letters)	61.9 ± 2.3	62.3 ± 2.1	0.4*
Glycaemia (mg/dL)	80.8 ± 5.6	82.4 ± 6.3	0.4*
LDL cholesterol (mg/dL)	82.2 ± 12.4	81.9 ± 11.9	0.9*
Total cholesterol (mg/dL)	139.6 ± 13.3	132.2 ± 12.9	0.1*
Systolic blood pressure (mmHg)	123.9 ± 7.1	122.8 ± 6.7	0.6°
Diastolic blood pressure (mmHg)	71.6 ± 4.2	70.8 ± 4.3	0.6°
Smoking/no smoking	12/6	9/9	0.5§

Values are mean ± SD unless otherwise indicated. *Unpaired t-test with Levene's test for equality of variances. °Mann–Whitney U test. §Fisher's exact test.

2.3. Statistical Analysis. Statistical analysis was performed with the SPSS for Windows (V 17.0, SPSS, Chicago, IL, USA). Normal distribution of data was analyzed by the Kolmogorov–Smirnov test. Parametric variables were compared using the unpaired t-test. Levene's test was used to verify variance homogeneity. Nonparametric distributed values were analyzed by the Mann–Whitney U rank sum test. Categorical variables were compared using Fisher's exact test. OCT measurements between groups were compared using the general linear model, including age, gender, axial length, and smoking as covariates. Interobserver repeatability for choroidal thickness measurements was tested with the intraclass test/retest correlation. We followed the methods of Häner et al. [21].

Bivariate relationships were evaluated by the Spearman coefficient or the Pearson analysis as appropriate. Data are reported as mean values ± standard deviation. p values of less than 0.05 were considered as statistically significant.

3. Results

Thirty-six eyes of 18 patients (mean age, 44.1 ± 9.8 years; range, 24 to 57 years; 10 women and 8 men) with a diagnosis of GO and 36 eyes of 18 age-matched control subjects (mean age, 44.2 ± 10.7 years; range, 26 to 60 years; 11 women and 7 men; $p > 0.05$ for age and sex) were consecutively included in this study.

Demographic and clinical characteristics of the patients with GO and control subjects are summarized in Table 1.

In the patients' group, the mean duration of Graves' disease was 8.9 ± 2.0 (range, 5 to 12 months). Eight (55.6%) out of 18 patients had diplopia. The exophthalmometry

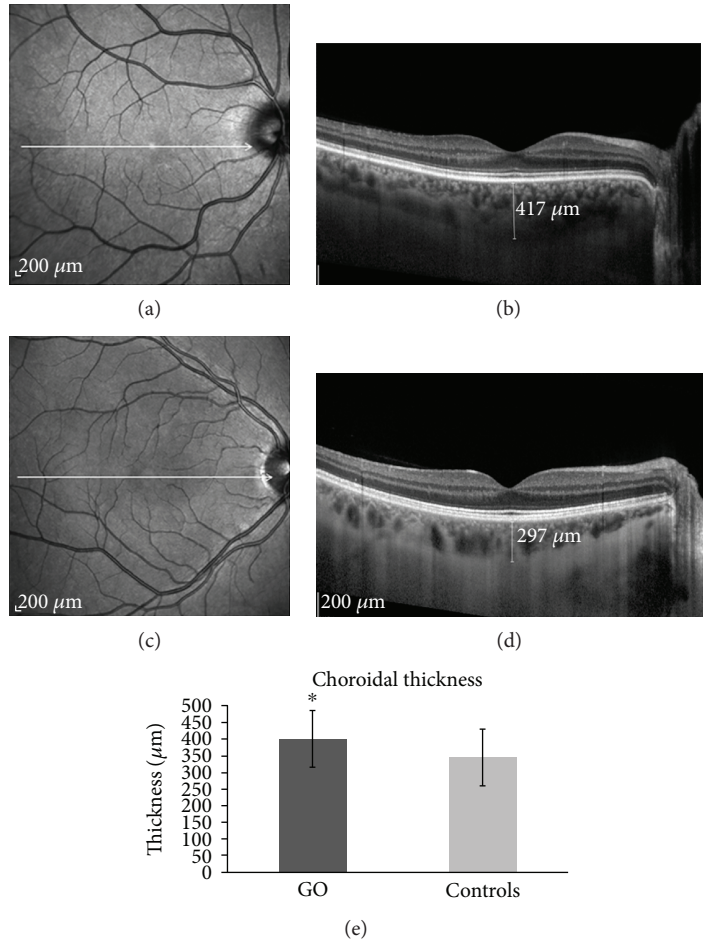


Figure 3: Subfoveal choroidal thickness measured by EDI SDOCT in a patient with Graves' orbitopathy (a, b) and in a healthy control (c, d). The graph (e) shows the significant increase of choroidal thickness (mean ± SD) in patients with Graves' orbitopathy ($n = 18$) versus controls ($n = 18$) ($^*p < 0.01$).

measurements ranged from 14 to 26 mm (mean ± SD, 20.1 ± 3.6 mm). According to the severity assessment, 10 (44.4%) patients had a mild GO, and 8 patients had a moderate to severe disease. No patient showed a sight-threatening GO. The CAS score was <3 in 10 patients and ≥3 in the remaining 8 patients.

The subfoveal choroid was significantly thicker in GO than in control eyes (399.2 ± 84.1 μm versus 344.5 ± 88.1 μm, respectively; $F = 9.6$, $p = 0.003$, adjusted for age, gender, axial length, and smoking) (Figure 3). The interexaminer correlation coefficients for the subfoveal choroidal thickness measurements were 0.98 (95% CI, 0.97–0.99).

Correlation analysis in the GO group showed a significant direct correlation between choroidal thickness and disease activity score (CAS) ($r = 0.40$, $p = 0.02$) as well as with the proptosis assessment with Hertel exophthalmometry ($r = 0.36$, $p = 0.03$). In patients with CAS ≥ 3, choroidal thickness was significantly increased than in the group with CAS < 3 (436.2 ± 97.5 μm versus 369.6 ± 89.3 μm, respectively, $p = 0.02$). Furthermore, choroidal thickness was negatively correlated with disease duration ($r = -0.43$, $p = 0.008$). No significant correlation was observed between choroidal thickness and habit of smoking, diplopia, or severity grading of GO.

4. Discussion

In this study, using newer generation, high-resolution, spectral domain OCT and EDI technique, we noninvasively assessed choroidal thickness change in a cohort of 18 GO patients. This study confirmed the previous studies reporting a significant increase in choroidal thickness in patients with GO when compared with healthy controls. In line with the other reports, we also found that choroidal thickness correlates with the clinical activity of GO (CAS score). In contrast with Ozkan et al., our data showed that the higher choroidal thickness in GO patients was significantly related with more severe proptosis. This finding may reflect the hemodynamics alterations of ophthalmic veins associated with orbital congestion. Indeed, increasing evidence suggests that ophthalmic vein congestion plays a significant role in the pathogenesis of the active stage of GO [9–11, 22]. A venous stasis has been described in several previous studies using color Doppler imaging, and a negative correlation has been found between

orbital blood flow parameters and the clinical activity scores of the ocular diseases [23]. The choroidal thickening found in our series is probably due to a reduced choroidal drainage in the ophthalmic veins and, similar to venous stasis, it correlates with the disease activity, including the degree of proptosis.

In our results, we further found a negative correlation between choroidal thickness and disease duration suggesting an early involvement of the choroid in the natural history of GO.

Hence, it is reasonable to speculate that choroidal thickness measurement in patients with GO may be used as an indirect parameter to estimate the degree of orbital congestion, especially in those patients with subclinical and early GO manifestations. It is known that orbital color Doppler imaging (CDI) is characterized by several limitations that may affect orbital congestion (i.e., difficulties in detecting retrobulbar vessels, the pressure applied on the globe may decrease flow velocity, and minimal lid and eye movements may cause artificial color noise) [23, 24]. In contrast, OCT is a noninvasive, no contact technique that may potentially overcome these aforementioned CDI-related limits.

The main limitations of the present study are the small sample size and that choroidal analysis was based on subjective, nonautomated measurements. Further investigations are needed to establish the diagnostic and prognostic role of OCT analysis of choroidal thickness in appropriate long-term follow-up of a larger GO population.

5. Conclusion

In conclusion, our results suggest a potential role of OCT choroidal thickness measurement in estimating the degree of orbital congestion in GO. In fact, choroidal thickness was significantly higher in patients with active and early GO and higher proptosis values. The noninvasive, no contact imaging modality of OCT is easily accessible and may enable the clinician to detect the retrobulbar GO involvement, even in those patients with subclinical manifestations and/or at the beginning of the disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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