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ORIGINAL ARTICLE

Increased risk of sudden sensory neural hearing loss in patients with rheumatoid arthritis: a longitudinal follow-up study using a national sample cohort

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Abstract

To evaluate the association between sudden sensorineural hearing loss (SSNHL) and rheumatoid arthritis (RA) among a national sample cohort from Korea. Data were collected from 2002 through 2013 for individuals aged ≥ 20 years in the Korean National Health Insurance Service (NHIS)-National Sample Cohort. We extracted the data from RA patients ($n = 7619$) and 1:4-matched controls ($n = 30,476$) and analyzed the occurrence of SSNHL. Matching was performed based on age, sex, income, region of residence, and medical history. RA was diagnosed based on International Classification of Disease-10 (ICD-10) codes (M05 or M06) and prescriptions for the antirheumatic drugs. SSNHL was diagnosed based on the relevant ICD-10 code (H912). Among the SSNHL participants, we included only those who had undergone an audiometry exam (claim codes: E6931–E6937, F6341–F6348) and received treatment with steroids. The crude and adjusted hazard ratios (HRs) were calculated using Cox-proportional hazard models, and the 95% confidence intervals (CIs) were determined. Subgroup analyses based on age and sex were also performed. The rate of SSNHL in the RA group (0.8% [62/7619]) was higher than that in the control group (0.6% [177/30,476], $P = 0.021$). The crude and adjusted HRs for SSNHL were 1.40 (95% CI = 1.05–1.87) and 1.39 (95% CI = 1.04–1.86), respectively, in the RA group (each $P < 0.05$). The relationship between RA and SSNHL was observed primarily in patients aged ≥ 50 years and men. The risk of SSNHL is higher in patients with RA.

Keywords Cohort study · Comorbidity · Rheumatoid arthritis · Sudden sensorineural hearing loss

Introduction

Rheumatoid arthritis (RA) is a common immune-mediated condition characterized by chronic systemic polyarthritis that affects approximately 1% of the population worldwide [1, 2]. In a Korean population-based case-control study, the overall weighted prevalence of RA was 1.5% [3]. This condition causes progressive destruction and deformity of bone and cartilage following synovitis and subsequently results in impaired joint function [4]. In addition, a high prevalence of comorbidities and risk factors associated with RA, such as cardiovascular events, diabetes mellitus, hypertension, and dyslipidemia, were reported [4]. RA, which may cause systemic vasculitis, is also known to stimulate extra-articular manifestations in other organs, including the auditory system [4]. Several studies have reported the risk of hearing impairment in patients with RA [3, 5–7]. In a population-based cohort study, RA was shown to be associated with low-/mid-frequency sensorineural hearing loss after adjusting for various known risk factors (odds ratios [OR], 1.47; 95% confidence interval [CI], 1.05 ± 2.06; $P = 0.025$) [3].

Sudden sensorineural hearing loss (SSNHL) is typically defined as a sensorineural hearing loss of more than 30 dB across three consecutive frequencies in a pure-tone audiogram occurring within a 72-h period. The global incidence of

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SSNHL has been reported to vary up to 20 per 100,000 individuals [8]. In Korea, the incidence is 10 per 100,000 individuals [9]. SSNHL can be an isolated symptom or the presenting symptom of a systemic disease [10]. A recent study showed that the risk of SSNHL in patients with immune-mediated disease was up to 4.27 times higher than that in the control group [11]. Similarly, a case study reported bilateral symmetrical SSNHL, predominantly over high frequencies, in patients with RA [6]. The exact pathophysiology of SSNHL has not been clearly elucidated in most cases, and specific etiological factors, such as viral infection, ischemia in the inner ear, and immune-mediated mechanisms, have been identified in approximately only 10% of patients [8, 12]. Systemic inflammatory mediators related to RA are presumed to be involved in the mechanisms underlying SSNHL [13–15].

Vascular supply to the inner ear, characterized by vulnerable blood circulation due to the end-arterial nature of this organ, may increase susceptibility to autoimmunity [9]. Autoantibodies against inner ear proteins can induce immune complex deposition in the labyrinthine vessels, resulting in endothelial damage and thrombus formation [16]. A recent study showed elevated levels of immune complexes and autoantibodies against inner ear proteins in RA patients with sensorineural hearing loss [17], suggesting that immune-mediated vasculitis may represent an increased risk of SSNHL.

Considering this evidence, an awareness of the association between SSNHL and RA may facilitate treatment and prognosis in such cases. However, currently, evidence of this association is limited. When we searched the PubMed and EMBASE databases using the keywords "([Rheumatoid arthritis] OR [idiopathic juvenile arthritis] AND ([Sudden sensorineural hearing loss] OR [sudden hearing loss] OR [sudden deafness])" and limited the results to human-based studies published in the English language prior to 1 March 2018; only one case report with a literature review addressed this association [6].

Thus, the present study aimed to evaluate the association between RA and SSNHL among the Korean population using a national sample cohort. We extracted the data from patients with RA and a 1:4-matched control group and then analyzed the occurrence of SSNHL in this cohort.

Materials and methods

Study population and data collection

The Ethics Committee of Hallym University (2014-I148) approved the use of these data. The study was exempted from the need for written informed consent by the Institutional Review Board. These data were fully anonymized before the authors accessed them.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC). The Korean National Health Insurance Service (NHIS) selects samples directly from the entire population database to avoid non-sampling errors. Approximately, 2% of the samples (1 million) were selected from the entire Korean population (50 million). These selected data can be classified at 1476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. After data selection, the appropriateness of the sample was verified by a statistician who compared the data from the entire Korean population to the sample data. The details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service (http://nhiss.nhis.or.kr/). This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) International Classification of Disease-10 (ICD-10) diagnostic codes, (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of disease), (v) socioeconomic data (residence and income), and (vi) medical examination data for each participant from 2002 to 2013.

Because all Korean citizens are recognized by a 13-digit resident registration number from birth to death, the exact population statistics can be determined using this database. Enrollment in the NHIS is mandatory for all Koreans. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. Moreover, all medical treatments in Korea can be tracked without exception using the Health Insurance Review and Assessment (HIRA) system. In Korea, providing notice of death to an administrative entity is legally required before a funeral can be held, and the cause and date of death are recorded by medical doctors on a death certificate.

Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, RA was diagnosed according to previous studies that reported the prevalence and incidence of RA in Korea [18, 19]. RA was diagnosed using ICD-10 codes (M05 or M06) and a prescription for a biologic agent or any disease-modifying antirheumatic drugs (DMARDs) ($n = 7783$).

SSNHL was diagnosed using the ICD-10 code (H912). Among the participants with SSNHL, we included only participants who underwent an audiometry exam (claim code: E6931-E6937, F6341-F6348) and were treated with steroids. Treatment with steroids included both systemic (oral steroids or intravenous dexamethasone injection) and local approaches (intratympanic dexamethasone injection). From 2002 to 2013, 5244 of the SSNHL participants were selected.

The RA group was matched 1:4 with participants (control group) who were not diagnosed with RA from 2002 to 2013. The control group was selected from the total population (n = 1,117,908). Matching was performed based on age, group, sex, income group, region of residence, and prior medical history (hypertension, diabetes, and dyslipidemia). To prevent selection bias in selecting the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. The matched control participants were assumed to be involved at the same time as the RA participants (index date). Therefore, control patients who died before the index date were excluded. Participants with a history of SSNHL before the index date were excluded from both the RA and control groups. In total, 24 participants were excluded from the RA group. RA patients for whom we could not identify sufficient matching participants were excluded (n = 9). We also excluded any participants younger than 20 years of age (n = 131). Finally, the 1:4 matching resulted in the inclusion of 7619 RA patients and 30,476 control participants (Fig. 1). However, the participants were not matched based on ischemic heart disease, cerebral stroke, or history of depression because strict matching based on these characteristics increased the subject dropout rate due to the lack of control participants.

Variables

The age groups were classified using 5-year age intervals as follows: 20–24, 25–29, 30–34…85+ years. In total, 14 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into five classes (class 1 [lowest income] to 5 [highest income]). The region of residence was divided into 16 areas according to the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants' prior medical histories were evaluated using ICD-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10–E14), and dyslipidemia (E78) were considered present if the participant was treated ≥ 2 times for these conditions. Ischemic heart disease (I24 and I25) and cerebral stroke (I60–I66) were considered present if the participant was treated ≥ 1 time for these conditions. Depression was diagnosed based on ICD-10 codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times for these conditions.

Statistical analyses

Chi-square tests were performed to compare the general characteristics between the RA and control groups. Cox-proportional hazard models were performed to assess the hazard ratios (HRs) for RA with respect to SSNHL. In this analysis, crude (simple) and adjusted (for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression) models were used, and the 95% confidence intervals (CIs) were calculated. For the subgroup analyses, we divided the participants by age (< 50 years and ≥ 50 years) and sex (men and women). The division of age was based on the median value. Two-tailed analyses were conducted, and P values less than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

Results

The rate of SSNHL in the RA group (0.8% [62/7619]) was higher than that in the control group (0.6% [177/30,476], P = 0.021, Table 1). The general characteristics (age, sex, income, region of residence, and history of hypertension, diabetes, or dyslipidemia) of the participants were the same due to the matching procedure (P = 1.000). The rates of ischemic heart disease and history of depression were higher in the RA group than those in the control group (each $P < 0.05$). The crude and adjusted HRs of SSNHL were 1.40 (95% CI = 1.05–1.87) and 1.39 (95% CI = 1.04–1.86), respectively, in the RA group (each $P < 0.05$, Table 2).

In the subgroup analyses performed according to age and sex, the crude and adjusted HRs of SSNHL in the RA group were higher among those aged ≥ 50 years and men (each $P < 0.05$, Table 3). The adjusted HRs were 1.43 (95% CI = 1.00–2.05) in the participants aged ≥ 50 years and 2.34 (95% CI = 1.23–4.46) in the men.

Discussion

In this study, the risk of SSNHL in the RA group was higher than that in the control group. Consistent with our results, previous population-based case-control studies have reported a higher risk of SSNHL development in patients with other common autoimmune diseases, such as systemic lupus erythematosus and psoriasis [20, 21]. Moreover, in the subgroup analyses performed according to age and sex, a significant association was observed between RA and SSNHL, primarily in patients aged ≥ 50 years and men.

Several studies have reported enhanced levels of inner ear target antigens and corresponding circulating autoantibodies in patients with systemic autoimmune diseases, including RA

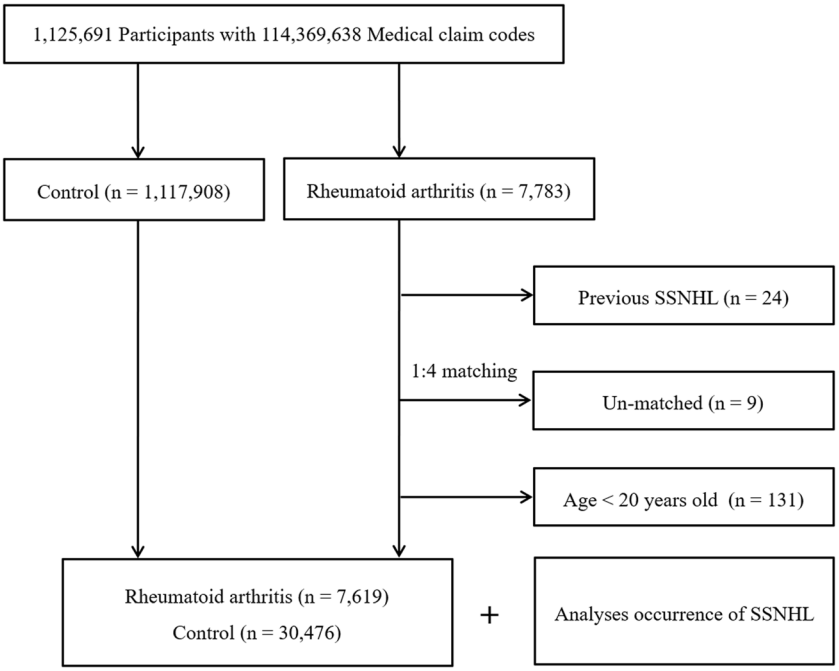

Fig. 1 Schematic illustration of the participant selection process used in the present study. Of a total of 1,125,691 participants, 7619 RA patients were matched with 30,476 control participants based on age, group, sex, income group, region of residence, and prior medical history

[11, 22]. Systemic immune-mediated changes have been proposed to be a possible cause of SSNHL. The rheumatoid factor, which is a diagnostic feature in RA, may lead to immediate hypersensitivity to the cochlear antigen and subsequent immune complex-mediated vasculitis, resulting in endothelial damage, perivascular cellular infiltration, and thrombus formation [23]. A recent study identified the presence of anticyclic citrullinated peptide, which is associated with atherosclerotic vascular involvement and decreased antioxidant enzyme activity in all patients with RA accompanied by sensorineural hearing loss [24]. Moreover, growing evidence suggests increased platelet activation, reflecting the platelet production rate and stimulation, in RA patients [25]. Platelet activity is known to be correlated with disease severity [26]. The immune complexes and autoantibodies in serum from RA patients, including the rheumatoid factor and anticitrullinated protein antibodies, were presumed to enhance platelet activity [27]. The resultant higher platelet function increases the risk factors for cardiovascular events and atherosclerotic plaque instability [25], thereby increasing the risk of ischemic or thrombotic events in the inner ear microvasculature, which could lead to SSNHL.

Meanwhile, a recent study assessing ear involvement in patients with RA reported that proinflammatory cytokines, such as interleukin-6 and metalloproteinase-3, play a significant role and may cause hearing deterioration via the direct action of cytotoxic T-cells in the cochlear hair cells as a result of oxidative stress [28]. In addition, medications used for the treatment of RA, including non-steroidal anti-inflammatory drugs, antimalarial agents, and several other DMARDs, can induce ototoxicity [29, 30]. Furthermore, patients with RA who undergo immunosuppressive therapy have been shown to exhibit increased viral replication [31, 32], which could increase the risk of SSNHL.

In the subgroup analyses, the incidence of SSNHL increased as the patients' age increased, particularly in the patients aged ≥ 50 years. The adjusted HR was 1.43 (95% CI = 1.00–2.05) in the patients aged ≥ 50 years. This finding is consistent with previous studies demonstrating a relationship between SSNHL and systemic autoimmune diseases, such as psoriasis and systemic lupus erythematous [20, 21]. Furthermore, the HR for SSNHL was relatively high in the male RA patients. The adjusted HR was 2.34 (95% CI = 1.23–4.46) in the men. Although RA, which is a form of chronic symmetric polyarthritis, predominantly affects women [4], our finding is consistent with a previous population-based cohort study showing a higher incidence (1.26 per 1000 person-years) of sensorineural hearing loss in men [7]. This phenomenon is enigmatic considering the hormonal aspects and effects of genetic factors (X-linked) on hearing deterioration in women [33]. Thus, age could be more important for hearing impairment in women than in men.

As described in detail previously, the present study utilizing HIRA-NSC has strengths, including a very large, representative, nationwide population [9, 34–37]. The characteristics of NHIS data that cover all citizens in Korea without exceptions elicited profound participation during the follow-up. The control group was randomly selected. Then, the group was matched to attenuate confounding effects on the basis of age, sex, income, region of residence, and medical history. An adjusted hazard model was used to further minimize the impact of confounders.

Table 1 General characteristics of participants

Characteristics	Total participants		
	Rheumatoid arthritis (*n*, %)	Control (*n*, %)	*P* value
Age (years old)			1.000
20–24	182 (2.4)	728 (2.4)	
25–29	297 (3.9)	1188 (3.9)	
30–34	418 (5.5)	1672 (5.5)	
35–39	565 (7.4)	2260 (7.4)	
40–44	721 (9.5)	2884 (9.5)	
45–49	1009 (13.2)	4036 (13.2)	
50–54	1215 (15.9)	4860 (15.9)	
55–59	967 (12.7)	3868 (12.7)	
60–64	877 (11.5)	3508 (11.5)	
65–69	658 (8.6)	2632 (8.6)	
70–74	409 (5.4)	1636 (5.4)	
75–79	221 (2.9)	884 (2.9)	
80–84	69 (0.9)	276 (0.9)	
85 +	11 (0.1)	44 (0.1)	
Sex			1.000
Male	1746 (22.9)	6984 (22.9)	
Female	5873 (77.1)	23,492 (77.1)	
Income			1.000
1 (lowest)	1233 (16.2)	4932 (16.2)	
2	1097 (14.4)	4388 (14.4)	
3	1358 (17.8)	5432 (17.8)	
4	1725 (22.6)	6900 (22.6)	
5 (highest)	2206 (29.0)	8824 (29.0)	
Region of residence			1.000
Urban	3345 (43.9)	13,380 (43.9)	
Rural	4274 (56.1)	17,096 (56.1)	
Hypertension			1.000
Yes	3291 (43.2)	13,164 (43.2)	
No	4328 (56.8)	17,312 (56.8)	
Diabetes			1.000
Yes	1638 (21.5)	6552 (21.5)	
No	5981 (78.5)	23,924 (78.5)	
Dyslipidemia			1.000
Yes	2698 (35.4)	10,792 (35.4)	
No	4921 (64.6)	19,684 (64.6)	
Ischemic heart disease			0.001*
Yes	603 (7.9)	2085 (6.8)	
No	7016 (92.1)	28,391 (93.2)	
Cerebral stroke			0.080
Yes	882 (11.6)	3314 (10.9)	
No	6737 (88.4)	27,162 (89.1)	
Depression			< 0.001*
Yes	1044 (13.7)	3299 (10.8)	
No	6575 (86.3)	27,177 (89.2)	
SSNHL			0.021*
Yes	62 (0.8)	177 (0.6)	
No	7557 (99.2)	30,299 (99.4)	

SSNHL sudden sensory neural hearing loss

*Chi-square test or Fisher's exact test. Significance at $P < 0.05$

There are several limitations to the present study. First, although this study used control groups matched for medical history in addition to demographic factors, we could not match the groups for ischemic heart disease, stroke, or depression, which may have affected the shared mechanism between RA and SSNHL. Moreover, the present study could not strictly consider SSNHL secondary to other clinical conditions, including neoplastic disease, traumatic injury, and infections, due to the acquisition of a cohort. Given that other clinical conditions underlying SSNHL manifested at a 7 to 45% rate in previous studies [38], a more strict matching may be warranted to reveal SSNHL as an independent risk factor for RA. Second, information regarding several suspected risk factors

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of rheumatoid arthritis for SSNHL

Characteristics	SSNHL			
	Crude	*P* value	Adjusted†	*P* value
Rheumatoid arthritis	1.40 (1.05–1.87)	0.022*	1.39 (1.04–1.86)	0.026*
Control	1.00		1.00	

SSNHL: Sudden sensory neural hearing loss

*Cox-proportional hazard regression model, significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of rheumatoid arthritis for SSNHL according to age and sex

Characteristics	SSNHL			
	Crude	*P* value	Adjusted†	*P* value
Age < 50 years old (*n* = 15,960)				
Rheumatoid arthritis	1.33 (0.81–2.19)	0.253	1.31 (0.80–2.14)	0.290
Control	1.00		1.00	
Age ≥ 50 years old (*n* = 22,135)				
Rheumatoid arthritis	1.44 (1.01–2.06)	0.045*	1.43 (1.00–2.05)	0.050*
Control	1.00		1.00	
Men (*n* = 8730)				
Rheumatoid arthritis	2.41 (1.27–4.57)	0.007*	2.34 (1.23–4.46)	0.010*
Control	1.00		1.00	
Women (*n* = 29,365)				
Rheumatoid arthritis	1.24 (0.89–1.72)	0.202	1.23 (0.89–1.71)	0.218
Control	1.00		1.00	

SSNHL: Sudden sensory neural hearing loss

*Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories

for SSNHL, such as smoking and noise exposure, was not available in the insurance database [39, 40]. Third, as demonstrated in our previous studies, some patients might not have visited a clinic for the treatment of RA and/or SSNHL, and these patients might have been omitted. Since the possibility of SSNHL detection can be increased due to a visit for RA, we examined the additional data 6 months after the detection of RA. The results of this analysis were consistent with our findings (adjusted SSNHL of RA = 1.42, 95% CI = 1.05–1.91, $P = 0.022$, Table S1). Finally, the insurance data did not include information regarding laboratory test results and the characteristics of hearing loss. Considering that immune-mediated hearing loss generally involves both ears [11], we were unable to evaluate the laterality of SSNHL. Moreover, the clinical picture of immune-mediated hearing loss can have a temporal profile coincident with SSNHL or can progress with an asymmetric and progressive pattern over a period of weeks [11]. This issue can lead to an underestimation of the incidence of hearing loss in the RA group because only those cases where SSNHL was established in less than 72 h were included.

Conclusion

The occurrence of SSNHL was significantly higher in the patients with RA than in the matched control participants.

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Compliance with ethical standards

Disclosures None

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