Associations of Autoimmune Diseases with Hearing Loss - an All of Us Analysis

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Abstract

Introduction: Autoimmune diseases have been implicated in inner ear injury, but phenotype-specific associations with hearing loss (HL) remain incompletely characterized. We evaluated associations between selected autoimmune diseases and sensorineural hearing loss (SNHL) and mixed HL in a large, diverse U.S. cohort.
Methods: The NIH All of Us Research Program was queried for patients with SNHL, mixed HL, and seven autoimmune diseases: antiphospholipid syndrome, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren disease, sarcoidosis, and systemic sclerosis. Patients with HL were propensity score matched 1:2 to non-HL controls. Multivariable logistic regression estimated adjusted odds ratios (aORs) with match-set cluster-robust 95% confidence intervals, adjusting for age, Charlson Comorbidity Index, modified sex, race/ethnicity, and configured additional covariates. False discovery rate (FDR) correction was applied for multiple comparisons.
Results: Among 481,919 All of Us participants with electronic health record data, 41,811 had SNHL and 6,572 had mixed HL. Propensity score matching achieved good covariate balance for most matching characteristics (standardized mean differences <0.10). All seven autoimmune diseases were more prevalent among patients with SNHL than matched controls (all P<.001) and among patients with mixed HL than matched controls (all P≤.01). After multivariable adjustment and FDR correction, all autoimmune diseases except systemic sclerosis were significantly associated with greater odds of SNHL. Sjögren disease demonstrated the strongest association (aOR 1.69, 95% CI 1.55–1.84), followed by sarcoidosis (1.44, 1.28–1.63), antiphospholipid syndrome (1.39, 1.12–1.72), SLE (1.30, 1.16–1.45), rheumatoid arthritis (1.29, 1.21–1.37), and multiple sclerosis (1.27, 1.13–1.42). For mixed HL, SLE (1.52, 1.30–1.78) and Sjögren disease (1.94, 1.56–2.41) remained significantly associated with greater odds after adjustment and FDR correction; estimates for other autoimmune diseases were nonsignificant or not estimable because of sparse data.
Conclusions: Multiple autoimmune diseases were independently associated with SNHL, with Sjögren disease demonstrating the strongest association. Sjögren disease and SLE were also independently associated with mixed HL. These findings support an association between systemic autoimmunity and hearing loss, while the smaller mixed-HL cohort and sparse disease-specific data warrant cautious interpretation and further study.

Introduction

- Autoimmune disorders have been increasingly studied with its association to sensorineural hearing loss
- There is an emerging understanding that autoimmune disorders can cause immune mediated injury to the middle and inner ear through multiple mechanisms including inflammation as well as self-reactivity and molecular mimicry
- Large-scale studies assessing the association of autoimmune disorders to sensorineural hearing loss (SNHL) remain limited due to the difficulty of obtaining sufficient sample sizes, and the use of biobanks such as the All of Us program can now make this possible.
- **Hypothesis: Autoimmune diseases would be independently associated with increased odds of SNHL and mixed hearing loss.**

Methods

Data Source & Study Population
The All of Us Research Cohort is a large, diverse U.S.-based cohort integrating. Data were obtained from Version 9 of the All of Us Research Program, a large, diverse U.S. cohort integrating electronic health records, survey data, and physical measurements.

Patients with sensorineural hearing loss (SNHL) or mixed hearing loss (Mixed HL) were identified using ICD-10 codes and analyzed separately. Each case was propensity score matched to two controls without hearing loss (1:2) based on age, sex, race, ethnicity, insurance status, and deprivation index. PSM was done with logistic regression, a caliper width of 0.25 and without replacement.

Seven autoimmune disorders previously associated with hearing loss were evaluated (Table 1)

Autoimmune Disease	ICD-9-CM	ICD-10-CM
Antiphospholipid Syndrome	289.81*	D68.61
Multiple Sclerosis	340	G35
Rheumatoid Arthritis	714.x	M05.x, M06.x
Systemic Lupus Erythematosus	710.0	M32.x
Sjögren Syndrome	710.2	M35.0x
Sarcoidosis	135	D86.x
Systemic Sclerosis	710.1	M34.x

Covariates
Demographic covariates included age, sex, race/ethnicity, insurance status, income, and deprivation index. Overall comorbidity burden was assessed using the Charlson Comorbidity Index (CCI).

Statistical Analysis
Associations between each autoimmune disorder and SNHL or Mixed HL were evaluated using multivariable logistic regression. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated after adjustment for demographic covariates and CCI. False discovery rate (FDR) correction was applied to account for multiple comparisons. Statistical significance was defined as $p < 0.05$. Analyses were preformed using R 4.4.3

Results

481,919 patients were identified within the AoU as having EMR data. 41,811 were identified with SNHL and 6,572 were identified with mixed hearing loss. Table 1A and 1B reflects the demographics of the patient groups. Propensity score matching achieved good covariate balance between cases and controls, with standardized mean differences (SMDs) <0.10 for matching covariates.

Table 1A. Demographic Characteristics of the SNHL Propensity-Matched Cohort

Characteristic	SNHL N = 41811[1]	Control N = 83622[1]	SMD[2]	P[3]
Age used for matching, years	72.0 [64.0, 78.0]	72.0 [64.0, 77.0]	0.03	<0.001
CCI used for matching	5.0 [3.0, 7.0]	4.0 [3.0, 6.0]	0.30	<0.001
Sex at birth			0.00	>0.9
Male	21,595 (51.6%)	43,190 (51.6%)		
Female	19,792 (47.3%)	39,584 (47.3%)		
Other	424 (1.0%)	848 (1.0%)		
Race/ethnicity			0.01	0.6
White	31,869 (76.2%)	63,602 (76.1%)		
Black	3,464 (8.3%)	7,114 (8.5%)		
Hispanic	3,786 (9.1%)	7,560 (9.0%)		
Other	2,692 (6.4%)	5,346 (6.4%)		
Health Insurance Status			-0.03	<0.001
0	759 (1.8%)	1,219 (1.5%)		
1	41,052 (98.2%)	82,403 (98.5%)		
Socioeconomic Deprivation Index (Quartile)			0.03	
Q1 (least deprived)	2,215 (5.3%)	3,906 (4.7%)		
Q2	36,600 (87.5%)	73,553 (88.0%)		
Q3	2,995 (7.2%)	6,163 (7.4%)		
Q4	1 (0.0%)	0 (0.0%)		

Table 1B. Demographic Characteristics of the Mixed Hearing Loss Propensity-Matched Cohort

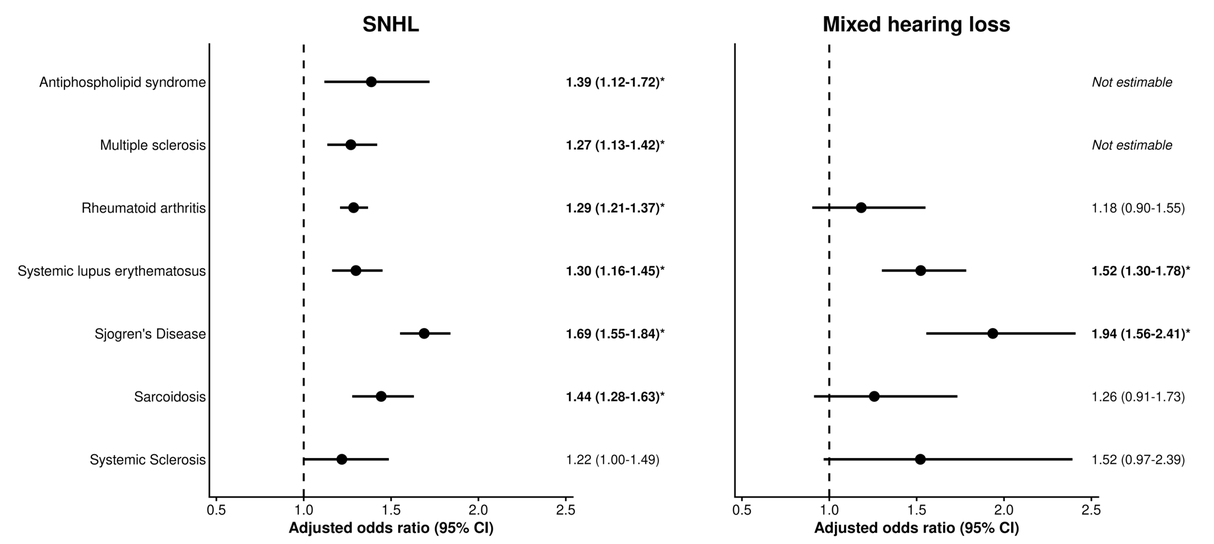
Characteristic	Mixed HL N = 6572[1]	Control N = 13144[1]	SMD[2]	P[3]
Age used for matching, years	70.0 [61.0, 77.5]	70.0 [61.0, 77.0]	0.02	0.076
CCI used for matching	5.0 [3.0, 7.0]	4.0 [2.0, 6.0]	0.39	<0.001
Sex at birth			0.00	>0.9
Male	3,101 (47.2%)	6,202 (47.2%)		
Female	3,415 (52.0%)	6,830 (52.0%)		
Other	56 (0.9%)	112 (0.9%)		
Race/ethnicity			0.01	>0.9
White	4,738 (72.1%)	9,471 (72.1%)		
Black	639 (9.7%)	1,309 (10.0%)		
Hispanic	756 (11.5%)	1,495 (11.4%)		
Other	439 (6.7%)	869 (6.6%)		
Health Insurance Status			-0.02	0.10
0	122 (1.9%)	203 (1.5%)		
1	6,450 (98.1%)	12,941 (98.5%)		
Socioeconomic Deprivation Index (Quartile)			0.01	0.7
Q1 (least deprived)	248 (3.8%)	465 (3.5%)		
Q2	5,796 (88.2%)	11,599 (88.2%)		
Q3	528 (8.0%)	1,080 (8.2%)		

[1] Median [Q1, Q3]; n (%)
[2] Standardized Mean Difference
[3] Wilcoxon rank sum test; Pearson's Chi-squared test
Abbreviation: CI = Confidence Interval

Table 2. Prevalence of Autoimmune Diseases in HL Cases & Matched Controls

Characteristic	SNHL cases (N = 41,811)	SNHL controls (N = 83,622)	P-Value	Mixed cases (N = 6,572)	Mixed controls (N = 13,144)	P-Value
Antiphospholipid syndrome	161 (0.39%)	182 (0.22%)	**<0.001**	34 (0.52%)	36 (0.27%)	**0.010**
Multiple sclerosis	532 (1.27%)	769 (0.92%)	**<0.001**	92 (1.40%)	132 (1.00%)	**0.016**
Rheumatoid arthritis	2,068 (4.95%)	2,576 (3.08%)	**<0.001**	370 (5.63%)	366 (2.78%)	**<0.001**
Systemic lupus erythematosus	648 (1.55%)	759 (0.91%)	**<0.001**	139 (2.12%)	138 (1.05%)	**<0.001**
Sjögren's Disease	1,087 (2.60%)	1,148 (1.37%)	**<0.001**	191 (2.91%)	170 (1.29%)	**<0.001**
Sarcoidosis	491 (1.17%)	571 (0.68%)	**<0.001**	71 (1.08%)	86 (0.65%)	**0.002**
Systemic Sclerosis	182 (0.44%)	224 (0.27%)	**<0.001**	41 (0.62%)	38 (0.29%)	**<0.001**

Figure 1. Association Between Hearing Loss and Autoimmune Disease
Adjusted odds ratios with matched-set cluster-robust 95% confidence intervals



* FDR-adjusted p < 0.05. Models adjusted for age, CCI, modified sex, race/ethnicity, and configured additional covariates. Non-estimable models reflect sparse data/separation.

Each autoimmune condition was significantly more prevalent among patients with SNHL than among matched controls (all P < .001). Similarly, all autoimmune conditions were significantly more prevalent among patients with mixed hearing loss 6,572, than among matched controls (all P ≤ .01).

After multivariable adjustment and correction for multiple comparisons, all autoimmune disorders except systemic sclerosis were significantly associated with greater odds of SNHL. Sjögren disease demonstrated the strongest association (aOR 1.69, 95% CI 1.55–1.84). For mixed hearing loss, SLE and Sjögren disease remained significantly associated with greater odds after adjustment. Mixed hearing loss estimates should be interpreted cautiously because of smaller sample sizes and sparse data.

Discussion

In this large, diverse, propensity-matched cohort from the All of Us Research Program, multiple autoimmune disorders were independently associated with SNHL, whereas associations with mixed hearing loss were less consistent.

- Rheumatoid arthritis had the highest prevalence among patients with both SNHL and mixed hearing loss, consistent with prior literature. To our knowledge, this represents the largest U.S.-based study examining these associations.
- Sjögren disease demonstrated the strongest adjusted association with SNHL. Proposed mechanisms include autoimmune-mediated inner ear injury, potentially involving anticardiolipin antibodies. However, the prevalence observed in our cohort was lower than estimates reported in prior systematic reviews.
- Despite their relatively low prevalence, most autoimmune disorders remained significantly associated with SNHL after multivariable adjustment and correction for multiple comparisons. Future examination of newly available clinical notes within All of Us may better characterize hearing-related symptoms, disease severity, and clinical context not captured by diagnosis codes alone.
- Associations with mixed hearing loss should be considered exploratory given the smaller sample size and sparse data. Larger cohorts are needed to validate these findings and better characterize the relationship between systemic autoimmunity and mixed hearing loss.

References/Acknowledgments

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