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Voice Symptoms in Patients with Autoimmune Disease: A Cross-sectional Epidemiological Study

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Abstract

Objective. To assess the prevalence and severity of voice symptoms in individuals with a diagnosis of autoimmune disease.

Study Design. Cross-sectional survey.

Setting. Study participants were recruited from a rheumatology tertiary referral clinic at Norfolk and Norwich University Hospital.

Subjects and Methods. A cross-sectional questionnaire analyzing 109 patients with autoimmune disease (rheumatoid arthritis, seronegative spondyloarthritis, connective tissue disease) and a control group of 41 patients with non-autoimmune disease (osteoarthritis/osteoporosis). Main outcome measures were the Voice Handicap Index–10 (VHI-10), xerostomia scale, acid reflux inquiry, and anxiety/depression scale.

Results. Patients with autoimmune disease were more likely to experience voice symptoms as assessed by the VHI-10 questionnaire ($P = .0035$). Subgroup analysis showed autoimmune patients were more likely to report voice symptoms regardless of whether they were on a disease-modifying antirheumatic drug (DMARD; $P = .0010$) or non-DMARD ($P = .017$), suggesting autoimmune disease may be an independent risk factor from pharmacotherapy. Xerostomia was more common in an autoimmune population compared with the control group ($P = .02$). A positive correlation between xerostomia and VHI-10 scores was found for the DMARD group (Spearman rank coefficient = 0.49, $P < .001$). No significant difference in acid reflux inquiry ($P = .44$) or the anxiety/depression scale ($P = .36$) was found when comparing the autoimmune and control groups.

Conclusion. Patients with autoimmune disease have increased likelihood of voice symptoms when compared with a control population with non-autoimmune disease. Further prospective studies to elucidate the cause of voice disorder would be valuable.

Keywords

voice disorders, autoimmune diseases, voice quality, laryngopharyngeal reflux, disease-modifying antirheumatic drugs, depression, xerostomia, cross-sectional survey

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Voice disorders are a diverse group of symptom-based diagnoses and may be divided into those affecting quality, loudness, pitch, or vocal effort.^{1,2} Although a small proportion of patients presenting with dysphonia have a neurological or structural laryngeal abnormality, the majority have a multifactorial functional cause for their symptoms with a normal larynx. The prevalence of voice disorders in the general population is high. One US study reports a 29.9% lifetime risk of voice disorders and 6.6% risk of experiencing recurrent symptoms.³ The US National Ambulatory Medical Care Survey,⁴ an analysis of more than 88,000 outpatient attendances, showed that voice complaints formed 3.2% of all otolaryngology appointments. A Scottish postal survey suggested 7.4% and 6.4% of respondents experienced hoarseness or weakness of voice, respectively, every day for at least 14 days in the past 12 months.⁵

Most patients with voice disorders do not present to the medical profession due to the transient nature of their symptoms, the problem being perceived as trivial or simply because of a lack of awareness that anything can be done about it. In the same Scottish survey referred to previously,⁵ a minority (18.9%) of patients with voice disorders

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presented to a general practitioner, and only 5% were referred to secondary care. Despite this, voice symptoms have been shown to be correlated with significant poorer quality-of-life outcomes, which are at least in part related to an association with depression and perception of emotional and physical well-being.⁶

The Voice Handicap Index (VHI) questionnaire is a quality-of-life instrument that aims to quantify voice symptoms based on the patient's perception of his or her own symptoms and has been validated in a number of languages and voice pathologies.^{7,8} The VHI-10 questionnaire is an abbreviated version of the VHI based on clinical value and has shown >0.90 correlation with the VHI (Pearson's correlation coefficient).⁹ A recent study suggested that a score of >7 on the VHI-10 should be considered abnormal.¹⁰

Gastroesophageal reflux, laryngopharyngeal reflux,^{11,12} depression, asthma,⁴ occupation, female sex, tobacco use, and structural changes to the vocal cords (inflammation, nodules, edema) have all been implicated as risk factors in the development of vocal symptoms. Voice disorders have also been observed in a wide range of autoimmune disease, including rheumatoid arthritis,¹³ Sjögren's syndrome, and scleroderma,¹⁴ sometimes with observed vocal cord abnormalities (eg, bamboo nodules). In addition, the most common disease-modifying antirheumatic drugs (DMARDs) have side effect profiles that may cause or exacerbate voice symptoms. Examples include methotrexate (oral mucositis), sulfasalazine (stomatitis, cough), leflunomide (oral mucositis), and sodium aurothiomalate (stomatitis).¹⁵

Our clinical experience suggests an association between voice symptoms and autoimmune conditions. We hypothesize that this patient group has an increased prevalence of voice symptoms due to disease-related xerostomia, pharmacotherapy, and other less well-understood processes involving immune-mediated mucosal changes and altered sensory perception.¹⁶ The aim of our study is to assess the prevalence and severity of voice symptoms, as measured by the VHI-10 score, in individuals who have a prior diagnosis of autoimmune disease.

Materials and Methods

Ethical Considerations

The study was formally approved by the Cambridgeshire Research Ethics Committee, UK (Ref: 2009ENT01L).

Subjects

We approached 210 consecutive patients from a rheumatology outpatient department of a tertiary teaching hospital, of whom 150 agreed to participate in the study. Age, sex, and details of the autoimmune disease and other current medications, including DMARDs, were recorded. One hundred nine patients with autoimmune disease were assigned to the study group, and a further group of 41 patients with non-autoimmune disease (osteoarthritis/osteoporosis) were assigned as a control.

Exclusions

We excluded the following individuals: patients younger than 16 years, those who declined participation, and those with insufficient comprehension of written English to complete the questionnaire.

Study Design

This is a cross-sectional study with concurrent control taken from a non-autoimmune group ($n = 41$) of patients attending rheumatology clinics with similar overall morbidity. On arrival in the outpatient department, participants were offered a patient information sheet, which explained the nature and purpose of the study. After a consent form was signed, each volunteer was asked to complete a questionnaire consisting of the abbreviated Voice Handicap Index (VHI-10),⁹ an acid reflux inquiry (scale of 1-5), a visual analog score for anxiety and depression (scale of 1-10), and a xerostomia score (scale of 1-80). In the acid reflux inquiry, patients were asked to score symptoms of acid reflux with regard to frequency, with 1 being "rarely experience acid reflux" and 5 being "experience acid reflux daily." The anxiety and depression inquiry was a visual analog scale where patients self-score symptoms of anxiety or depression from 1 to 10. Flexible laryngoscopy or videostroboscopy was not performed in this patient cohort. The questionnaires were all completed within a 1-month period (July 2009) to minimize the effect of seasonal variation.

Power Calculation

Previous research¹⁴ has suggested that the prevalence of voice disorder in the autoimmune population is 35% to 38% compared with 5% to 8% in a control population. To detect this proportional difference at a 5% two-sided significance level and 90% power, at least 39 patients should be included in each study group.

Statistical Analysis

Statistical calculations were performed using R,¹⁷ an open-source software environment for statistical computing. The χ^2 test was used to analyze differences in sex proportions. Data from the reflux symptom index, visual analog scale, and xerostomia scale were compared using the Mann-Whitney U test due to the nonparametric nature of score distributions. Subgroup analysis used a Kruskal-Wallis test (a nonparametric test for simultaneous comparison of multiple samples). χ^2 and Fisher exact tests were used to compare VHI-10 in control with study groups, using a score of 7 or greater as the threshold for significantly abnormal voice symptoms.¹⁰ Spearman Rank and Kendall correlation tests were used to determine the degree of correlation between VHI-10 and xerostomia scores in each study group.

Results

The autoimmune study group ($n = 109$) consisted of 74 women (68%; mean age, 57 years) and 35 men (32%; mean age, 62 years) (**Table 1**). The breakdown of autoimmune

Table 1. Demographic Data

	Non-Autoimmune (n = 41)	Autoimmune (n = 109)
Average age, y	58.2	58.6
Total males, %	43.4	32.2

disease within this group reveals that the diagnosis of rheumatoid arthritis (RA) accounts for the majority (60%), which reflects the findings of previous large-scale autoimmune population studies.^{18,19} The next largest group (17%) included those with mixed autoimmune disease (RA/ankylosing spondylitis, n = 5; RA/psoriatic arthritis, n = 3; RA/Raynaud's disease, n = 2; RA/polymyalgia rheumatica, n = 2; psoriatic arthritis/Sjögren's syndrome, n = 2; RA/Sjögren's syndrome, n = 1; lupus/Behçet's disease, n = 1; Sjögren's syndrome/Behçet's disease, n = 1). Patients with a sole diagnosis of seronegative spondylitis (psoriatic arthritis/ankylosing spondylitis), connective tissue disease, or systemic vasculitis comprised 11%, 7%, and 5% of the study group, respectively. The average ages for both males and females in each group were similar. There was no significant difference found when analyzing the reflux symptom index and anxiety assessment scale for the autoimmune and non-autoimmune groups (**Table 2**).

The VHI-10 results were interpreted in light of a previous normative study¹⁰ suggesting a score >7 on the VHI-10 represented significant voice abnormality. Our control group (non-autoimmune arthritis) had a mean (SD) score of 0.95 (1.56) comparable to scores seen in a healthy population.¹⁰ The autoimmune group was split into the non-DMARD and DMARD groups, and the following results contain subgroup analyses. The autoimmune, DMARD, and non-DMARD

groups had mean (SD) VHI-10 scores of 2.95 (5.4), 3.19 (5.17), and 2.8 (6.21), respectively (**Table 2**). The VHI-10 score was heavily left-skewed; a majority of the patients across all study groups scored zero (control, 63.4%; autoimmune, 61%; DMARD, 57.3%; non-DMARD, 65%). However, 0% of patients in the control group scored over 7, whereas 16.6% of the autoimmune, 17.6% of the DMARD, and 14.3% of the non-DMARD group scored 7 or more on the VHI-10 (**Table 3**). Fisher exact test (using VHI-10 <7 to dichotomize the data) demonstrated that all 3 study groups were significantly more likely to experience voice disorder when compared with the control group (autoimmune, $P = .0035$; DMARD, $P = .00104$; non-DMARD, $P = .0176$).

Of the patients in the autoimmune group who reported voice symptoms, the most commonly reported item in the VHI-10 was "My voice makes it difficult for people to hear me" (68%), followed closely by "People have difficulty understanding me in a noisy room" (61%). Patients were least likely to complain "My voice problem causes me to lose income" (22%) or that "My voice makes me feel handicapped" (22%).

No significant difference was found in the subgroup analysis between RA and the other autoimmune groups when using the VHI-10 score as an outcome measure (17% in RA with VHI-10 >7 vs 16% in all other autoimmune pathologies). The influence of medication (DMARD) within the autoimmune group was analyzed. Seventy-five patients were undergoing this treatment at the time of completing the questionnaire. Methotrexate was the most common prescribed immune-modulating medication (77%) and has a broad side effect profile that can include mucosal ulceration. Hydroxychloroquine sulfate was the second most common DMARD in use.

We also analyzed VHI-10 scores with respect to sex and subgroup, as females were more common in the autoimmune group. Our results demonstrate that in both autoimmune

Table 2. Summary of Voice, Xerostomia, Reflux and Anxiety/Depression Results

	Autoimmune	Non-Autoimmune	P Value
VHI-10	2.95 (5.4)	0.95 (1.56)	.0035*
Xerostomia scale	10.84 (16.01)	3.56 (5.48)	.02*
Reflux scale	2.26 (1.38)	2.44 (1.27)	.44
Anxiety/depression scale	4.2 (2.64)	4.57 (2.01)	.36

Values are presented as mean score (SD). Abbreviation: VHI-10, Voice Handicap Index–10. * $P < .05$.

Table 3. Voice Handicap Index–10 (VHI-10) Score by Autoimmune Condition Subgroup

	VHI-10 = 0, %	VHI-10 = 1-7, %	VHI-10 >7, %
Control	63.4	36.5	0
Rheumatoid arthritis	35.4	47.7	16.9
Autoimmune other than rheumatoid arthritis	59.1	25.0	15.9

Table 4. Comorbidity Profile by Patient Group

Control		Autoimmune			
		Non-DMARD		DMARD	
Comorbidity	%	Comorbidity	%	Comorbidity	%
GERD	17	GERD	31	GERD	28
Hypertension	20	Hypertension	22	Hypertension	26
Hypercholesterolemia	12	Hypercholesterolemia	11	Hypercholesterolemia	11
Depression	5	Depression	14	Depression	16
Osteoporosis	5	Osteoporosis	14	Osteoporosis	14
Hypothyroidism	7	Hypothyroidism	11	Hypothyroidism	7
Fibromyalgia	5	Fibromyalgia	8	Iron deficiency anemia	5
No comorbidity	39	Asthma/bronchiectasis	19	Asthma/bronchiectasis	11
		Other miscellaneous	67	Other miscellaneous	53
		No comorbidity	22	No comorbidity	21

Abbreviations: DMARD, disease-modifying antirheumatic drug; GERD, gastroesophageal reflux disease.

groups DMARD ($P = .042$) and non-DMARD ($P = .0087$), females were more likely to experience significant voice pathology (VHI >7) than females in the non-autoimmune control group. We did not find any significant difference in prevalence of voice pathology between male and female subjects in our analysis; however, power is low due to small numbers of male subjects in the autoimmune group.

Analysis of xerostomia scale data showed that the autoimmune group was significantly more likely to report higher scores than the control group (Mann-Whitney U test, $P = .021$) with a mean (SD) score of 10.84 (16.01) compared with 3.56 (5.48) in the control population (Table 2). The DMARD subgroup was also more likely to report symptoms of xerostomia compared with the control group ($P = .022$; DMARD mean score, 11.38 [range, 0-72]). There was a weak positive correlation between xerostomia score and VHI-10 scores in the DMARD group (Spearman rank $\rho = 0.49$, $P < .001$; Kendall's $\tau = 0.38$, $P < .001$). No correlation was found between xerostomia and VHI-10 scores in the autoimmune, control, or non-DMARD groups.

Discussion

Voice symptoms account for approximately 3% to 4% of all otolaryngology referrals.⁴ After exclusion of organic pathology, speech and language therapy and symptom explanation are key to the successful management of these patients.² So far, the comorbidities associated with voice symptoms include vocal abuse, smoking, alcohol, asthma, and laryngopharyngeal reflux.⁴ Also of clinical importance is the current psychosocial environment in which the patient is exposed. Our findings suggest xerostomia alone does not account for voice symptoms in autoimmune disease.

In systemic autoimmune disease, the immune system attacks many different organs, tissues, and cells of the body manifesting commonly in mucosal changes.²⁰ Examples include Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis, and the vasculitides that frequently affect the head

and neck region. Case series of directly visualized vocal cord abnormalities in autoimmune disease suggest that autoimmune disease may be not only a risk marker but also a causative factor in voice disorder.²⁰⁻²² A wide range of pathologies are implicated, from cricoarytenoiditis and vocal cord nodules in rheumatoid arthritis,²¹ to cranial nerve abnormality in Sjögren's syndrome,²² to laryngeal inflammation in lupus.²³ Some groups report correlation with activity of disease and voice symptoms,²⁴ but this has not been replicated in other studies.¹⁴

We used a tertiary control population with osteoarthritis/osteoporosis in our study. A patient cohort with autoimmune disease is likely to have multiple comorbidities and poorer quality of life than a healthy population. Quality-of-life studies have reported comparable scores for patients with osteoarthritis and rheumatoid arthritis.^{25,26} Table 4 shows our control and autoimmune populations are generally well matched in terms of comorbidity, with the exception that asthma and bronchiectasis are more prevalent in the autoimmune population. This is a potential source of bias, as asthma has been associated with voice disorder. However, it can be argued that both asthma and bronchiectasis are recognized features of some autoimmune conditions; for example, bronchiectasis has been reported in up to 30% of patients with rheumatoid arthritis.²⁷

The prevalence of voice symptoms in autoimmune disease on a population level is poorly documented, and there is no large-scale epidemiological study to systematically correlate endoscopic visualization of the larynx to voice symptoms in an autoimmune patient group. In our study, 16.6% of the autoimmune group reported significant voice symptoms defined by the VHI-10 cutoff of >7 (Table 3). This is lower than the 32% to 38% reported by a similar study¹⁴; however, the use of different cutoff points and the higher proportion of patients with lupus in that study may account for the differences observed. Both DMARD and non-DMARD subgroups were more likely to experience

significant voice symptoms than the control group. Twenty percent of patients on DMARDs had a VHI-10 score >7 compared with 14.3% in the non-DMARD group. There was no difference between the 2 groups (Fisher exact test, $P = .60$), suggesting that autoimmune disease is a risk factor for voice symptoms regardless of the use of DMARDs. However, it would seem only logical to assume that potent disease-modifying medications (eg, methotrexate) can have an adverse influence on voice symptoms. Disease-modifying antirheumatic drugs may cause voice symptoms in some patients by inducing xerostomia but ameliorate them in others by reducing inflammation affecting the vocal cords. Receiving a DMARD may also be a proxy marker for disease severity. A prospective study, looking at the effect of DMARDs as an independent variable, is required to address this issue further. In particular, it would be relevant to study any cumulative voice symptom effect that DMARDs may have over time in patients with the various autoimmune diseases. Methotrexate and hydroxychloroquine also may interact with other medication (eg, aspirin, nonsteroidal anti-inflammatory drugs, steroids) to cause increased acid reflux and hence influence the VHI-10 score. It should be noted, however, that no objective difference was found in the acid reflux enquiry for DMARD and non-DMARD patients.

We also investigated 3 functional and psychological factors that may cause voice symptoms—namely, xerostomia, acid reflux, and depression. Of these, only xerostomia was found to be more prevalent in the autoimmune group (Table 2). This is unsurprising as xerostomia can both be a manifestation of the underlying autoimmune disorder (primary or secondary Sjögren's syndrome) or a side effect of DMARDs.¹⁵ A large proportion of the autoimmune population in our study were diagnosed with RA ($>60\%$). One study from North America suggests that the risk of developing undiagnosed secondary Sjögren's syndrome in this group can be up to 5% to 10%.²⁸ Sjögren's syndrome is associated with inflammation of the salivary glands, leading to underproduction of saliva. As expected from known drug side effect profiles, xerostomia scores were also positively correlated with VHI-10 scores in the DMARD group, but this finding was not replicated in any other study group. Given that both DMARD and non-DMARD subgroups are likely to report higher incidence of voice disorder, this suggests that drug-related xerostomia may play a part in causing voice symptoms in some autoimmune patients but is unlikely to be the only factor.

Our study may suggest a confounding bias toward females in the autoimmune group. This high female prevalence reflects the wider autoimmune population.¹⁹ However, our results show that females with autoimmune disease were significantly more likely to report voice pathology than females in the control group (Table 5). Clinically presenting voice symptoms are reported to be more common in female sufferers aged 40 to 59 years.³ If postmenopausal effects on the mucosal lining of the upper aerodigestive tract influence these symptoms, this would correlate well

Table 5. Voice Handicap Index–10 (VHI-10) Scores Compared by Sex and Patient Subgroup^a

Patient Subgroup	P Value (χ^2)
DMARD male vs female	.36
Non-DMARD male vs female	.94
DMARD male vs control male	.56
DMARD female vs control female	.042*
Non-DMARD male vs control male	.8
Non-DMARD female vs control female	.0087*

Abbreviation: DMARD, disease-modifying antirheumatic drug. * $P < .05$.

^aVHI-10 >7 considered to be positive for voice pathology.

with the autoimmune model of mucosal changes contributing to voice symptoms.

The apparent influence of autoimmune disease on voice symptoms may suggest a role for autoimmune screens in selected patients who present with dysphonia. Although it can be argued that most clinicians would further investigate a patient with arthralgia, dry eyes, or xerostomia (with or without voice symptoms), we suggest a potential benefit in applying screening questions to detect subclinical autoimmune disease. The main importance of our results, however, is the ability to offer a research-based explanation to patients known to have autoimmune disease who present with voice symptoms. This explanation and reassurance are often overlooked as a crucial part of the voice consultation. Such explanations may help reduce patient stress and anxiety, which may be additional factors increasing the severity of their voice disorder.

The limitations of this study include its cross-sectional nature and the lack of direct clinical assessment of the larynx. Our comparison does try to take into account the possible effects of the general disease burden on voice symptoms as a separate factor from the autoimmune disease by assessing an active control group of non-autoimmune patients with either osteoarthritis or osteoporosis. Further prospective studies with direct correlation of laryngeal pathology and autoimmune sensory or mucosal changes to symptoms would fill an important gap in our knowledge.

Conclusion

Patients with autoimmune disease appear to have a significantly increased prevalence of voice symptoms when compared with a tertiary population without autoimmune disease. Although it is not possible to confirm causality through this cross-sectional study, there does appear to be an association. The mechanisms underlying this are likely to be multifactorial and not entirely accounted for by xerostomia of autoimmune disease.

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Author Contributions

Zi Wei Liu, study design, data analysis, manuscript drafting, revision; **Liam M. Masterson**, study design, data collection, manuscript drafting, revision; **Ibrahim A. Srouji**, study design, data analysis, manuscript drafting, revision; **Patrick Musonda**, study design, data analysis, manuscript revision; **David G. I. Scott**, study design, data analysis, manuscript drafting, revision.

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