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Hearing Assessment in Adult Patients with Common Variable Immunodeficiency

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ABSTRACT

Objective: Common Variable Immunodeficiency (CVID) is a primary antibody disorder characterized by impaired B cell differentiation. Patients commonly present with acute and chronic sinusitis as well as otitis media, which may lead to hearing loss.

Materials and Methods: Thirty-three CVID patients (20 male /13 female) with a mean age of 35 years (range 19-65 years) and 33 healthy individuals as a control group were included.

Results: Among CVID patients, 17 (51.5%) had conductive hearing loss (CHL) , being unilateral in 4 (12.1%) and bilateral in 13 (39.4%). Unilateral and bilateral sensorineural hearing loss (SNHL) were detected in 2 (6.1%) and 5 (15.2%) respectively. CD4/CD8 cell ratio was significantly lower while CD8+ T lymphocyte ratio was significantly higher in those with CHL than in those without it (p=0.045 and p=0.009). Elevated CD8+ T cell ratio was an independent risk factor for CHL (p=0.015). Patients with SNHL were significantly older than those without it (p=0.040). CD16-56+ cell count was significantly lower in those with SNHL (p=0.031).

Conclusion: CVID patients have an increased occurrence of CHL and SNHL, regardless of the cause. They provide evidence for the notion that these two types of hearing loss are not unrelated, immune dysregulation also plays a role in the process, and SNHL is not independent of CHL.

Keywords: Common variable immune deficiency, conductive hearing loss, sensorineural hearing loss

INTRODUCTION

Common Variable Immunodeficiency (CVID) is a primary antibody disorder characterized by impaired and/or inadequate B cell differentiation (1). Patients with CVID have an increased risk of frequent and recurrent infections, chronic lung diseases, autoimmune disorders, gastrointestinal diseases, and malignancy (1). Although many organs and systems may be affected, infections show a predilection for the lower and upper airways (2). Patients commonly present with acute and chronic sinusitis and otitis media, which may lead to conductive hearing loss (CHL) in untreated patients (3). Furthermore, these patients may experience sensorineural hearing loss (SNHL) due to several factors such as the increased risk of autoimmunity, prophylactic antibiotics, or effects of toxins produced by microorganisms on the inner ear structures (4). Studies evaluating otologic findings in adult patients with CVID are very few in number. Therefore, we aimed to evaluate conductive and sensorineural hearing in patients with CVID.

MATERIAL and METHODS

Study Population

This study was conducted at the Department of Immunology and Allergy (Necmettin Erbakan University, Meram Faculty of Medicine) with the inclusion of 33 adult CVID patients receiving regular immunoglobulin replacement as well as 33 age- and gender-matched controls with no known medical conditions. An Ear Nose Throat physician evaluated all CVID patients. Audiological tests of patients with tympanic membrane rupture, chronic

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otitis, otitis with effusion, and otosclerosis were performed after treating these pathologies. Exclusion criteria were the use of diuretics, salicylates, or cisplatin; the presence of functional (Arnold Chiari malformation) or anatomic malformation affecting the nervous system; underlying disorders associated with hearing loss (jaundice of the newborn, hearing loss due to trauma, history of congenital injections); a history of ototoxic drugs; patients with congenital hearing loss and history of acoustic trauma. Patients with lymphocyte count less than 1000 cells/mm^3 were considered lymphopenic. The Institutional Ethics committee approved the study protocol. Informed consent was obtained from study participants.

Immunological Analyses

The quantitative evaluation of serum immunoglobulins (IgG, IgM, IgA, and IgE) was performed by particle-enhanced immunonephelometry using a Siemens BN II / BN ProSpec system (Erlangen, Germany). Complete blood counts were performed with Sheath reagent using an Abbott Cell Dyn 3700 (USA) device. Peripheral blood lymphocyte subsets were measured with BD FACSCanto II flow cytometer, using an eight-color configuration (San Jose, CA, USA) with fluorescent-labeled antibodies. CVID diagnosis was based on the ESID (European Society of Immune Deficiency) criteria (5).

Spirometric Measurements

Spirometric measurements were obtained using a standard protocol with the nSpire ZAN 100 spirometer (Health Inc., Germany). At least three maneuvers were performed; however, additional maneuvers were also performed if one or more of the curves was unacceptable. The forced expiratory volume (FEV) within one second (FEV1), FEV1 / FVC ratio (forced vital capacity), peak expiratory flow (PEF), and mean expiratory flow 25-75% (MMEF25-75) were recorded.

Audiological Tests and Description of Hearing Loss

For audiology tests, an AC33 clinical audiometer device (Assens, Denmark) was used. An impairment >20 dB of the bone threshold for at least one frequency (500 Hz, 1000 Hz, 2000 Hz, 4000 Hz) was considered SNHL. All audiological tests were performed by an experienced audiometrist. An impairment >20 dB of air threshold for at least one frequency (500 Hz, 1000 Hz, 2000 Hz, 4000 Hz) was considered CHL. An impairment >20 dB of both air and bone threshold for at least one frequency was considered as mixed type hearing loss.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation, and skewed parameters were expressed as median (interquartile range: minimum-maximum). Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann–Whitney rank-sum, Fisher exact or Chi-square tests where appropriate. A binomial logistic regression analysis was performed to determine independent predictors for SNHL and CHL. We used the One-way Anova test for those parameters with normal distribution and homogenous variances in patients without hearing loss, patients with pure conductive hearing loss, and mixed hearing loss patients. We used a Kruskal-Wallis method if a parameter did not show a normal distribution or homogeneity between variances. Tamhane's T2 test was used for post hoc analysis. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

Thirty-three CVID patients (20 male and 13 female) with a mean age of 35 years (range 19-65 years) who had adequate data in the medical files and agreed to participate in the study were included. The control group consisted of 33 age- and sex-matched healthy individuals.

Among CVID patients, 17 (51.5%) had CHL, being unilateral in 4 (12.1%) and bilateral in 13 (39.4%). Also, unilateral and bilateral SNHL were detected in 2 (6.1%) and 5 (15.2%) CVID patients, respectively. Additionally, ten patients (30.3%) had pure conductive, and seven (21.2%) had mixed type hearing loss. Bone and air conduction tests were in the normal range in all control subjects.

The air and bone hearing test results in CVID patients were 6.90 ± 5.75 dB and 8.26 ± 6.51 dB for the right ear, and 2.00 (0-27) dB and 1.0 (0-20.30) dB for the left ear, respectively. The corresponding values among controls were 7.71 ± 5.87 dB and 11.03 ± 5.96 dB for the right ear and 1.00 (0-11) dB and 4.40 (0.1-52) dB for the right ear, respectively. CVID and control subjects did not differ significantly in terms of mean and median air and bone conduction thresholds in the right and left ears (p=0.313, p=0.802, p= 0.905, and p=0.994, respectively) (Table I).

Patients with or without CHL were not significantly different in terms of age at diagnosis, current age, gender, consanguineous marriage between parents, presence/

absence of splenomegaly, history of azithromycin prophylaxis, presence/absence of bronchiectasis, forced expiratory volume at 1 sec. (FEV1); IgG, IgM, and IgA at diagnosis; and complete blood count results. CD4/CD8 T cell ratio was significantly lower in those with CHL than in those without it, while the $CD8^+$ T lymphocyte ratio was significantly higher in those with the CHL as compared to those without it (p=0.045 and p=0.009, respectively) (Table II).

Both univariate and multivariate regression analyses suggested that IgG at diagnosis, neutrophil count, lymphocyte count, platelet count, $CD4^+$ T ratio, and CD4/CD8 ratio were not independent risk factors for CHL, while elevated $CD8^+$ T lymphocyte ratio was an independent risk factor for CHL (p=0.015) (Table III).

Among the patient group, those with or without SNHL did not differ significantly concerning the age at diagnosis, current age, gender, consanguineous marriage between parents, presence of splenomegaly, history of azithromycin prophylaxis, presence of bronchiectasis, forced expiratory volume at 1 sec. (FEV1), IgG, IgM, and IgA at diagnosis, and complete blood count results. However, those with

Table I: Demographic and Otologic Properties of the Study Population

	Controls (n=33)	CVID (n=33)	P value
Gender (Female), n (%)	13 (39.4)	13 (39.4)	0.999
Current Age, years	35 (19-65)	35 (19-65)	0.999
Right ear, Air conduction threshold, dB	7.71 ± 5.87	6.90 ± 5.75	0.313
Right ear, Bone conduction threshold, dB	11.03 ± 5.96	8.26 ± 6.51	0.802
Left ear, Air conduction threshold, dB	1.00 (0-11)	2.00 (0-27)	0.905
Left ear, Bone conduction threshold, dB	4.40 (0.1-52)	1.0 (0-20.30)	0.994

CVID: Common variable immune deficiency

Table II: Demographic, clinic and laboratory properties of CVID patients with or without CHL

	Total (n=33)	Patients without CHL (n=16)	Patients with CHL (n=17)	P value
Gender (Female), n (%)	13 (39.4)	8 (50)	5 (29.4)	0.226
Current age, years	36.77 ± 13.42	34.8 ± 13.93	40.53 ± 12.38	0.245
Age at diagnosis, years	29.88 ± 14.06	28 ± 14.78	33.5 ± 12.83	0.220
Consanguinity, n (%)	14 (42.4)	8 (50)	6 (35.3)	0.579
Splenomegaly, n (%)	16 (48.5)	8 (50)	8 (47.1)	0.866
Prophylaxis, n (%)	26 (78.8)	13 (81.3)	13 (76.5)	0.737
Bronchiectasis, n (%)	20 (60.6)	8 (50)	12 (70.6)	0.226
Lymphopenia, n (%)	10 (30.3)	5 (31.3)	5 (29.4)	0.909
IgG, at diagnosis, (g/dl)	2.38 (0.33-7.48)	3.51 (1.17-6.90)	1.51 (0.33-6.71)	0.171
Lymphocyte count (mm^3)	1510 (400-8900)	1200 (553-2400)	1800 (400-8900)	0.087
Diagnostic delay, month	60 (0-360)	48 (0-264)	108 (0-360)	0.382
Platelet count (mm^3)	214166 ± 99769	180500 ± 106807	244812 ± 91888	0.084
$CD3^+$ T cell (%)	78.15 ± 11.00	76.86 ± 8.18	79.50 ± 13.85	0.506
$CD4^+$ T cell (%)	34.35 ± 14.25	39.93 ± 16.28	28.97 ± 10.44	0.068
$CD8^+$ T cell (%)	40.64 ± 14.11	33.20 ± 7.49	48.13 ± 15.20	**0.009**
CD4/CD8	0.84 (0.22-0.358)	1.14 (0.22- 3.58)	0.57 (0.23-1.79)	**0.045**
$CD19^+$ B cell (%)	6.88 ± 6.16	6.73 ± 5.38	7.13 ± 7.00	0.871
$CD16^+$-56^+ NK cell (%)	9 ± 6.42	8.60 ± 3.66	9.44 ± 8.61	0.832
IgD^- IgM^- $CD27^+$ B cells	2.4 (0-52)	2.20 (0-27)	2.5 (0-52)	0.901

CVID: Common variable immunodeficiency, **CHL:** Conductive hearing loss, **FEV1:** Forced expiratory volume in 1. Second, **Ig:** Immunoglobulin, **CD:** Cluster of differentiation, **NK:** Natural killer

SNHL were significantly older than those without it SNHL (p=0.040). Also, the CD(16-56)$^+$ NK cell ratio was significantly lower in those with SNHL (p= 0.031) (Table IV).

Both univariate and multivariate regression analyses suggested that age at diagnosis, current age, platelet count, azithromycin prophylaxis, CD (16-56)$^+$ NK cell ratio, and IgA at diagnosis were not independent risk factors for SNHL (Table V).

A significant difference was found between the CD8$^+$ T cell ratio among CVID patients with no hearing loss, pure CHL, and mixed hearing loss (p=0.026) (Table VI). The post hoc analysis showed that this difference was between the patients without hearing loss and those with pure CHL (p= 0.037) (Table VII).

Table III: Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and conductive hearing loss

Variables	Univariants		Multivariants	
	OR (95% CI)	P value	OR (95% CI)	P value
IgG, at diagnosis	0.781 (0.557-1.097)	0.154	1.281 (0.421-1.004)	0.317
Lymphocyte count	1.001 (1.000-1.002)	0.078	0.999 (0.999-1.002)	0.516
Platelet count	1000 (1.000-1.000)	0.096	1.000 (1.000-1.000)	0.155
CD4$^+$ T cell (%)	0.950 (0.898-1.006)	0.080	0.983 (0.908-1.064)	0.667
CD8$^+$ T cell (%)	1.086 (1.012-1.166)	**0.023**	1.107 (1.020-1.201)	**0.015**
CD4/CD8	0.300 (0.080-1.124)	0.074	1.209 (0.006-229.091)	0.943

Ig: Immunoglobulin, **CD:** Cluster of differentiation

Table IV: Demographic, clinic and laboratory properties of CVID patients with or without SNHL

	Total (n=17)	Patients without SNHL (n=10)	Patients with SNHL (n=7)	p
Gender (female), n (%)	5 (38.5)	3 (30)	2 (28.6)	0.949
Current age	40.53 ± 12.38	34.31 ± 12.91	45.93 ± 11.92	**0.040**
Age at diagnosis	33.5 ± 12.83	27.77 ± 13.96	37.71 ± 12.37	0.097
Consanguinity, n (%)	8 (47.1)	4 (40)	4 (57.1)	0.519
Splenomegaly, n (%)	8 (47.1)	6 (60)	2 (28.6)	0.201
Prophylaxis, n (%)	13 (76.5)	9 (90)	4 (57.1)	0.115
Bronchiectasis, n (%)	12 (70.6)	7 (70)	5 (71.4)	0.949
Lymphopenia, n (%)	5 (29.4)	3 (30)	2 (28.6)	0.949
IgG, at diagnosis, (g/dl)	1.51 (0.33-6.71)	1.85 (0.33-6.90)	3.66 (1.35-6.71)	0.789
Lymphocyte count (mm^3)	1800 (400-8900)	1300 (553-8900)	1900 (400-3500)	0.215
Diagnostic delay, month	108 (0-360)	60 (0-288)	96 (0-360)	0.949
Platelet count (mm^3)	244812 ± 91888	199942 ± 100957	267000 ± 80531	0.116
CD3$^+$ T cell (%)	79.50 ± 13.85	73.81 ± 9.00	75.71 ± 17.28	0.116
CD4$^+$ T cell (%)	28.97 ± 10.44	34.46 ± 14.94	33.93 ± 12.36	0.518
CD8$^+$ T cell (%)	48.13 ± 15.20	40.85 ± 14.83	39.86 ± 12.03	0.932
CD4/CD8	0.57 (0.23-1.79)	0.81 (0.22- 3.58)	1.00 (0.40-1.79)	0.983
CD19$^+$ B cell (%)	7.13 ± 7.00	6.62 ± 6.24	7.86 ± 6.23	0.644
CD16$^+$-56$^+$ NK cell (%)	9.44 ± 8.61	11.03 ± 5.96	8.26 ± 6.51	**0.031**
IgD$^-$ IgM$^-$ CD27$^+$ B cells	2.5 (0-52)	1.70 (0-0.52)	5.80 (0-20.30)	0.308

CVID: Common variable immunodeficiency, **SNHL:** Sensorineural hearing loss, **FEV1:** Forced expiratory volume in 1. Second, **Ig:** Immunoglobulin, **CD:** Cluster of differentiation, **NK:** Natural killer

Table V: Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and sensorineural hearing loss

Variables	Univariants		Multivariants	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, at diagnosis	1.053 (0.989-1.121)	0.107	0.979 (0.829-1.155)	0.789
Current Age, years	1.069 (0.999-1.144)	0.054	1.066 (0.990-1.149)	0.64
Platelet count	1.000 (1.000-1.000)	0.126	1000 (1.000-1.000)	0.132
Prophylaxis	4.125 (0.657-25.904)	0.131	8.320 (0.304-227.360)	0.209
$CD16^{+}$-56^{+} NK cell (%)	1.151 (1.001-1.323)	**0.048**	1.142 (0.989-1.317)	0.070
IgA, at diagnosis (%)	2.711 (0.633-11.603)	0.179	3.518 (0.489-24.326)	0.212

CD: Cluster of differentiation, **NK:** Natural killer, **Ig:** immunoglobulin

Table VI: Demographic and laboratory properties of CVID patients with, pure conductive hearing loss, mixed type hearing loss, and without hearing loss

	Patients without CHL (n=16)	Patients with pure CHL (n=10)	Patients with mix type HL (n=7)	P value
Gender (Female), n (%)	8 (50)	3 (30)	2 (28.6)	0.480
Current age, years	34.8 ± 13.93	34.31 ± 12.91	45.93 ± 11.92	0.124
Age at diagnosis, years	28 ± 14.78	27.77 ± 13.96	37.71 ± 12.37	0.221
Consanguinity, n (%)	8 (50)	4 (40)	4 (57.1)	0.708
Splenomegaly, n (%)	8 (50)	6 (60)	2 (28.6)	0.437
Prophylaxis, n (%)	13 (81.3)	9 (90)	4 (57.1)	0.250
Bronchiectasis, n (%)	8 (50)	7 (70)	5 (71.4)	0.388
Lymphopenia, n (%)	5 (31.3)	3 (30)	2 (28.6)	0.991
IgG, at diagnosis, (g/dl)	3.51 (1.17-6.90)	1.85 (0.33-6.90)	3.66 (1.35-6.71)	0.186
Lymphocyte count (mm^3)	1200 (553-2400)	1300 (553-8900)	1900 (400-3500)	0.203
Diagnostic delay, month	48 (0-264)	60 (0-288)	96 (0-360)	0.567
Platelet count (mm^3)	180500 ± 106807	199942 ± 100957	267000 ± 80531	0.162
$CD3^{+}$ T cell (%)	76.86 ± 8.18	73.81 ± 9.00	75.71 ± 17.28	0.419
$CD4^{+}$ T cell (%)	39.93 ± 16.28	34.46 ± 14.94	33.93 ± 12.36	0.119
$CD8^{+}$ T cell (%)	33.20 ± 7.49	40.85 ± 14.83	39.86 ± 12.03	**0.026**
CD4/CD8	1.14 (0.22- 3.58)	0.81 (0.22- 3.58)	1.00 (0.40-1.79)	0.069
$CD19^{+}$ B cell (%)	6.73 ± 5.38	6.62 ± 6.24	7.86 ± 6.23	0.811
$CD16^{+}$-56^{+} NK cell (%)	8.60 ± 3.66	11.03 ± 5.96	8.26 ± 6.51	0.090
IgD^{-} IgM^{-} $CD27^{+}$ B cells	2.20 (0-27)	1.70 (0-0.52)	5.80 (0-20.30)	0.909

CVID: Common variable immunodeficiency, **CHL:** Conductive hearing loss, **HL:** Hearing loss, **Ig:** Immunoglobulin, **CD:** Cluster of differentiation, **NK:** Natural killer

Table VII: Post hoc analysis of CVID patients according to $CD8^{+}$ T cell ratio

Parameters			P value
CD8+ T cell (%)	Patients with mix hearing loss	Patients with pure CHL	0.327
		Patients without hearing loss	0.646
	Patients with pure CHL	Patients with mix hearing loss	0.327
		Patients without hearing loss	**0.037**
	Patients without hearing loss	Patients with pure CHL	**0.037**
		Patients with mix hearing loss	0.646

CVID: Common variable immune deficiency, **CD:** Cluster of differentiation, **CHL:** Conductive hearing loss

DISCUSSION

Common variable immune deficiency (CVID) is the most common symptomatic antibody deficiency among adults and is characterized by recurrent and frequent infections, autoimmune disorders, and lymphatic malignancies (5). While infections such as otitis media and sinusitis are also common in these patients, studies assessing hearing loss associated with these infections are limited. External and middle ear injury due to recurrent infections, delayed diagnosis, or inadequate or inappropriate treatments may prevent sound waves' conduction to the inner ear, leading to CHL. In our study, CVID patients had a significantly increased CHL occurrence in both ears and at all frequencies compared to controls.

In addition to CHL, CVID patients may also develop SNHL due to the impact of recurrent infections and bacterial toxins on the cochlea and the increased risk of autoimmunity (6-9). Also, antibiotics used for the treatment of infections may lead to SNHL (10). Immunohistochemical studies have shown the presence of IgG and IgA in the inner ear and endolymphatic channel. This finding may suggest that the reduced serum IgG levels in CVID patients, as well as the lower IgA and/or IgM levels, may affect the immunoglobulin concentrations in the inner ear and endolymphatic channel and that a deficit in the immune responses may emerge in case of inflammation in the endolymphatic canal (11). In support of this view, Bertoli et al. detected subnormal IgG1 and IgG3 levels in patients with autoimmune SNHL (7). In that study, 3 of the 441 patients diagnosed with CVID/IgG subgroup deficiency had autoimmune SNHL (7). In the current study, SNHL was significantly more frequent among CVID patients as compared to controls.

Tavakol et al. found hearing loss in 54.5% of 55 patients with hypogammaglobulinemia, and of these, 73.3% had a CHL, while 23.2% had SNHL (4). In the Berlucchi et al. study involving 47 patients with CVID and XLA, SNHL was detected in 28% and 50% of these patients, respectively (12). Among our CVID patients, 51.5% had CHL, and 21.3% had SNHL. These figures are in line with the previous reports.

When CVID patients were grouped into those with or without CHL, a significant difference was found in the CD4/CD8 T cell ratio and $CD8^+$ T counts. An association between reduced CD4/CD8 T cell ratio and increased autoimmune complications and lymphoproliferative disorders has been reported in many studies on CVID (13-16). Muşabak et al. reported a low CD4/CD8 ratio, reduced IgG and B lymphocytes, and increased active T lymphocyte count in CVID patients (16). Again Mokhtari et al. found reduced memory B cells, reduced regulatory T cells, and increased $CD8^+$ T cell count in patients with reduced $CD4^+$ T counts (15). The decrease in regulatory cells and increased $CD8^+$ T cells suggest immune dysregulation. In the study by Tavakol et al., the decrease in CD4/CD8 T cell ratio was found to predict a CHL in CVID patients. Also, in the same study, other factors related to CHL in XLA patients included lymphopenia, lymphoproliferative complications, and absolute T cell count (4). In the current study, CHL patients had increased $CD8^+$ T cell ratio and reduced CD4/CD8 ratio compared to patients without CHL. Regression analysis showed that $CD8^+$ T cell count was an independent risk factor for CHL. This finding suggests that CHL in CVID patients may not be solely due to mechanical conduction defects, with contributions of lymphoproliferation, immune dysregulation, and T cell abnormalities to CHL development. CVID patients with or without SNHL also showed statistically significant differences in terms of current age and CD $(16\text{-}56)^+$ NK cell counts.

Age-related hearing loss is an important cause of SNHL, not only in patients with immune deficiency but also in the general population (17). Therefore, it is not surprising to observe that CVID patients with SNHL were older than those without. Also, in one study by Berlucchi et al., XLA patients with SNHL were older than those without XLA (12). Although Ig replacement therapy, which is the mainstay of treatment in this patient group, reduces the frequency of infections, some patients continue to experience recurrent infections involving mucosal surfaces. A plausible explanation for this phenomenon is related to the fact that the administered immunoglobulins fail to replace the secretory IgA in the mucosal membranes (4). Therefore, in patients with immune deficiency, SNHL may occur during later life stages despite Ig replacement due to the increasing frequency of infections, bacterial toxins, and antibiotic use (12).

Natural killer cells (CD16+-CD56+ T cells-NKs) are lymphocytes that have critical roles in the immune response against viral antigens and transformed cells. In experimental studies with mice, it has been shown that

NKs confer a protective effect against Cytomegalovirus infections, which represent one of the most common causes of non-hereditary SNHL (18). A study by Williams et al. showed an increased but inefficient T cell function in patients with severe hearing loss due to rubella infection (19). In addition, Masuda et al. reported reduced NK cell activity in patients with idiopathic SNHL compared to those without (20). It may be assumed that reduced NK cell count may predispose the individuals to viral infections, making the cochlea, cranial nerves, and even the central auditory center more vulnerable to the effect of infections and/or antigens and leading to SNHL.

Interestingly, there were no patients with pure SNHL in our study. All patients with SNHL also had CHL. Jokay et al., in their autopsy study examining the temporal bones of 10 patients with chronic otitis media, showed three patients had staining with monocyte/macrophage markers in the cochlea, which was explained by the transfer of monocytes from the systemic circulation to the endolymphatic fluid via chronic antigenic stimulation (21). Our and Jokay et al.'s findings suggest that while infections cause CHL development, they also affect the cochlea due to chronic antigen stimulation and that CHL and SNHL do not represent two unrelated processes and actually develop concurrently to result in the occurrence of SNHL.

Many CVID patients receive prophylactic antibiotics due to frequent infections, bronchiectasis, etc. In the study by Tavakol et al., prophylactic antibiotic use was associated with reduced otitis media frequency with effusion in patients with XLA (4). Therefore, antibiotic prophylaxis may be expected to reduce the incidence of conductive and sensorineural hearing loss. On the other hand, there have been many cases developing SNHL with azithromycin prophylaxis (22-24). Although aminoglycoside-related ototoxicity is a well-established phenomenon, in one study of patients with primary antibody defects, aminoglycoside use did not show a significant association with SNHL (12). Based on our results, azithromycin prophylaxis does not represent a risk factor for both conductive and SNHL hearing loss.

T regulatory cell values, IgG subgroups, and presence of anti-nuclear antibodies were not studied in the current study. The cross-sectional design is another limitation of the study.

In conclusion, although our study's cross-sectional design is a limitation, we believe that our results bear considerable significance as, to the best of our knowledge, it is the most extensive study up to date to examine sensorineural and conductive hearing loss in adult CVID patients. Our results show that CVID patients have an increased incidence of conductive and sensorineural type hearing loss, regardless of the cause. In addition, they provide evidence for the notion that these two types of hearing loss are not unrelated, immune dysregulation also plays a role in the process, and SNHL is not independent of CHL. Thus, complete audiological assessment at diagnosis and follow-up should be considered an essential element that should not be overlooked in CVID patients.

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