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Cochlear histopathologic findings in patients with systemic lupus erythematosus: A human temporal bone study

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Abstract

Hypothesis—We hypothesized that, in archived human temporal bone samples from patients with systemic lupus erythematosus (SLE), a pathologic condition exists in the stria vascularis and cochlear hair cells.

Background—Sensorineural hearing loss is a common feature in SLE patients. However, the pathophysiologic mechanism of cochlear dysfunction is unclear.

Methods—We examined 15 temporal bone samples from 8 SLE patients, along with 17 samples from 10 age-matched healthy control patients. The samples were serially sectioned in the horizontal plane and stained with hematoxylin and eosin. We determined the area of the stria vascularis in a midmodiolar section of each cochlear turn. Then, we made cytocochleograms and calculated the percentage of missing inner and outer hair cells.

Results—The area of the stria vascularis in our SLE group was significantly smaller than in our control group. The number of remaining inner hair cells in our SLE group was smaller than in our control group; however, the difference did not reach statistical significance. The loss of outer hair cells in our SLE group was significantly higher than in our control group. There was a tendency toward a positive correlation between the loss of cochlear hair cells and the duration of SLE.

Conclusion—The stria vascularis and cochlear hair cells are affected in SLE patients. Our findings could provide the histopathologic basis for the cochlear dysfunction, including sensorineural hearing loss, experienced by SLE patients.

Keywords

cochlea; hearing loss; ear; hair cell; stria vascularis

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder of unknown etiology. It affects numerous organs and systems (including the skin, mucous membrane, joints, lungs, kidneys, brain, and heart) and has numerous clinical manifestations. Diagnostic criteria include skin lesions, mouth or nose ulcers, alopecia, arthritis, serositis, renal failure, seizures, psychosis, hemolytic anemia, leukopenia, thrombocytopenia, excessive autoantibody production, and low complement (C3, C4, or CH50) levels (1).

Otologic symptoms (hearing loss, tinnitus, and vestibular disorders) are not included in the diagnostic criteria for SLE. However, sensorineural hearing loss and tinnitus are associated with SLE (2). Inner ear dysfunction is frequently detected in both adult and pediatric SLE patients (3–5). Despite the high incidence of ear symptoms in SLE patients, a definitive management strategy for their hearing loss has not been established. Roverano et al. recommended audiometric tests as part of initial studies in all SLE patients, because more than 60% of them have asymptomatic sensorineural hearing loss (6). But García-Berrocal et al. reported no evidence of progressive hearing loss in SLE patients who did not describe hearing loss at the beginning of the study; therefore, García-Berrocal et al. recommend audiometric tests only for SLE patients who describe hearing loss (7).

A few studies have reported cochlear histopathologic findings in human temporal bone samples from SLE patients (8–10). However, to the best of our knowledge, no previous study has compared such findings in samples from SLE patients and healthy control patients. The purpose of our study was to compare histopathologic findings in the stria vascularis and cochlear hair cells of samples from SLE patients vs. age-matched healthy control patients.

Materials and Methods

Samples

We examined 15 temporal bone samples (from 1 male and 14 females), from a total of 8 SLE patients. The mean age $\pm$ standard deviation (SD) of those 8 patients was 40.3 ± 20.2 years (range, 14 to 76 years). Their mean duration $\pm$ SD of SLE was 11.8 ± 10.1 years.

In addition, we examined 17 temporal bone samples (from 11 males and 6 females), from a total of 10 age-matched healthy control patients. The mean age $\pm$ SD of those 10 patients was 45.0 ± 24.2 years (range, 9 to 67 years). The mean age in our SLE group and in our control group did not significantly differ.

We obtained samples from the human temporal bone collection of the University of Minnesota. All temporal bones had previously been removed at autopsy, fixed in 10% formalin solution, decalcified with ethylenediaminetetraacetic acid (EDTA), and embedded

in celloidin. Each temporal bone was serially sectioned in the horizontal plane at a thickness of 20 μm from superior to inferior. Every 10th section was stained with hematoxylin and eosin. This study was approved by the institutional review board of the University of Minnesota (0206M26181).

Area of Stria Vascularis

We measured the area of the stria vascularis in lower basal turn, upper basal turn, lower middle turn, upper middle turn, and apical turn of the cochlea in the midmodiolar section and in the 2 adjacent sections above and below; we determined the mean area of those 3 sections. To examine the sections, we used conventional light microscopy with a digital camera connected to a personal computer, whose monitor displayed the sections. Using commercially available image analysis software (SPOT Advanced software, SPOT Imaging Solutions, Sterling Heights, MI, USA), we determined the area of the stria vascularis—only the cellular part, excluding all observed cystic-like structures and concretions.

Loss of Cochlear Hair Cells

To reconstruct cochleae, we made standard cytochleograms, according to the methods of Schuknecht and Gacek (11). In each section, we counted the number of present and missing cochlear hair cells. In 3 turns (basal, middle, and apical) of the cochlea, we calculated the percentage of loss of hair cells by dividing the number of missing hair cells by the total number of hair cells possible in that turn.

Statistical Analysis

All data represent the mean $\pm$ SD. Because the data did not have normal distribution, we used the nonparametric Mann-Whitney *U* test to compare our SLE group and our control group. To determine correlation between our 2 groups, we used the Spearman rank correlation coefficient. Significance was defined as $P < 0.05$ (SPSS Statistics, IBM, New York, NY, USA).

Results

The 8 patients in our SLE group had characteristic features of SLE, such as skin rashes ($n = 7$), arthritis ($n = 6$), central nervous system involvement ($n = 6$), renal failure ($n = 5$), and cardiomyopathy ($n = 4$). All 8 SLE patients were treated with prednisolone, 7 were on an immunosuppressive agent, and 2 (who contributed 4 temporal bone samples) were on an ototoxic drug (gentamicin). Of the 4 SLE patients whose hearing level had been examined, all 4 had elevated bone-conduction thresholds.

The right cochlea of 22-year-old female was filled with fibrous tissue, with inflammatory cell infiltration. Normal cochlear structures (including the basilar membrane, organ of Corti, and stria vascularis) had completely disappeared (see Figure, Supplemental Digital Content 1, which demonstrates the light micrograph of a cross-section of a hematoxylin/eosin stained cochlea). One patient (47-year-old female) had cochlear hydrops in her right cochlea. The basophilic deposits were in the stria vascularis (Figure 1, 76-year-old female).

For all 8 patients with SLE in our study, the mean area $\pm$ SD of the stria vascularis in all 5 turns of the cochlea (lower basal turn, upper basal turn, lower middle turn, upper middle turn, and apical turn) is shown in Figure 2. The stria vascularis in our SLE group had degenerated (Figure 3A), and its area was significantly smaller than in our control group (Figure 3B). The area of the stria vascularis and the duration of SLE were not significantly correlated.

For all 8 patients with SLE in our study, the loss of cochlear inner hair cells is shown in Figure 4. The severity and extent of inner hair cell damage varied greatly in our SLE group. The mean loss of inner hair cells in our SLE group was higher than in our control group; however, the difference did not reach statistical significance in any cochlear turn.

The loss of inner hair cells in the basal cochlear turn and the duration of SLE were positively correlated ($P < 0.05$). But we noted only a tendency toward such a positive correlation with the loss of inner hair cells in the middle turn and the apical turn.

For all 8 patients with SLE in our study, the loss of cochlear outer hair cells is shown in Figure 5. The outer hair cells in our SLE group were affected (Figure 6A), as compared with normal controls (Figure 6B). The mean loss of outer hair cells in our SLE group in the basal turn ($P < 0.05$), the middle turn ($P < 0.05$), and the apical turn ($P < 0.05$) was significantly higher than in our control group.

The duration of SLE and the loss of outer hair cells in the basal turn ($P < 0.05$) and the middle turn ($P < 0.05$) were positively correlated. But we noted only a tendency toward such a positive correlation with the loss of outer hair cells in the apical turn.

Because 2 SLE patients (who contributed 4 temporal bone samples) were on an ototoxic drug (gentamicin), we excluded those 4 samples from one of our analyses, in order to avoid the effect of the ototoxicity of aminoglycoside antibiotics. Thus, for the 6 SLE patients *not* on gentamicin (who contributed 11 temporal bone samples), we compared their loss of cochlear inner (Figure 4) and outer (Figure 5) hair cells vs. our control group. We found no significant difference between the 2 groups in the loss of inner hair cells (Figure 4). In contrast, the loss of outer hair cells in those SLE patients *not* on gentamicin was significantly higher than in our control group—in all cochlear turns (Figure 5). But in those SLE patients *not* on gentamicin, we noted only a tendency toward a positive correlation between the duration of SLE and the loss of inner and outer hair cells.

Discussion

Hearing loss is frequently found in SLE patients (12). Such patients can develop sensorineural hearing loss during their course of the disease (13). A population-based retrospective cohort study involving 7,168 SLE patients showed that the disease was significantly associated with an increased risk of developing sensorineural hearing loss (14). Moreover, SLE patients can have abnormal distortion product otoacoustic emissions and abnormal transient evoked otoacoustic emissions (15). Audiovestibular symptoms and abnormal otologic examination results are not currently listed in the diagnostic criteria for SLE. However, audiologic examinations may be considered in the management of SLE.

One experimental SLE study involving C3H/lpr autoimmune strain mice showed accelerated age-related hearing loss, particularly in the high frequencies; cochlear dysfunction in the mice was the result of stria vascularis pathology (16). The atrophy of stria vascularis in SLE patients was reported (8); however, the control was not used in the study. In our human temporal bone study, we showed, for the first time, that the stria vascularis was more atrophic in our SLE group than in our control group. The stria vascularis regulates ionic concentrations within the endolymph and generates the endocochlear potential. Cochlea endolymph, produced by the stria vascularis, is essential for normal hearing. The degenerated stria vascularis with basophilic deposits that we found in the temporal bones of our SLE patients could have some role in cochlear dysfunction.

An experimental study reported that age-related cochlear hair cell loss in mice advanced from the basal turn to the apical turn, with a higher loss of outer hair cells than inner hair cells (17). Another experimental study also reported that outer hair cells were more vulnerable than inner hair cells in the rodent cochlea (18). Outer hair cells have both sensory and motor functions, so the interactive network of outer hair cells might be part of a feedback pathway to regulate cochlear sensitivity. Acoustic signals are primarily transmitted to the central nervous system through the inner hair cells, whereas the main task of the outer hair cells is to boost the acoustic stimulus by a feedback function. Destruction of outer hair cells results in a greatly elevated sound threshold (19). In our study, we clearly showed that cochlear hair cells were affected in temporal bone samples from SLE patients, whose hair cell loss predominantly occurred in outer hair cells (rather than inner hair cells). Sensorineural hearing loss in SLE patients might therefore be associated with cochlear hair cell damage.

A recent clinical study found a significant positive correlation between mean air-conduction hearing thresholds and the duration of SLE (20). Another recent cohort study showed that chronic inflammation and immune dysregulation, the characteristics of SLE, induce a high incidence of atherosclerotic vascular events and accelerated cardiovascular disease (21). The stria vascularis requires a high level of blood supply to maintain the endocochlear potential levels and that the impaired homeostasis of the cochlear blood supply due to arteriosclerosis results in degeneration of the stria vascularis (22, 23). A human temporal bone study by Nomiya et al. showed that patients with arteriosclerosis had a decreased number of cochlear hair cells, as compared with normal controls (24). In our study, the area of the stria vascularis in our human temporal bone samples from SLE patients was small, but did not significantly correlate with the duration of SLE. In contrast, we found a tendency toward a positive correlation between the loss of cochlear hair cells and the duration of SLE. Our findings suggest that the loss of cochlear hair cells is largely responsible for hearing loss in SLE patients.

In conclusion, hearing loss is a major complication of SLE. Systemic organ-nonspecific autoimmune diseases, including SLE, involve the inner ear, thereby inducing a secondary autoimmune inner ear disorder (25–27). In SLE patients, the stria vascularis and cochlear hair cells are affected. Our findings could provide the histopathologic basis for the cochlear dysfunction, including sensorineural hearing loss, experienced by SLE patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun.* 2014; 48–49:10–3.
2. Batuecas-Caletrío A, del Pino-Montes J, Cordero-Civantos C, Calle-Cabanillas MI, Lopez-Escamez JA. Hearing and vestibular disorders in patients with systemic lupus erythematosus. *Lupus.* 2013; 22:437–42. [PubMed: 23423252]
3. Gomides AP, do Rosário EJ, Borges HM, Gomides HH, de Pádua PM, Sampaio-Barros PD. Sensorineural dysacusis in patients with systemic lupus erythematosus. *Lupus.* 2007; 16:987–90. [PubMed: 18042593]
4. Gad GI, Mohamed ST, Awwad KS, Mohamed RF. Study of audiovestibular dysfunction in children with systemic lupus erythematosus. *Int J Pediatr Otorhinolaryngol.* 2013; 77:1561–6. [PubMed: 23916731]
5. Gad GI, Abdelateef H. Function of the audiovestibular system in children with systemic lupus erythematosus. *Curr Allergy Asthma Rep.* 2014; 14:446. [PubMed: 24803303]
6. Roverano S, Cassano G, Paira S, et al. Asymptomatic sensorineural hearing loss in patients with systemic lupus erythematosus. *J Clin Rheumatol.* 2006; 12:217–20. [PubMed: 17023806]
7. García-Berrocal JR, De Diego B, Roldán-Fidalgo A, et al. Young systemic lupus erythematosus patients with no hearing involvement: 10-year follow up. *J Laryngol Otol.* 2013; 127:38–42. [PubMed: 23217277]
8. Sone M, Schachern PA, Paparella MM, Morizono N. Study of systemic lupus erythematosus in temporal bones. *Ann Otol Rhinol Laryngol.* 1999; 108:338–44. [PubMed: 10214779]
9. Yoon TH, Paparella MM, Schachern PA. Systemic vasculitis: a temporal bone histopathologic study. *Laryngoscope.* 1989; 99(6 Pt 1):600–9. [PubMed: 2566880]
10. Fukushima N, Fukushima H, Cureoglu S, Schachern PA, Paparella MM. Hearing loss associated with systemic lupus erythematosus: temporal bone histopathology. *Otol Neurotol.* 2006; 27:127–8. [PubMed: 16371860]
11. Schuknecht HF, Gacek MR. Cochlear pathology in presbycusis. *Ann Otol Rhinol Laryngol.* 1993; 102(1 Pt 2):1–16. [PubMed: 8420477]
12. Kastanioudakis I, Ziavra N, Voulgari PV, Exarchakos G, Skevas A, Drosos AA. Ear involvement in systemic lupus erythematosus patients: a comparative study. *J Laryngol Otol.* 2002; 116:103–7. [PubMed: 11827581]
13. Abbasi M, Yazdi Z, Kazemifar AM, Bakhsh ZZ. Hearing loss in patients with systemic lupus erythematosus. *Glob J Health Sci.* 2013; 5:102–6. [PubMed: 23985111]
14. Lin C, Lin SW, Weng SF, Lin YS. Risk of sudden sensorineural hearing loss in patients with systemic lupus erythematosus: a population-based cohort study. *Audiol Neurotol.* 2013; 18:95–100. [PubMed: 23257626]
15. Karabulut H, Dagli M, Ates A, Karaaslan Y. Results for audiology and distortion product and transient evoked otoacoustic emissions in patients with systemic lupus erythematosus. *J Laryngol Otol.* 2010; 124:137–40. [PubMed: 19852869]
16. Trune DR, Kempton JB, Mitchell C. Decreased auditory function in the C3H/lpr autoimmune disease mouse. *Hear Res.* 1996; 95:57–62. [PubMed: 8793508]

17. McFadden SL, Ding D, Reaume AG, Flood DG, Salvi RJ. Age-related cochlear hair cell loss is enhanced in mice lacking copper/zinc superoxide dismutase. *Neurobiol Aging*. 1999; 20:1–8. [PubMed: 10466888]
18. Kariya S, Okano M, Maeda Y, et al. Role of macrophage migration inhibitory factor in age-related hearing loss. *Neuroscience*. 2014; 279:132–8. [PubMed: 25194790]
19. Fettiplace R, Hackney CM. The sensory and motor roles of auditory hair cells. *Nat Rev Neurosci*. 2006; 7:19–29. [PubMed: 16371947]
20. Maciaszczyk K, Durko T, Waszczykowska E, Erkiert-Polguj A, Pajor A. Auditory function in patients with systemic lupus erythematosus. *Auris Nasus Larynx*. 2011; 38:26–32. [PubMed: 20576373]
21. Koenig KF, Ribi C, Radosavac M, Zulewski H, Trendelenburg M, Swiss SLE cohort study (SSCS). Prevalence of vascular disease in systemic lupus erythematosus compared with type-1 diabetes mellitus: a cross-sectional study of two cohorts. *Lupus*. 2015; 24:58–65. [PubMed: 25182169]
22. Tabuchi K, Nishimura B, Tanaka S, Hayashi K, Hirose Y, Hara A. Ischemia-reperfusion injury of the cochlea: pharmacological strategies for cochlear protection and implications of glutamate and reactive oxygen species. *Curr Neuropharmacol*. 2010; 8:128–34. [PubMed: 21119884]
23. Kariya S, Cureoglu S, Fukushima H, et al. Vascular findings in the stria vascularis of patients with unilateral or bilateral Ménière's disease: a histopathologic temporal bone study. *Otol Neurotol*. 2009; 30:1006–12. [PubMed: 19668098]
24. Nomiya R, Nomiya S, Kariya S, et al. Generalized arteriosclerosis and changes of the cochlea in young adults. *Otol Neurotol*. 2008; 29:1193–7. [PubMed: 18833016]
25. Merchant, SN. Disorders of the immune system. In: Merchant, SN.; Nadol, JB., Jr, editors. *Schuknecht's Pathology of the Ear*. 3rd. Shelton: People's Medical Publishing House-USA; 2010. p. 537-570.
26. Bovo R, Ciorba A, Martini A. The diagnosis of autoimmune inner ear disease: evidence and critical pitfalls. *Eur Arch Otorhinolaryngol*. 2009; 266:37–40. [PubMed: 18777037]
27. Kariya S, Hızlı Ö, Kaya S, et al. Histopathologic findings in peripheral vestibular system from patients with systemic lupus erythematosus: A human temporal bone study. *Otol Neurotol*. 2015; 36:1702–7. [PubMed: 26571410]

Figure 1. Histopathologic findings in the upper basal turn of the left cochlea in the patient with systemic lupus erythematosus (SLE). The organ of Corti was relatively preserved. The stria vascularis was atrophic, and basophilic deposit (arrow) was observed in the stria vascularis. (hematoxylin and eosin staining)

Figure 2.

Mean area of the stria vascularis in the 8 systemic lupus erythematosus (SLE) patients (black bar) and in the 10 healthy control patients (white bar). The area of the stria vascularis in our SLE group was smaller than in our control group. * $P < 0.05$

Figure 3. Histopathologic findings showing the stria vascularis in the systemic lupus erythematosus (SLE) patient (A) and in the control patient (B). The stria vascularis in SLE patients was atrophic. (hematoxylin and eosin staining)

Figure 4.

Mean loss of cochlear *inner* hair cells in the 8 systemic lupus erythematosus (SLE) patients (black bar), in the 6 SLE patients *not* on gentamicin (gray bar), and in the 10 healthy control patients (white bar). The mean loss of inner hair cells in our SLE group was higher than in our control group; however, the difference did not reach statistical significance. n.s. = not significant

Figure 5.

Mean loss of cochlear *outer* hair cells in the 8 systemic lupus erythematosus (SLE) patients (black bar), in the 6 SLE patients *not* on gentamicin (gray bar), and in the 10 healthy control patients (white bar). The mean loss of outer hair cells in our SLE group in the basal, middle, and apical turns was significantly higher than in our control group. * $P < 0.05$

Figure 6. Histopathologic findings showing the inner (arrowhead) and outer (arrow) hair cells in the systemic lupus erythematosus (SLE) patient (A) and in the control patient (B). The loss of hair cells was detected in the patients with SLE. (hematoxylin and eosin staining)