Sensorineural hearing loss as a common manifestation in patients with mixed connective tissue disease

Evaluation of: Hajas A, Szodoray P, Barath S *et al.*: Sensorineural hearing loss in patients with mixed connective tissue disease: immunological markers and cytokine levels. *J. Rheumatol.* 36, 1930–1936 (2009). In this study, Hajas *et al.* examined the prevalence of sensorineural hearing loss in patients with mixed connective tissue disease and its underlying mechanisms by measuring a series of immunological markers. Sensorineural hearing loss is a frequent organ manifestation affecting nearly half of patients with mixed connective tissue disease. Raynaud's phenomenon, antiphospholipid and antiendothelial cell antibodies, increased serum levels of proinflammatory cytokines and a reduced number of regulatory T cells were found to be associated with sensorineural hearing loss in mixed connective tissue disease patients.

KEYWORDS: antiphospholipid antibody ▪ mixed connective tissue disease ▪ regulatory T cell ▪ sensorineural hearing loss

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Hajas *et al.* recently examined the prevalence of sensorineural hearing loss (SNHL) in patients with mixed connective tissue disease (MCTD) [1]. Auditory symptoms are relatively frequent, but apparently underestimated, in patients with connective tissue disease [2]. SNHL is rapidly progressive and accompanied by vertigo and/or tinnitus in some patients, but it is often asymptomatic. Since SNHL can be treated successfully in some patients when it is identified in an early disease phase, it is important for rheumatologists to be aware of this complication. SNHL has been observed in patients with various connective tissue diseases, including systemic lupus erythematosus (SLE) [3–8], Sjögren's syndrome [9], systemic sclerosis [10], Wegener's granulomatosis [11] and primary antiphospholipid syndrome (APS) [12], but SNHL in association with MCTD has never been described. In addition, vasculitis and immune complex-mediated inflammation are reported as potential pathogenic mechanisms for SNHL, although the involvement of these underlying mechanisms remains a mere hypothesis.

Methods

The study by Hajas *et al.* is a cross-sectional study evaluating 71 MCTD patients (two men and 69 women) aged 57.1 ± 7.9 years with disease duration of 14.5 ± 8.0 years. A total of 51 age- and sex-matched healthy individuals served as a control. All subjects underwent complete otolaryngologic and audiologic evaluations involving pure tone and speech audiometry. Immunological assessments included: antinuclear antibodies by indirect immunofluorescence; IgM rheumatoid factor by nephelometry; anti-U1RNP, anti-SSA, anti-SSB, anti-Jo-1, anti-Scl-70, anti-dsDNA, anticardiolipin (aCL) and anti-β_2-glycoprotein I antibodies by ELISA; anti-endothelial cell antibody (AECA) by a cellular ELISA with cultured human umbilical vein endothelial cells; and serum IFN-γ, TNF-α, IL-10 and IL-4 levels by ELISA. Finally, the absolute number of $CD4^+CD25^{high}$ Fox $P3^+$ naturally occurring regulatory T cells (Treg), and $CD4^+$ and $CD8^+$ T cells producing IL-10 were measured using flow cytometry combined with intracellular staining.

Results

Hajas *et al.* found that 33 (46%) of 71 patients with MCTD had SNHL by audiogram, whereas only 11 (22%) controls had SNHL ($p < 0.007$). Hearing loss in all patients was bilateral. There was no significant difference between MCTD patients with or without SNHL with regard to the patient age, duration of disease, or previous treatment with cytotoxic drugs or corticosteroids. A total of 10 (30%) out of 33 MCTD patients with SNHL complained of diminished hearing acuity, while the remaining 23 patients were asymptomatic and hearing loss was detectable only on audiograms. In patients with MCTD, SNHL was associated with Raynaud's phenomenon (relative risk [RR]: 3.1; 95% CI: 1.1–8.7; $p = 0.03$), secondary APS (RR: 3.3; 95% CI: 1.0–10.8; $p = 0.05$), anti-U1RNP antibody (RR: 2.683; 95% CI: 1.0–7.0; $p = 0.05$), IgG aCL (RR: 37.0; 95% CI: 9.7–141; $p = 0.0001$) and AECA (RR: 8.8; 95% CI: 3.0–25.6; $p = 0.0001$).

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The association between aCL and SNHL was also detected in controls: aCL was detected in 27% of individuals with SNHL versus none of those without SNHL ($p < 0.008$), indicating that aCL is a risk factor for developing SNHL irrespective of the presence or absence of MCTD. Interestingly, aCL positivity was transient in eight patients with MCTD and SNHL, while the remaining 11 patients had had thrombotic events and fulfilled the diagnostic criteria for APS [13]. Serum concentrations of IFN-γ, TNF-α and IL-10 were significantly higher in patients with MCTD compared with controls, but IL-4 levels were similar between these two groups. The levels of IFN-γ and TNF-α were increased in MCTD patients with SNHL compared with those without SNHL ($p < 0.05$ for both comparisons), while there was no difference in IL-10 level. Tregs were decreased, but IL-10-producing $CD4^+$ T cells were increased in MCTD patients, compared with controls ($p < 0.001$ for both comparisons). Further analysis showed that Tregs were the only regulatory T-cell population reduced in MCTD patients with SNHL compared with those without SNHL ($p = 0.05$). Finally, the absolute number of Tregs was negatively correlated with the serum levels of aCL ($r = -0.742$; $p < 0.001$) or anti-U1RNP antibody ($r = -0.598$; $p < 0.01$).

Discussion

Several interesting findings are described in this study. First, SNHL was detected in nearly half of MCTD patients. The frequency of SNHL in MCTD patients appears to be higher than expected by the majority of rheumatologists, and is comparable to the frequencies reported in other connective tissue diseases, including SLE, Sjögren's syndrome and systemic sclerosis (Table 1). In connective tissue disease, it is likely that SNHL is a part of the systemic disease process, which involves the inner ear, causing auditory dysfunction. It is of note that SNHL observed in all MCTD patients was bilateral, while both unilateral and bilateral SNHL were reported in nearly equal frequencies in the previous studies analyzing patients with SLE [3–5,7,8]. This may reflect differences in pathogenic processes of SNHL between MCTD and SLE. Perhaps the most important message in this study is that SNHL often occurs slowly over several months or years in MCTD patients without notice. Therefore, audiologic evaluations should be routinely performed in rheumatology clinics.

This study provided valuable information on the pathogenic processes of SNHL in patients with MCTD by comprehensive analysis of immune parameters. Since MCTD is an immune-mediated disease, it has been postulated that vasculitis within the cochlea may involve the internal auditory artery, although this process appears to be more relevant to acute symptomatic SNHL. On the other hand, a report examining the temporal bone of SLE patients by autopsy found loss of hair cells, atrophy of the stria vascularis and spiral ganglion damage [14], indicating that chronic ischemic change of the inner ear plays a more important role in the pathogenesis of SNHL, especially in the chronic form. In this regard, the study by Hajas *et al.* [1] demonstrated cardinal associations of SNHL with Raynaud's phenomenon and aCL in MCTD patients. Raynaud's phenomenon is one of the typical features of MCTD and results from recurrent vasospasm in the presence of the obliterative vascular change, often associated with exposure to cold temperature or emotional stress. Raynaud's phenomenon affects the fingers and toes, but may involve internal auditory artery in patients with MCTD. On the other hand, it has been reported that antiphospholipid antibodies are involved in the pathogenesis of SNHL in patients with connective tissue disease as well as in idiopathic cases, presumably by causing microthrombus formation in the small vessels of the labyrinthine circulation [15]. In contrast to these mechanisms, several indirect lines of evidence reported by Hajas *et al.* and others demonstrated the potential involvement of immune-mediated mechanisms in the pathogenesis of SNHL [1]. These included associations of SNHL with AECA, increased circulating levels of IFN-γ and TNF-α, and reduction of Tregs in patients with MCTD. Since AECA is known as the pathogenic autoantibody that binds to endothelial cell antigens

Table 1. Frequency of sensorineural hearing loss in various connective tissue diseases.

Disease	Study (year)	Patients evaluated (n)	Frequency of SNHL (%)	Ref.
SLE	Andonopoulos *et al.* (1995)	40	58	[3]
	Sperling *et al.* (1998)	84	33	[4]
	Kastanioudakis *et al.* (2002)	38	23	[5]
	Roverano S *et al.* (2006)	30	66	[6]
	Gomides *et al.* (2007)	45	16	[8]
	Karatas *et al.* (2007)	28	21	[7]
Sjögren's syndrome	Tumiati *et al.* (1997)	30	47	[9]
Systemic sclerosis	Kastanioudakis *et al.* (2001)	34	20	[10]
MCTD	Hajas *et al.* (2009)	71	46	[1]

MCTD: Mixed connective tissue disease; SLE: Systemic lupus erythematosus; SNHL: Sensorineural hearing loss.

and induces endothelial damage and activation, leading to microvasculopathy [16], one can hypothesize that AECA may cause endothelial cell activation and damage in the inner ear microcirculation. Upregulated expression of IFN-γ and TNF-α in MCTD patients with SNHL indicates potential involvement of inflammatory process in association with the T helper 1-type immune response. Impaired Treg function due to reduced numbers of Tregs may contribute to induction and/or promotion of SNHL by dysregulating the immune system. Together, these findings indicate that a variety of nonimmune and immune processes are involved in the pathogenesis of SNHL in patients with MCTD.

Future perspective

This study, along with others, demonstrates the heterogeneous mechanisms associated with SNHL in patients with connective tissue diseases, such as SLE and MCTD. Identification of the pathogenic mechanism of SNHL would be essential for development of specific therapies to this complication. Corticosteroids and immunosuppressants were shown to be effective in treating acute progressive SNHL [17], but are unlikely to be effective against asymptomatic SNHL, typically seen in patients with MCTD. Potential drugs that may be useful in treating SNHL in patients with MCTD include prostanoids and calcium channel blockers used for treatment of Raynaud's phenomenon, and aspirin and anticoagulation therapies used for the treatment of APS. Alternatively, molecular targeting therapies, such as TNF-α blockade, may be effective. Further studies to investigate the effectiveness of these potential therapies are warranted.

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Executive summary

- The study by Hajas *et al.* indicates that sensorineural hearing loss is fairly common in patients with mixed connective tissue disease.
- Since sensorineural hearing loss observed in mixed connective tissue disease patients is often asymptomatic, audiologic evaluations should be performed to find this manifestation.
- The study by Hajas *et al.* and the literature on the subject demonstrated that Raynaud's phenomenon, antiphospholipid antibody, overexpression of inflammatory cytokines and dysregulated immune regulatory mechanisms play a role in the pathogenesis of sensorineural hearing loss.

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