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Temporal bone histopathology and immunoglobulin deposition in Sjogren's syndrome

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Abstract

Hypothesis—The histopathology of Sjogren's syndrome (SS) in the human inner ear correlates with mouse models of autoimmune inner ear disease (AIED).

Background—SS is an autoimmune disease in which 25% of patients have sensorineural hearing loss (SNHL). The inner ear histology in a SS mouse model has shown degeneration of the stria vascularis (SV) and IgG deposition on the basement membrane (BM) of SV blood vessels. Correlation with human temporal bone histopathology has not been addressed.

Methods—The histopathology and immunohistochemistry of the inner ear in 4 patients with SS is described and compared to SS mouse models.

Results—The histopathology of the inner ear in 3 patients with SS and SNHL showed severe loss of the intermediate cells of the SV and IgG deposition on the BM of SV blood vessels. These results parallel those of known SS mouse models. Additionally, there was shrinkage of the spiral ganglia neurons in two patients, while vestibular ganglia neurons were preserved. The fourth patient with SS and normal hearing showed only mild SV atrophy.

Conclusions—This is the first study describing the pathological changes in the inner ear of 4 patients with SS. The 3 SS specimens with SNHL showed pathologic changes in the SV similar to the mouse model of AIED. Additionally, we propose that spiral ganglia neurons may be directly affected by SS pathology. These results highlight the importance of correlating the histopathology of human temporal bones with animal models to better understand inner ear disease in future research.

Introduction

SS is the second most common autoimmune rheumatic disease affecting approximately 500,000 to 2 million patients in the United States. It is characterized by keratoconjunctivitis sicca and xerostomia resulting from lymphocytic infiltration of the lacrimal and salivary glands (1). Some patients demonstrate systemic manifestations such as skin lesions, Raynaud phenomena, interstitial pneumonitis, autonomic dysfunction, and central nervous system dysfunction, which are attributed to the deposition of immune complexes.

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Hearing loss is believed to be the first otologic manifestation of SS. In a study of 40 female SS patients, 22.5% of patients demonstrated cochlear sensorineural hearing loss (SNHL) mainly in the high frequencies and was associated with disease duration (2). Also, subclinical SNHL is likely more common than clinically significant SNHL in patients with SS. In a study of 30 patients with primary SS and 40 age-matched controls, 46% of the SS group had SNHL ($p < 0.001$). While 5 patients had clinically significant SNHL, 9 had SNHL detected only by audiologic evaluation (3).

SS is one of several autoimmune disorders in which hearing loss has been described. This group of “autoimmune inner ear disorders” (AIED) was first described by McCabe in 1979 (4). AIED are believed to be associated with immunoreactivity to inner ear components and describe a syndrome of SNHL often accompanied by vertigo and tinnitus responsive to immunosuppressive treatment (5,6). The pathogenesis of immune-mediated SNHL is unclear but may include immune complex-mediated vasculitis in the inner ear or autoantibodies directed against inner-ear antigenic epitopes (3).

The histopathologic changes of the inner ear have been described in the MRL/lpr mouse model of immune-mediated inner ear disease (7,8). In studies of these mouse models, there is degeneration of stria intermediate cells and IgG deposition on the basement membrane (BM) of stria blood vessels. To our knowledge, the histopathology of the inner ear in humans with SS has never been reported. We describe here the histopathology of the inner ear in four patients with SS and correlate these findings to known mouse models of autoimmune disease.

Materials and Methods

The temporal bones of four patients with SS were harvested at the time of autopsy (Table 1). The Institutional Review Boards of UCLA and the Massachusetts Eye and Ear Infirmary approved this study. The temporal bone donors are part of a National Institute of Health funded Human Temporal Bone Consortium for Research Resource Enhancement through the National Institute on Deafness and Other Communication Disorders. Appropriate informed consent for inclusion in the study was obtained from each temporal bone donor before death.

Patient 1 was a 55-year-old female at the time of death, diagnosed with juvenile rheumatoid arthritis and SS at the age of 14. Audiograms at ages 39 and 42 showed bilateral mild high frequency SNHL and she complained of increased hearing loss toward the end of her life. The patient developed poorly differentiated histiocytic lymphoma and was treated with multiple rounds of chemotherapy (cytoxan, vincristine, prednisone) with steroids in the 6 months prior to her death. Patient 2 was a 65-year-old female at the time of death with SS diagnosed at age 60. There are no available audiograms, but clinical notes document bilateral hearing loss. The patient expired from congestive heart failure due to a systemic vasculitis. Autopsy confirmed SS and also showed glomerular disease consistent with lupus nephritis. Patient 3 was a 63-year-old female at the time of death, with adult onset SS and Felty's syndrome (rheumatoid arthritis, splenomegaly, leukopenia, and pigmented cutaneous spots). The patient had a long history of progressive left greater than right hearing loss and five months prior to her death, an audiogram showed a flat bilateral SNHL averaging around 50 dB. Patient 3 ingested large amounts of salicylates; serum levels around the time of her audiogram were 20.5mg/100ml and 11.5mg/100ml. Patient 4 was a 66-year-old female with a diagnosis of SS with an audiogram 3 years prior to death showing normal hearing.

The temporal bone specimens from patients 1, 2 and 4 were fixed in 10% formalin solution at the time of collection; specimen 3 was fixed in Heidenhain-Susa solution and decalcified

in trichloroacetic acid. All specimens were embedded in celloidin. Serial sections were obtained in the axial plane at 20 μ m thickness. Every 10th section was stained with hematoxylin and eosin. Celloidin sections were stained for periodic acid-Schiff (PAS) to visualize extracellular matrix depositions. Temporal bone specimens were retrieved from the Victor Goodhill Temporal Bone Bank at the University of California-Los Angeles and from the Massachusetts Eye and Ear Infirmary Temporal Bone Bank. The area of spiral ganglia neurons was computed using the CAST-grid morphometry system.

Immunohistochemistry was performed on the celloidin embedded sections. Celloidin sections were floated in 80% ethanol and mounted on subbed glass slides (9). Sections were incubated with a blocking solution containing bovine serum albumin and Triton X-100 at 20°C for one hour. Incubation with IgG1 antibody was performed for 48 hours at 4°C. Sections were incubated for one hour with biotinylated 2nd antibody at 20°C. Incubation was then performed with Vectastain Elite ABC reagent (Vector laboratories; Burlingame, CA, USA) and staining was completed using Diaminobenzidine solution.

Results (Summarized in Table 1)

Loss of cells in stria vascularis (SV) in SS

The cochleas from patients 1, 2 and 3 showed SV atrophy with evidence of vacuolization. A low magnification view of the cochlea from SS patient 1 is shown in Fig. 1A with higher magnification views shown along the apical, middle and basal turns (Fig. 1B-D). Atrophy and vacuolization within the SV is evident. The cochlea is normal in appearance with a mild collapse of Reissner's membrane. Figure 2 shows a higher magnification view of the organ of Corti from patient 1, which appeared normal with preservation of the inner and outer hair cell architecture. The morphology of the cochlea from patient 2 was similar to patient 1 (not shown here).

Similarly, in patient 3, there was evidence of SV atrophy and mild vacuolization in the intermediate cell area (Fig. 3A, B). However, unlike patients 1 and 2, the organ of Corti from patient 3 shows degeneration of the inner and outer hair cells with preservation of the architecture of Reissner's membrane (Fig. 3A1, higher magnification).

In the patient with documented SS and normal hearing (patient 4), the cochlea was relatively normal. There was only mild atrophy in the SV with a preserved Reissner's membrane and organ of Corti (Fig. 4A-C).

SV BM thickening

The BM was thickened under the stria marginal cells in SS specimens 1 and 2 adjacent to the basal cells, which was demonstrated with the deposition of PAS positive material (Fig 5A). A normal age-matched cochlea specimen is shown for comparison (Fig 5B). The fibrocytes in the spiral ligament were well-preserved.

Shrinkage of spiral ganglia neurons

In SS patients 1 and 2, there was marked shrinkage of the neurons of the spiral ganglia in the apical, middle and basal turns (Fig. 6A-C). The cross sectional areas of the spiral ganglia neurons from both SS patients 1 and 2 were decreased by 50% in the apical, middle and basal turns when compared to the normal specimen (Fig. 6D). The spiral ganglia neurons in SS patient 3 (Fig. 3C) and SS patient 4 did not show any shrinkage or abnormality, and the cross sectional areas of the spiral ganglia neurons did not differ significantly from those of age-matched normal control specimens.

Immunohistochemistry showing IgG antibody deposition within capillaries of SV

IgG antibody deposition was seen in the capillaries within the stria vascularis in SS patients 1, 2 and 3 (Fig. 7A, 7A1, 7B). Specimen 4 (from the normal hearing patient with SS) did not show IgG deposition within the SV (Fig. 7C). Figure 7D shows the stria vascularis incubated with the same antibodies in a normal age-matched specimen.

Normal vestibular end organs

The sensory epithelia and stromal tissue in the cristae and utricle of the vestibule from SS patients 1, 2 and 4 were well preserved (Fig. 8A and 8A1) when compared with a normal specimen (Fig. 8B and B1). In addition, Scarpa's ganglion appeared normal when compared with an age-matched control (Fig. 8A2). Patient 3 showed disorganized epithelium in both the utricle and cristae, which was similar to the degeneration seen in the organ of Corti (Fig. 3A1).

Discussion

SS is a chronic autoimmune disorder with no known etiology and is part of a broader group of secondary autoimmune inner ear disorders (AIED) in which varying degrees of SNHL develop. The pathogenesis of immune-mediated SNHL is unclear but may include immune complex-mediated vasculitis in the inner ear or autoantibodies directed against inner-ear antigens (3). Studies have thus far supported both hypotheses in SS and have been limited by the difficulty in obtaining human temporal bone specimens.

There have, however, been multiple studies examining the inner ear in murine models of autoimmune disease. The MRL-Fas (lpr) mouse is the proposed model of immune-mediated inner ear disease based on studies by Ruckenstein et al (7). These mice spontaneously develop multisystemic autoimmune disease and progressive hearing loss. Female MRL-Fas (lpr) autoimmune mice have been shown to have greater hearing loss than males (10), which is also true in human autoimmune disease. Autoimmune mice have also been shown to have higher levels of circulating antibodies to various reported cochlear antigens when compared to control mice (11). For these reasons, the MRL-Fas (lpr) mouse inner ear has been studied extensively.

While the MRL-Fas (lpr) mouse is the currently accepted murine model of autoimmune disease, there have been several studies questioning the degree of hearing loss in MRL-Fas (lpr) mice. Park et al. reported essentially unchanged ABR thresholds in 18-week versus 4-week old MRL/lpr mice (12). Inoue et al. also found no statistical difference in ABR thresholds between young and old MRL/lpr mice (13). They found IgG deposited on the capillary walls of the SV in mice of all ages, which led the authors to question whether this mouse model consistently has spontaneous deterioration of hearing. In contrast, Kusakari et al. found that 20-week-old mice had elevated hearing thresholds compared to 4-week-old MRL/lpr mice and 20-week old control mice (14). This group also reported that structures of the organ of Corti were well preserved under light microscopy. The authors noted deposition of IgG on the capillary walls in the SV in the older mice confirming studies done previously by Ruckenstein et al.

Histopathologic analysis of the autoimmune mouse inner ear has consistently shown cochlear pathology notable for stria vascularis antibody deposition and an absence of an inflammatory infiltrate. Furthermore, in examining antibody deposition in the stria vascularis of the MRL-Fas (lpr) mouse, Ruckenstein et al. noted that all antibody isotypes and subclasses could be identified within the stria vascularis in the absence of complement proteins (8). Other studies have suggested that cochlear cell surface DNA receptors are the potential targets of autoantibodies (15), which have been shown to bind with less affinity to

DNA in autoimmune mice. The hypothesis from these studies is that autoantibody binding to cell surface DNA receptors prevents DNA binding in cochlear membranous labyrinth cells, contributing to cochlear dysfunction (16). Under electron microscopy, the autoimmune mouse model exhibited cochlear pathology exclusively in the SV where cells demonstrated hydropic degeneration (17).

We describe here the first temporal bone histopathology in four patients with documented SS. Similar to the mouse model, the human inner ear specimens showed changes in the SV with increased antibody deposition, vacuolization and a thickened stria BM in three of the four specimens. This is the first study to our knowledge which correlates findings in patients with autoimmune disease to an animal model, further validating the MRL-Fas (lpr) mouse as a model for AIED and specifically for SS.

Patient 4 is unique in that she had documented SS without hearing loss. The only temporal bone abnormality in this patient was mild atrophy of the SV, similar to specimens from age-matched controls. The inclusion of this patient with SS, normal hearing, and essentially normal inner ear structures suggests that the histopathologic findings of SV atrophy with IgG deposition in patients 1-3 correlate with the degree of SNHL, and thus may be the underlying mechanism.

Interestingly, our study of the temporal bones in two of the patients with SS also showed shrinkage of the spiral ganglia neurons. This was also seen in a previous report by Sone et al. who described the histopathologic features in temporal bones of 7 patients with systemic lupus erythematosus (SLE) (18). These temporal bones also showed varying degrees of hair cell loss and atrophy of the SV. The loss of spiral ganglia neurons as a contributing factor in AIED represents another avenue for future research using a larger number of patients. Atrophy of the spiral ganglia may also contribute to hearing pathology in patients with SS-associated hearing loss. .

The animal model for autoimmunity has provided a large base of research regarding the etiology of AIED. Though our study is limited in number from the availability of human temporal bone specimens with clinically documented SS, we present the first description of temporal bone findings in four subjects with documented SS.

The study is also limited by other confounding clinical factors in the patients' histories, which is unavoidable given the high association of SS with other autoimmune diseases. Patients 1-3 had associated autoimmune diseases (juvenile rheumatoid arthritis in patient 1, SLE in patient 2, and rheumatoid arthritis in patient 3; see Table 1). It is therefore conceivable that these other systemic conditions are responsible for the presented temporal bone findings.

With regard to rheumatoid arthritis, there are not any reported human temporal bone studies to our knowledge. Sone et al. has published the only series of temporal bone findings in patients with SLE, though several of these cases were discussed in more detail in other publications by the same group (18-20). They reported varying degrees of SV atrophy and shrinkage of spiral ganglia neurons in the temporal bones of patients with SLE. Interestingly, in the 7 patients (14 temporal bones) with SLE studied by Sone et al., immunoglobulin deposition was not seen in the SV; this contrasts to our 3 patients with SS and some degree of hearing loss (patient 4 had SS and normal hearing) who did have IgG antibody deposition in the SV (Fig. 7). The authors attributed their negative immunohistochemistry results to antigenic instability or the use of immunosuppressive medications prior to death. We suspect the reason may lie in the technique used in performing immunohistochemistry, as even the positive control specimens with multiple myeloma were negative. It is possible that systemic autoimmune diseases such as SLE,

rheumatoid arthritis and SS have similar inner ear histopathologic findings, and therefore it is unknown the extent to which our reported findings are specific to SS. However, of note, the histopathologic findings in the three SS patients with documented hearing loss are similar, despite each of them having different accompanying autoimmune diseases.

The other confounding clinical factor was in patient 3, who had a significant salicylate exposure and an accompanying 50dB flat SNHL consistent with salicylate ototoxicity. In addition to SV atrophy and IgG deposition within the capillaries of the SV, patient 3 also had degenerative changes in the inner and outer hair cells of the organ of Corti as well as the vestibular endorgans. There have been several reports of temporal bone histopathology in patients known to have salicylate toxicity at similar doses to our patient. These patients, who had similar audiologic findings, had normal inner ear findings (21). Alternatively, there is also one report by de Moura and Hayden describing a patient with rheumatoid arthritis and high levels of salicylate exposure with a flat bilateral 50dB SNHL and recovery to 25dB (normal) after ceasing salicylate intake. That patient's temporal bone, harvested 13 months later, showed a normal organ of Corti and normal hair cells, but an atrophic SV and decreased spiral ganglia neurons. The authors concluded at that time that her temporal bone findings were more likely due to presbycusis than salicylate ototoxicity (22). Thus, though it is possible that the findings in patient 3 of mild SV atrophy and disorganized hair cells are in fact due to her salicylate exposure, it is unlikely given the deposition of IgG antibody in the SV and the fact that salicylate exposure has been shown to be reversible without any known longstanding affects in the inner ear.

SS, as in other AIED's, is clinically diverse and hearing loss is not a constant finding. There remains ongoing discussion regarding the relationship of autoimmunity and SNHL. Clearly, more studies are needed examining the effects of autoimmune disease on the inner ear with correlation to degree of SNHL. The histopathology from the presented human temporal bones with SS correlate well with the temporal bones in the murine model of autoimmunity, providing further validation for future research using the mouse model.

Conclusion

This is the first study describing the histopathologic changes in the inner ear of four patients with known SS. The findings of damage to the SV and deposition of IgG has also been described in mouse models of autoimmunity. Additionally, spiral ganglia neurons may be directly affected by SS pathology. These results highlight the importance of correlating the histopathology of human temporal bones with animal models to better understand inner ear disease in future research.

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FIG. 1.

The cochlea from SS Specimen 1. *A*, Low magnification view ($\times 40$) of the cochlea. *B*, High magnification view ($\times 200$) of the apical turn of the cochlea. *C*, Middle turn of the cochlea. *D*, Basal turn of the cochlea. There are signs of vacuolization in the SV in all 3 regions of the cochlea and collapse of Reissner's membrane. OC indicates organ of Corti; RM, Reissner's membrane; SL, spiral ligament. Hematoxylin and eosin (H&E). Bar is 100 μm in *A* and 200 μm in *B*, *C*, and *D*.

FIG. 2.

The organ of Corti in SS Specimen 1. Apical (*A*), medial (*A1*), and basal zone (*A2*) of normal organ of Corti. Apical (*B*), medial (*B1*), and basal zone (*B2*) of organ of Corti in SS Specimen 1. The organ of Corti is normal. ihc indicates inner hair cells; ohc, outer hair cells; tc, tunnel of Corti; tm, tectorial membrane. H&E. Bar is 100 μ m.

FIG. 3.

Cochlea from SS Specimen 3. *A*, Organ of Corti of SS Specimen 3 showing an atrophic SV and degenerated organ of Corti. *A1*, Higher magnification of organ of Corti showing degeneration of inner and outer hair cells. *B*, Higher magnification of the SV showing diffuse atrophy. *C*, Spiral ganglion neurons, which appear normal in SS Specimen 3. *B* indicates basal cells; I, intermediate; M, marginal. H&E. Bar is 100 μm in *A* and 20 μm in *A1*, 25 μm in *B*, and 120 μm in *C*.

FIG. 4. Cochlea of SS Specimen 4. Apical (*A*), medial (*B*), and basal zone (*C*) of cochlea showing mild atrophy of the SV and a normal organ of Corti and Reissner's membrane.

FIG. 5. PAS staining in SS specimen 1. *A*, Left-side panel shows the SV from Specimen 1, showing prominent deposition of PAS-positive material in the BM adjacent to basal cells (*B*). *B*, SV from a normal temporal bone, showing basal level of PAS-positive material. Bar is 100 μ m.

FIG. 6.

Spiral ganglia neurons (SGNs) in Sjogren's temporal bones. Apical (*A*), middle (*A1*), and base of cochlea (*A2*) in SS Specimen 1 showing shrinkage of SGNs (*arrows*). Apical (*B*), middle (*B1*), and base of cochlea (*B2*) in SS Specimen 2 also showing shrinkage of SGNs (*arrows*). Apical (*C*), middle (*C1*), and base of the cochlea (*C2*) in a normal specimen (H&E). Histogram (*D*) showing the cross-sectional area of SGNs in 2 SS specimens and 1 normal. The SGNs in SS specimens decreases significantly at the apical, middle, and basal turn, when compared with the normal.

FIG. 7.

Antibody deposition in SS specimens. *A*, IgG immunoreactivity in SV blood vessels (arrowheads) in SS Specimen 1. *A1*, High magnification of *A*. There was no immunoreactivity in the spiral ligament (SL). *B*, IgG immunoreactivity in SV blood vessels (arrowheads) of Specimen 3. *C*, IgG immunoreactivity in Specimen 4 did not show IgG deposition in the SV. *D*, Normal cochlea with no immunoreactivity in the SV. Cell nuclei (purple color) counterstained with hematoxylin. Bar is 200 μm in *A* and *B* and 40 μm in *B*.

FIG. 8. Vestibular end organs in SS specimen. *A*, Crista ampullaris, macula utriculi (*A1*), Scarpa's ganglion (*A2*) from SS Specimen 2. *B*, Crista ampullaris, macula utriculi (*B1*), and Scarpa's ganglion (*B2*) from normal specimen. The sensory epithelia (SE), stroma (ST), and ganglia in the SS specimens are normal. H&E. Bar is 100 μ m.

Summary of SS patients. SV: stria vascularis, OC: Organ of Corti, SGN: spiral ganglia neurons, IHC: Immunohistochemistry, ihc: inner hair cells, ohc: outer hair cells, RM: Reissner's membrane, N: Normal, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, ASA: aspirin.

Table 1

Patient	Age	Sex	Hearing Status	Vestibular symptoms	SV	OC	SGN	IgG IHC	Other Diseases
1	55	F	Bilateral High frequency SNHL	None known	Atrophic	Normal, collapse of RM		IgG in SV	Juvenile RA
2	65	F	Subjective bilateral hearing loss	None known	Atrophic	Normal, collapse of RM		IgG in SV	SLE
3	63	F	Flat bilateral SNHL (50dB)	None known	Mildly Atrophic	Disorganized ihc/ohc	N	IgG in SV	RA, ASA exposure
4	66	F	Normal	Mild Vertigo	Mildly Atrophic	Normal	N	No reaction	None known