

Title: Risk and protective factors for spasmodic dysphonia: A case-control investigation

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ABSTRACT

Objectives: Spasmodic dysphonia (SD) is a chronic, incurable and often disabling voice disorder of unknown pathogenesis. The purpose of this study was to identify possible endogenous and exogenous risk and protective factors uniquely associated with SD. **Study Design:** Prospective, exploratory, case-control investigation. **Methods:** One hundred and fifty (150) patients with SD and 150 medical controls (MC) were interviewed regarding their personal and family histories, environmental exposures, illnesses, injuries, voice use patterns, and general health using a previously-vetted, validated epidemiologic questionnaire. **Results:** Odds ratios and multiple logistic regression analyses ($\alpha < 0.15$) identified several factors which significantly increased the likelihood of having SD. These factors included: 1) a personal history (PH) of mumps, blepharospasm, tremor, intense occupational and avocational voice use, and a family history of voice disorders, 2) an immediate family history (IFH) of meningitis, tremor, tics, cancer, and compulsive behaviors, and 3) an extended family history (EFH) of tremor and cancer. **Conclusions:** SD is likely multifactorial in etiology, involving both genetic and environmental factors. Viral infections/exposures, along with intense voice use may trigger the onset of SD in genetically predisposed individuals. Future studies should examine the interaction among genetic and environmental factors to determine the pathogenesis of SD.

Key Words: spasmodic dysphonia, epidemiology, risk factors

INTRODUCTION

Spasmodic dysphonia (SD) is an idiopathic, often disabling voice disorder with no known cure. Although the etiology of SD is unclear, it is considered to be an action-induced, task-dependent, focal laryngeal dystonia.¹⁻⁴ In 90% of cases, SD involves adductor spasms of the vocal folds during speech, causing the voice to sound intermittently or continuously strained-strangled.⁵ Abductor and mixed SD variants have also been identified.^{6,7} Approximately 50,000 individuals in North America have SD, with incidence estimates ranging from 1.1 to 4.26 cases per 100,000 people.⁸ SD typically presents early in the 5th decade of life and remains chronic thereafter. Women are at greater risk for developing SD as compared to men, with a reported 3:1 ratio.⁹⁻¹¹ Although incidence rates and phenomenological features of SD have been well-described, the pathogenesis of SD remains unknown. Current treatments are neither permanent, nor do they provide complete relief of symptoms. To guide disease prevention and treatment development, the pathogenesis of SD must be better understood.

Epidemiology is the study of the relationships of various factors determining the frequency and distribution of diseases in a population. Epidemiology research has helped to identify risk and protective factors associated with adult-onset, idiopathic focal dystonias. A risk factor is a variable associated with an increased risk of disease or disorder, whereas a protective factor refers to anything that prevents or reduces vulnerability for the disorder. Risk and protective factors are correlational and not causal. Based upon a review of the literature, genetic factors, including autosomal dominant traits with reduced penetrance, or alternatively polygenic inheritance may predispose individuals to dystonia development;¹²⁻¹⁵ however, repetitive, attended fine motor movements involving the affected limb or structure may trigger or localize the dystonia.¹⁶⁻¹⁸ Additionally, head, neck, trunk, or limb trauma, ocular diseases, and social anxiety/phobias have also been linked to adult-onset dystonia.^{19,20}

Although epidemiology research has suggested that focal dystonias are associated with a combination of genetic mechanisms and environmental triggers, few studies have attempted to identify risk and protective factors uniquely associated with SD. In one investigation questionnaire responses from 200 patients with SD were compared with 200 controls comprised of treatment-seeking patients, spouses, and the general population. Viral infections, health problems, surgeries, and family histories of neurological conditions were more frequently reported by the SD group, and stress and infectious illness also preceded onset of symptoms in some cases.²¹ Another study described the incidence of other neurological conditions associated with SD patients and their families.¹⁰ Most recently, Schweinfurth and colleagues²² explored family history and environmental factors associated with SD as compared to a first-degree relative control group. Of the 168 patients with SD, 65% reported measles or mumps exposure, 26% had essential tremor, and 11% had experienced writer's cramp. Acute life stress or viral exposure was reported near the onset of symptoms in 51% of cases. Collectively, these studies provide some evidence for both genetic and environmental risk factors for SD. Unfortunately, interpretation of the results from previous attempts to identify risk factors is complicated by sampling procedures, control group selection—or lack thereof—and the absence of statistical analysis procedures commonly employed in epidemiology research. These shortcomings make it difficult to determine the true extent to which specific risk factors, if any, contribute to the development of SD. Therefore this exploratory, case-control study was undertaken to identify endogenous and exogenous/environmental risk and protective factors uniquely associated with SD.

METHODS

Sampling Procedures

One hundred and fifty (150) patients with SD were identified and recruited at The University of Utah Voice Disorders Center (IRB approval 00025341). Participants were recruited based on a retrospective chart review and from consecutive patients seen for diagnosis or treatment during the course of the study. The SD diagnosis was confirmed by a multidisciplinary team including a laryngologist and speech-language pathologist. Diagnosis was assigned using an extensive protocol previously established and reported in the literature, including a detailed case history, auditory-perceptual evaluation and videolaryngostroboscopy.²³⁻²⁶ Medical controls (MC) included 150 patients who were seeking assessment or management of ear, nose, or sinus complaints in ENT clinics within The University of Utah Hospital and Clinics. These help-seeking, medical controls were genetically independent (unrelated) to the SD group. Female participants in the MC group were oversampled to better approximate the disproportionate number of females represented in the SD group. Participants with documented cognitive impairments were excluded from participating in the study. None of the participants were symptomatic for moderate or severe hearing loss at the time of the study. A 78% recruitment success rate was obtained for SD participants (i.e., of the 192 participants originally identified and recruited, 150 completed the study); a 52% recruitment success rate was obtained for MC participants (i.e., 150 of 286 identified and recruited).

Questionnaire Administration

The survey instrument was developed from a previously-vetted, validated questionnaire used in other epidemiologic studies of voice disorders.²⁷⁻³⁰ Participants were asked about their

personal and family medical histories—including histories of neurological conditions and symptoms—as well as environmental exposures, illnesses, injuries and voice use patterns. Interviewers were trained in administration of the questionnaire and were periodically audited to ensure accuracy. The interview process required approximately one hour to complete. In addition to the interview, the Short Form (SF) 36 was administered. The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an eight scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure, as compared to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases. The SF-36 was administered in this study to assess the relative burden of SD as compared to the medical control group, so as to ensure that if risk factors for SD were identified, they would not merely reflect between-group differences related to disease burden and severity.

Statistical Analysis

Data were examined using frequencies, proportions, means and standard deviations. Cross-tabulations were used to perform bivariate analyses between SD and MC participants, with statistical significance based on the chi-square test for independence. Variables were included in the Tables 2 through 6 if they were significant at the 0.15 level. Given the exploratory nature of this study, a more liberal 0.15 alpha level was selected to reduce Type II errors and avoid overlooking potentially important risk factors associated with SD. Logistic regression was used to obtain odds ratios (*OR*) adjusted for potential confounding factors. *ORs* assess the risk of a particular outcome (disease or disorder) if a certain factor or exposure is present. The *OR* is a

relative measure of risk indicating how much more likely it is that someone who is exposed or possesses the factor under study will develop the disorder as compared to someone who is not exposed. Adjusted *ORs* (via logistic regression) permit an examination of the influence of other variables on that relationship (e.g., age, sex, race/ethnicity, education, income). An *OR* less than 1.0 indicates a negative association; an *OR* equal to 1.0 indicates no association. An *OR* greater than 1.0 indicates a positive association between two variables. Ninety-five percent confidence intervals were obtained for the estimated *ORs*. Confidence intervals that do not overlap 1.0 indicate statistical significance at the 0.15 level. The generalized coefficient of determination was used for estimating variation in SD explained by selected demographic and other variables in the logistic model.³¹ Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA, 2003).

RESULTS

Demographics

Demographic data for SD versus MC participants are provided in Table 1. SD participants ranged in age from 23.6 to 87.8 years (Mean = 61.3 years; SD = 12.2 years); MC participants ranged from 19.4 to 86.5 years (Mean = 54.2 years; SD = 13.8 years). The SD group was significantly older as compared to the control group ($t = 4.45$, $P < 0.001$). Years of education ranged from 8 to 26 (Mean = 15.4, SD = 2.6). Mean years of school did not significantly differ between the SD group compared with the control group ($P = 0.064$). In sum, SD participants were older and more frequently White, non-Hispanic.

Short Form (SF) 36

Scores from the SF-36 were compared for the SD versus MC control groups. Subtests included: physical functioning, role limitations due to physical health, role limitations due to emotional stresses, energy/fatigue, emotional well-being, social functioning, pain levels, and general health. Higher scores for individual scales indicate better health, whereas lower scores indicate compromised health with a greater disease burden. Both SD and MC groups were within normative values for all subscales except general health, with both groups reporting below normal health scores (SD Mean = 53.1, MC Mean = 49.6; Normative Mean = 72.0). Furthermore, the two groups did not differ significantly on any of the subscales with the exception of “general health” wherein the MC group scored statistically significantly lower than the SD group ($t = 2.29$, $P = 0.023$).

Endogenous Factors

Bivariate analyses were used to assess the association between SD and numerous medical and health history factors. Personal histories (PH), immediate family histories (IFH) and extended family histories (EFH) for each factor were examined for SD versus MC participants. For purposes of this study, immediate family members included parents, brothers, sisters and children; extended family members included grandparents, grandchildren, aunts, uncles, nieces, nephews and cousins. An extensive list of factors was examined based on the following categories: generalized and focal dystonias, essential tremor variants, central/autonomic/metabolic/immune system diseases, upper respiratory conditions, health/medical conditions, and psychological features/personality traits. Significant risk and protective factors for SD participants based on PH, IFH, and EFH are presented in Tables 2 through 6. In order to distinguish which endogenous and exogenous risk factors were associated with individuals who had “SD only” versus those factors associated with “SD with coexisting vocal tremor,” additional statistical analyses were undertaken for these subgroups. The results of both analyses are summarized in the following sections.

Personal history (PH) factors. Significant PH factors unique to the entire SD group (i.e., including SD only and SD with coexisting vocal tremor) are presented in Table 2. A PH of hand tremor, vocal tremor, blepharospasm, and social anxiety were significantly associated with SD as compared to MCs based on logistic regression adjusted *ORs*. Additionally, a family history of voice disorders was significantly associated with SD (16% for SD vs. 3% for MC, $P < 0.001$; $OR = 5.3$, $95\% CI = 1.8-15.5$). No PH protective factors were identified.

In order to distinguish risk factors associated with “SD only” versus “SD with coexisting tremor”, additional analyses were undertaken. SD participants with coexisting vocal tremor were

significantly more likely to have a history of essential tremor (18% vs. 4%), head or neck tremor (25% vs. 5%), immune disorder (16% vs. 6%), thyroid problems (41% vs. 20%), and panic disorder (16% vs. 6%). For participants with SD only, adjusted for age and race/ethnicity, all of the disorders and conditions presented in Table 2 continued to be significantly positively associated with SD at the 0.15 level with the exception of essential tremor ($P = 0.397$), thyroid problems ($P = 0.632$), respiratory allergies ($P = 0.804$), and arthritis ($P = 0.361$). In a multiple regression model involving the SD only group, hand tremor ($OR = 2.5$, 95% $CI = 1.0-6.1$), blepharospasm/blinking spasm ($OR = 5.2$; 95% $CI = 1.3-10.0$) and social anxiety ($OR = 4.0$, 95% $CI = 1.6-10.0$) remained statistically significant.

Immediate family history (IFH) factors. Significant IFH factors unique to the entire SD group are presented in Table 3. An IFH of essential tremor, tic disorder, cancer, meningitis, and compulsive behaviors were significantly associated with SD as compared to MCs based on adjusted ORs using logistic regression. An IFH of “get hurt feelings easily” was identified as a potential protective factor based on MC comparisons.

SD participants with coexisting vocal tremor were significantly more likely to have an IFH of SD (11% vs. 1%), ocular disease (34% vs. 19%), and asthma (41% vs. 22%). For SD only participants, adjusted for age and race/ethnicity, all of the disorders and conditions presented in Table 3 continued to be significantly positively associated with SD at the 0.15 level with the exception of an IFH of SD ($P = 0.375$), panic disorder ($P = 0.294$), and “get hurt feelings easily” ($P = 0.318$). In a multiple regression model involving the SD only group, an IFH of essential tremor ($OR = 8.1$, 95% $CI = 1.5-41.7$), tic disorder ($OR = 16.8$, 95% $CI = 1.7-166.6$), asthma ($OR = 0.4$, 95% $CI = 0.2-0.8$), and cancer ($OR = 2.4$, 95% $CI = 1.4-4.2$) remained statistically significant.

Extended family history (EFH) factors. Significant EFH factors unique to the entire SD group are presented in Table 4. An EFH of vocal tremor and cancer were significantly associated with SD as compared to MCs based on logistic regression adjusted *ORs*. An EFH of “get hurt feelings easily” was identified as a potential protective factor based on MC comparisons.

SD participants with coexisting vocal tremor showed no increased risk for other endogenous risk factors; alternatively, they were slightly, but significantly less likely to have an EFH of muscular dystrophy (95% vs. 100%). For SD only participants, all of the disorders and conditions presented in Table 4, adjusted for age and race/ethnicity, continued to be significantly positively associated with SD at the 0.15 level with the exception of an EFH of vocal tremor ($P = 0.222$) and stroke ($P = 0.194$). In a multiple regression model involving the SD only group, an EFH of cancer ($OR = 2.3$, 95% $CI = 1.3-4.2$), other neurological symptoms ($OR = 0.2$, 95% $CI = 0.1-0.7$), and “get hurt feelings easily” ($OR = 0.1$, 95% $CI = 0.0-0.5$) remained statistically significant.

Exogenous/Environmental Factors

Bivariate analyses were used to assess the association between SD and numerous environmental exposures and diseases. A comprehensive list of factors was examined based on the following categories: surgeries, traumas/injuries, chemical exposures, viral infections, vaccinations, alcohol/tobacco/drug use, musculoskeletal tension, and voice use patterns. Significant environmental factors unique to the entire SD group are presented in Table 5. Several factors predicted SD as compared to MCs based on logistic regression adjusted *ORs*, including neck/throat tension, mumps, volunteer voice use, and intense occupational voice use. Histories of

head/neck surgery and hepatitis vaccine were identified as possible protective factors based on MC comparisons. For the entire SD group, 14% reported that the onset of their voice problems coincided with upper respiratory infection symptoms.

For SD participants with coexisting vocal tremor, all of the disorders and conditions presented in Table 5 continued to be significantly positively associated with SD at the 0.15 level with the exception of past singing ($P = 0.200$) and past public speaking ($P = 0.323$). For the SD only group, adjusted for age and race/ethnicity, neck/throat tension ($OR = 2.0$, $95\% CI = 1.0-4.2$ occasionally vs. never/rarely; $OR = 2.8$, $95\% CI = 1.4-5.6$ often/constantly vs. never/rarely), head/neck surgery ($OR = 0.2$, $95\% CI = 0.1-0.5$), other surgery ($OR = 1.9$, $95\% CI = 1.1-3.4$), mumps vaccine ($OR = 0.3$, $95\% CI = 0.2-0.7$, yes vs. no; $OR = 0.6$, $95\% CI = 0.3-1.3$, don't know vs. no), hepatitis vaccine ($OR = 0.5$, $95\% CI = 0.3-1.0$, yes vs. no; $OR = 1.5$, $95\% CI = 0.6-3.8$, don't know vs. know), and past volunteer voice use ($OR = 2.1$, $95\% CI = 1.2-3.6$) were statistically significant.

Risk Factor Summary

The generalized coefficient of determination (R^2) was calculated for all significant variables that predicted SD, including risk and protective factors. The amount of variance explained in having SD, based upon the significant endogenous, environmental, and demographic variables is presented in Table 6. Cumulatively, the significant variables identified in this study accounted for 67.8% of the variance in SD classification based on all SD participants (i.e., including SD only and SD with coexisting vocal tremor). Age, race/ethnicity, and a history of tremor had the greatest influence on predicting SD, followed by a history of mumps, family histories of SD and other voice disorders, and avocational and occupational voice

use. Results were similar for participants with SD only, accounting for 59.9% of the variance between SD and MC groups.

DISCUSSION

This study represents one of the largest case-control investigations of risk and protective factors for SD reported in the literature, and is the first to employ conventional epidemiologic statistical analysis techniques. The inclusion of a genetically unrelated, relatively homogeneous, treatment-seeking medical control (MC) group represents an improvement over previous research, making it possible to ascertain which risk factors were uniquely associated with SD. Furthermore, group equivalence between the SD and MC groups for non-voice-specific physical and emotional health complaints was established using the SF-36. Because the groups were essentially equivalent on the majority of health factors as determined by the SF-36, and other potential covariates/confounding variables (i.e., age, gender, and income level) were adequately accounted for statistically, we have greater confidence that the risk factors identified in this study are associated with the disease itself, and not related to other extraneous or spurious variables. Although a statistically significant difference between the SD and MC groups was identified for the general health subtest, both groups scored approximately 25% below norms for the general population. This finding is not surprising given the fact that both groups of patients were seeking medical treatment at tertiary care centers related to chronic or recurrent conditions of the ears, nose, or throat.

This investigation identified several factors uniquely associated with SD, cumulatively accounting for 67.8% of its variance between the SD and MC groups. Significant endogenous risk factors included: 1) a PH of blepharospasm, tremor, and a family history of voice disorders, 2) an IFH of meningitis, tremor, tics, cancer, and compulsive behaviors, and 3) an EFH of tremor and cancer. Environmental factors included a history of mumps, as well as intense occupational and avocational voice use. SD participants with coexisting vocal tremor were significantly more

likely to have a PH of several endogenous factors, including essential tremor, head or neck tremor, immune disorders, thyroid problems, and panic disorder, as well as an IFH of SD, ocular disease, and asthma. These findings are generally consistent with previous studies of risk factors for SD.^{10,14,21,22} However, several new factors emerged and other previous research findings failed to be replicated. Each of the significant risk factors identified in this study, as well as those findings previously reported in the literature that were not validated, are discussed below.

Endogenous Risk Factors

Essential tremor. It was presumed, based on previous research and theories surrounding the origin of SD, that several neurological risk factors would be associated with the presence of SD. In this study, a PH, IFH, and EFH of essential tremor was a significant discriminating factor, a finding that is consistent with previous studies related to SD heritability.^{10,19,21,22} Essential tremor is a chronic, progressive neurological disease process that involves repetitive, involuntary shaking or bobbing of the affected structure(s) in the body. Kinetic essential tremor has been attributed to abnormalities of the olivo-cerebellar-thalamic pathway. Patients with essential tremor may also experience more widespread cerebellar involvement.³² In addition to SD, tremor has been documented as a risk factor for other forms of adult onset dystonia.^{15,19}

This study supports previous research findings that vocal tremor and SD coexist in approximately 25% of cases.^{10,22} However, patients with SD and coexisting vocal tremor have a greater frequency as well as family history of neurological conditions than patients with SD alone. Although SD and tremor are thought to be distinct in terms of pathogenesis and pathophysiology,^{32,33} perhaps the coexistence of SD and tremor reflects greater neurological vulnerability to movement disorders than SD without tremor. This would explain our finding that

SD patients with tremor have a greater family history of SD, another possible indication of neurological vulnerability, as compared to patients with SD only.

Focal dystonia. Dystonia is a movement disorder involving sustained or intermittent muscle contractions frequently causing twisting and repetitive movements or abnormal posture.³⁴ An increased PH and IFH of other focal dystonias in SD, including blepharospasm, tics, and compulsive behaviors provides further evidence supporting a genetic transmission model leading to increased vulnerability for movement disorders, including SD. The present findings confirm previous reports that patients with SD and their families have increased frequency of dystonia, perhaps due to an inherited/shared predisposition for movement disorders.

Family history of voice disorders. Twenty four (24) of the 150 patients with SD reported a family history of voice disorders, including both immediate and extended family members. *ORs* indicated that individuals with SD are five times more likely to have a family history of voice disorders than individuals without SD. This might be partially explained by the co-occurrence of other neurological conditions affecting the voice in these families. We established that immediate and extended family members of patients with SD had an increased frequency of tremor and focal dystonias. Perhaps the presence of these neurological conditions (with associated voice problems) contributed to the increased frequency of voice disorders in SD families as compared to MC families (i.e., 16% versus 3%). It is impossible to determine what proportion of these data can be explained by neurological voice disorders in family members of patients with SD, versus those that could be related to other shared environmental factors. Future studies should examine the nature and type of these voice disorders, to better understand the link between family history of voice problems and SD.

Cancer. No previous research has established a family history of cancer as a possible risk factor for SD. In this study, an IFH and EFH of cancer were significantly associated with increased likelihood of SD. Given the wide variability of cancers and the combined genetic and environmental influences, it is difficult to determine the precise influence of cancer history on SD pathogenesis. It is possible that these findings might also be related to the differences in mean age between the SD and MC groups. Future studies should also explore these factors in greater detail, including specific cancer types and possible singular or combined etiologies.

Environmental Factors

Viral exposure. Consistent with previous research surrounding the onset of SD symptoms, 22 of the 150 patients with SD in the present study (14%) reported that the onset of their voice symptoms were associated with upper respiratory infection (URI) symptoms. Additionally, 101 (67%) reported a PH of mumps, which significantly discriminated the SD and MC groups. Another significant risk factor was meningitis, with 16 SD patients (11%) reporting an IFH. Patients with SD also reported a greater incidence of measles than the MCs (i.e., 71% versus 54%) although this factor failed to remain statistically significant in the regression model. Together, a PH of mumps and IFH of meningitis accounted for nearly 10% of the variance in SD classification. Adjusted *ORs* indicate that individuals with SD are twice as likely to have a PH of mumps and an IFH of meningitis.

Given the increased frequency of mumps and meningitis observed in the SD group, a brief review of these conditions is warranted. Mumps is a viral infection that primarily affects the parotid glands, with complications including encephalitis—an inflammation of the brain—and meningitis. Meningitis may be caused either by viral, bacterial or fungal infections, resulting in

swelling of the leptomeninges and subarachnoid cerebrospinal fluid. The possible encephalitic changes associated with mumps, as well as the outward symptoms of mild meningitis (headache, stiffness, fever) may go undiagnosed or treated. Therefore, it is possible for individuals with mumps to develop subclinical encephalitis, and patients exposed to meningitis to unknowingly contract the condition, without being diagnosed or treated for it. Simonyan and colleagues⁴ documented several differences in the brains of patients with SD versus healthy controls involving white matter in the internal capsule and cerebellum, as well as additional changes in the thalamus, corticobulbar tract, and the basal ganglia. The authors suggested that slow, neurodegenerative or metabolic processes might be responsible for the pathophysiology of SD. Therefore, it is possible that in some cases of SD, early viral exposures might result in pathophysiologic changes in the brain that are triggered or surface later in life. We speculate that the viral exposures documented in this study may trigger neuropathophysiologic changes in genetically predisposed individuals, ultimately later contributing to SD development.

Intense voice use. Remarkably, 124 of the 150 SD patients in this study (83%) reported a history of intense occupational voice use during their lifetimes. Additionally, 59% reported a history of frequent avocational voice use. Intense occupational and avocational voice use both discriminated the SD from the MC group, and accounted for approximately 10% of the variance in SD membership. Adjusted *ORs* indicated that individuals with SD are twice as likely to have a history of intense occupational and avocational voice use. Although this finding has not been previously documented in the SD epidemiology literature, intense voice use might be analogous to other repetitive fine motor tasks of the hands or limbs that have been shown to contribute to focal dystonia. Frucht (2004) and others have documented that repetitive motor tasks performed

by musicians place them at greater risk for developing dystonia in the affected body locus. Similarly, it is possible that the extended voice use demanded by vocally intense occupations and/or hobbies which involve repeated movements of the laryngeal musculature during voicing onset and offset might help to localize the dystonia to the larynx. Thus, these individuals might be susceptible to developing a focal dystonia of the affected body locus (i.e., the larynx). Additional research is needed to determine if a history of intense voice use is more prevalent in patients with voice disorders in general, or if it is specific to those with SD.

Qualifications and Caveats

Several possible protective factors were also identified in this study that might potentially insulate individuals from SD. Similar to the risk factors identified in this study, we suggest caution in the interpretation of these findings, and the assumption of disease prevention, based on these data. Histories of head or neck surgery and respiratory allergies were significant discriminating factors between the two groups in this study. It is essential that we consider the nature of the control group when evaluating these data however. A medical treatment-seeking group of individuals with chronic or recurrent complaints of the ears or nose were identified at hospital-based tertiary care clinics. This was intended, in order to provide a similar comparison group based on health, demographic, and other medical history factors, including the general locus of the problem. A control group selected from the general population or from other medical specialty clinics would not have afforded the homogeneity of groups based on likely covariates as was accomplished with the MC group. However, the frequency of “head” (nasal or sinus) surgery and respiratory allergies was likely to be greater in the MC group in this study. It is also important to recognize the homogeneous nature of the SD group (i.e., predominantly Caucasian)

in the generalization of these findings. Given that SD is most prevalent in Caucasian individuals, however, we feel confident that our sample represents the larger population of patients with SD.

Regarding immunization history, only the Hepatitis vaccine significantly discriminated the SD and MC groups, with a greater frequency of vaccination in the MC group. In general, the SD group reported fewer immunizations than the MC group. Again, it might not be the Hepatitis vaccine that protects against SD, but rather the general lack of immunizations in SD patients that perhaps make these individuals more vulnerable to the viral exposures that could trigger SD onset.

A multidisciplinary working group recently identified epidemiology research to identify risk factors for SD as a “high priority” research area.³³ This case-control study represents a significant first step toward the goal of identifying possible risk factors contributing to the development of SD. Future studies involving medical, voice-disordered, and general population comparison groups are warranted. Ultimately, genetic studies will be required to examine the pathogenesis of SD; additional investigation of the environmental factors identified in this and other studies will also be needed.

CONCLUSIONS

SD is likely multifactorial in etiology, involving both inherited traits and environmental factors. Viral infections and intense voice use patterns may trigger and localize the onset of SD in genetically predisposed individuals. Future studies should examine the interaction among genetic and environmental factors to determine the pathogenesis of SD.

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TABLE 1. Frequency Distributions of the SD and MC Groups According to Selected Demographic Variables, Including Chi-Squares (X^2) and Odds Ratios (OR)

Variable	SD		MC		X^2, df	OR†	95% CI†
	No.	%	No.	%	P value		
Gender							
Male	56	37	57	38	0.01, 1	1.0	---
Female	94	63	93	62	0.905	1.1	0.7-1.8
Age							
23-49	28	18	56	37		1.0	---
50-59	43	29	40	27	19.06, 3	2.2*	1.2-4.2
60-69	37	25	36	24	< 0.001*	1.8*	0.9-3.4
70+	42	28	18	12		4.2*	2.0-8.6
Race/Ethnicity							
White, non-Hispanic	149	99	133	89	15.13, 1	1.0	---
Other	1	1	17	11	< 0.001*	0.1*	0.01-0.46
Education (years)							
12	26	17	23	16		1.0	---
13-15	50	33	39	26	2.68, 3	1.5	0.7-3.1
16-17	40	27	45	30	0.444	0.9	0.4-2.0
18+	34	23	42	28		0.8	0.4-1.8
Gross Annual Income							
< \$20,000	8	5	16	11		1.0	---
\$20,000 - \$39,999	17	11	17	11		1.8	0.5-5.8
\$49,000 – \$59,999	21	14	30	20	5.84, 4	1.6	0.5-4.9
≥ \$60,000	76	51	62	41	0.2110	3.3	1.2-9.1
Do not know	28	19	25	17		2.2	0.7-6.5

* = Statistically Significant at $\alpha < .15$
† = Adjusted for Age and Race/Ethnicity
--- = Not Computed/Not Applicable

TABLE 2. Frequency Distributions of the SD and MC Groups According to Significant Personal History Factors, Including Chi-Squares (X^2) and Odds Ratios (OR)

Variable	SD		MC		X^2, df <i>P</i> value	OR†	95% CI†	OR‡	95% CI‡
	No.	%	No.	%					
Essential Tremor									
No	138	92	147	98	5.68, 1	1.0	---	NS	---
Yes	12	8	3	2	0.017*	1.6*	0.8-3.2		
Head/Neck Tremor									
No	134	89	149	99	14.03, 1	1.0	---	NS	---
Yes	16	11	1	1	< 0.001*	11.1*	1.4-87.1		
Hand Tremor									
No	120	80	140	93	11.54, 1	1.0	---	1.0	---
Yes	30	20	10	7	< 0.001*	2.8*	1.3-6.0	2.1*	0.9-5.0
Vocal Tremor									
No	106	71	149	99	48.3, 1	1.0	---	1.0	---
Yes	44	29	1	1	< 0.001*	70.9*	7.8-644.4	62.2*	6.6-582.3
Blepharospasm									
No	137	91	147	98	6.60, 1	1.0	---	1.0	---
Yes	13	9	3	2	0.012*	4.1*	1.1-15.1	4.5*	1.2-17.4
Cervical Dystonia/ Torticollis									
No	139	93	149	99	8.68, 1	1.0	---	NS	---
Yes	11	7	1	1	0.003*	10.8*	1.4-86.7		
Restless Leg									
No	118	79	131	87	3.99, 1	1.0	---	NS	---
Yes	32	21	19	13	0.046*	1.7*	0.9-3.3		

Thyroid Problem										
No	111	74	123	82	2.80, 1	1.0	---		NS	---
Yes	39	26	27	18	0.094*	1.2*	0.7-2.2			
Respiratory Allergies										
No	106	71	92	61	2.91, 1	1.0	---		NS	---
Yes	44	29	58	39	0.088*	0.7*	0.4-1.1			
Arthritis										
No	88	59	101	67	2.42, 1	1.0	---		NS	---
Yes	62	41	49	33	0.120*	1.0	0.6-1.7			
Social Anxiety										
No	124	83	141	94	9.35, 1	1.0	---	1.0		---
Yes	26	17	9	6	0.002*	3.3*	1.4-7.5	2.8*		1.1-6.8

* = Statistically Significant at $\alpha < .15$

NS = Not Significant at $\alpha < .15$

† = Adjusted for Age and Race/Ethnicity

‡ = Adjusted for All Other Variables in the Table, as well as Age and Race/Ethnicity

--- = Not Computed/Not Applicable

TABLE 3. Frequency Distributions of the SD and MC Groups According to Significant Immediate Family History Factors, Including Chi-Squares (X^2) and Odds Ratios (OR)

Variable	SD		MC		X^2, df	OR†	95% CI†	OR‡	95% CI‡
	No.	%	No.	%	<i>P</i> value				
Essential Tremor									
No	135	90	148	99	10.43, 1	1.0	---	1.0	---
Yes	15	10	2	1	0.001*	7.4*	1.6-33.9	8.7*	1.8-43.0
Head/Neck Tremor									
No	140	93	146	97	2.70, 1	1.0	---	NS	---
Yes	10	7	4	3	0.101*	2.0*	0.6-6.9		
Vocal Tremor									
No	138	92	150	100	12.50, 1	---	---	---	---
Yes	12	8	0	0	< 0.001*				
Leg/Foot Tremor									
No	150	100	146	97	4.05, 1	---	---	---	---
Yes	0	0	4	3	0.044*				
SD									
No	143	95	149	99	4.62, 1	1.0	---	---	---
Yes	7	5	1	1	0.032*	7.8*	0.9-66.7		
Oromandibular									
Dystonia									
No	150	100	147	98	3.03, 1	---	---	---	---
Yes	0	0	3	2	0.082*				
Tic Disorder									
No	141	94	148	99	4.62, 1	1.0	---	1.0	---
Yes	9	6	2	1	0.032*	6.1*	1.2-30.2	4.7*	0.9-25.7

Asthma										
No	109	73	97	65	2.23, 1	1.0	---	NS	---	
Yes	41	27	53	35	0.135*	0.8*	0.5-1.3			
Cancer										
No	71	47	97	65	9.14, 1	1.0	---	1.0	---	
Yes	79	53	53	35	0.002*	1.8*	1.1-3.0	1.8*	1.1-3.0	
Meningitis										
No	134	89	145	97	6.20, 1	1.0	---	1.0	---	
Yes	16	11	5	3	0.013*	3.7*	1.2-11.0	2.6*	0.8-8.4	
Multiple Sclerosis										
No	145	97	149	99	2.72, 1	1.0	---	NS	---	
Yes	5	3	1	1	0.099*	5.5*	0.6-49.2			
Bipolar Disorder										
No	144	96	149	99	3.66, 1	1.0	---	NS	---	
Yes	6	4	1	1	0.056*	5.5*	0.6-47.7			
Panic Disorder										
No	131	87	140	93	3.09, 1	1.0	---	NS	---	
Yes	19	13	10	7	0.079*	2.2*	0.9-5.0			
Compulsive Behaviors										
No	127	85	139	93	4.78, 1	1.0	---	1.0	---	
Yes	23	15	11	7	0.029*	2.5*	1.1-5.7	2.3*	0.9-5.9	
Get Hurt Feelings Easily										
No	133	89	124	83	2.20, 1	1.0	---	1.0	---	
Yes	17	11	26	17	0.138*	0.7*	0.3-1.3	0.4*	0.2-0.9	

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NS = Not Significant at $\alpha < .15$

- † = Adjusted for Age and Race/Ethnicity
- ‡ = Adjusted for All Other Variables in the Table, as well as Age and Race/Ethnicity
- = Not Computed/Not Applicable

TABLE 4. Frequency Distributions of the SD and MC Groups According to Significant Extended Family History Factors, Including Chi-Squares (X^2) and Odds Ratios (OR)

Variable	SD		MC		X^2, df	OR†	95% CI†	OR‡	95% CI‡
	No.	%	No.	%	<i>P</i> value				
Vocal Tremor									
No	140	93	147	98	3.94, 1	1.0	---	1.0	---
Yes	10	7	3	2	0.047	3.8*	1.0-14.7	7.6*	1.6-37.1
Blepharospasm									
No	142	95	150	100	8.22, 1	---	---	---	---
Yes	8	5	0	0	0.004*				
SD									
No	139	93	150	100	11.42, 1	---	---	---	---
Yes	11	7	0	0	< 0.001*				
Hypertension									
No	131	87	114	76	6.43, 1	1.0	---	1.0	---
Yes	19	13	36	24	0.011*	0.4*	0.2-0.8	0.4*	0.2-0.8
Cancer									
No	85	57	103	69	4.62, 1	1.0	---	1.0	---
Yes	65	43	47	31	0.032*	1.8*	1.1-3.0	2.2*	1.2-3.8
Stroke									
No	121	81	110	73	2.28, 1	1.0	---	NS	---
Yes	29	19	40	27	0.131*	0.7*	0.4-1.3		---
Other Neurological Symptoms									
No	145	97	132	88	7.96, 1	1.0	---	1.0	---
Yes	5	3	18	12	0.005*	0.3*	0.1-0.8	0.2*	0.1-0.6

Mood Disorder										
No	146	97	140	93	2.70, 1	1.0	0.1-1.0			
Yes	4	3	10	7	0.101*	0.3*		NS	---	
Distrust of Others										
No	150	10	142	95	8.22, 1					
Yes	0	0	8	5	0.004*	---	---	---	---	---
Social Anxiety										
No	147	98	142	95	2.36, 1	1.0	---			
Yes	3	2	8	5	0.124*	0.4*	0.1-1.8	NS	---	
Overly Emotional										
No	149	99	140	93	7.64, 1	1.0	---			
Yes	1	1	10	7	0.006*	0.1*	0.0-0.5	NS	---	
Get Hurt Feelings Easily										
No	146	97	133	89	8.65, 1	1.0	---	1.0	---	
Yes	4	3	17	11	0.003*	0.2*	0.1-0.6	0.1*	0.0-0.4	

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NS = Not Significant at $\alpha < .15$

† = Adjusted for Age and Race/Ethnicity

‡ = Adjusted for All Other Variables in the Table, as well as Age and Race/Ethnicity

--- = Not Computed/Not Applicable

TABLE 5. Frequency Distributions of the SD and MC Groups According to Significant Environmental Factors, Including Chi-Squares (X^2) and Odds Ratios (OR)

Variable	SD		MC		X^2, df	OR†	95% CI†	OR‡	95% CI‡
	No.	%	No.	%					
Neck/Throat Tension									
Never/Rarely	49	33	71	47	6.75, 2	1.0	---	1.0	---
Occasionally	46	31	35	23	0.034*	2.0*	1.1-3.6	2.0*	1.0-3.9
Often/Constantly	55	37	44	29		1.9*	1.1-3.3	2.2*	1.1-4.2
Head/Neck Surgery									
No	115	77	74	49	24.04, 1	1.0	---	1.0	---
Yes	35	23	76	51	< 0.001*	0.3*	0.2-0.5	0.2*	0.1-0.4
Other Surgery									
No	49	33	78	52	11.48, 1	1.0	---	NS	---
Yes	101	67	72	48	< 0.001*	2.0*	1.3-3.3		
Measles									
No	35	23	65	43	13.78, 2	1.0	---	NS	---
Yes	106	71	80	54	0.001*	1.5*	0.8-2.7		
Don't Know	9	6	5	3		2.2*	0.6-7.3		
Mumps									
No	45	30	74	49	15.87, 2	1.0	---	1.0	---
Yes	101	67	67	45	< 0.001*	1.7*	1.0-2.9	1.8*	1.0-3.3
Don't Know	4	3	9	6		0.4*	0.1-1.4	0.2*	0.0-1.0
Measles Vaccine									
No	67	45	46	31	9.61, 2				
Yes	51	34	77	51	0.008*	NS	---	NS	---
Don't Know	32	31	27	18					

Mumps Vaccine

No	78	52	55	37	10.28, 2				
Yes	42	28	68	45	0.006*	NS	---	NS	---
Don't Know	30	20	27	18					

Rubella Vaccine

No	60	40	41	27	9.13, 2				
Yes	49	33	74	49	0.010*	NS	---	NS	---
Don't Know	41	27	35	23					

Hepatitis Vaccine

No	53	35	38	25	12.58, 2	1.0	---	1.0	---
Yes	64	43	94	63	0.002*	0.6*	0.3-1.0	0.5*	0.3-0.9
Don't Know	33	22	18	12		1.3*	0.6-2.8	1.6*	0.7-3.7

Past Singing

No	42	28	58	39	3.84, 1				
Yes	108	72	92	61	0.050*	NS	---	NS	---

Past Public Speaking

No	56	37	74	49	4.40, 1	1.0	---		
Yes	94	63	76	51	0.036*	1.6*	1.0-2.6	NS	---

Past Volunteer Voice Use

No	61	41	91	61	12.00, 1	1.0	---	1.0	---
Yes	89	59	59	39	< 0.001*	2.1*	1.3-3.5	2.2*	1.3-3.9

Intense Occupational Voice Use

No	26	17	50	33	10.15, 1	1.0	---	1.0	---
Yes	124	83	100	67	0.001*	2.4*	1.3-4.3	2.3*	1.2-4.4

- * = Statistically Significant at $\alpha < .15$
- NS = Not Significant at $\alpha < .15$
- † = Adjusted for Age and Race/Ethnicity
- ‡ = Adjusted for All Other Variables in the Table, as well as Age and Race/Ethnicity
- = Not Computed/Not Applicable

TABLE 6: Percentage of SD Classification Explained by Significant Risk Factors

Variable	<i>Generalized Coefficient of Determination</i>	<i>Generalized Coefficient of Determination*</i>
Vocal Tremor	24.2%	24.2%
Head/Neck Surgery (protective)	10.4%	31.5%
Age	8.4%	34.8%
Race/Ethnicity	7.8%	41.5%
Vocal Tremor (IFH)	7.4%	43.9%
Head/Neck Tremor	7.2%	44.0%
Mumps	6.9%	45.5%
SD (EFH)	6.8%	47.3%
Family History of Voice Disorder	6.4%	47.6%
Hepatitis Vaccine (protective)	5.5%	49.1%
Past Volunteer Voice Use	5.3%	50.3%
Hand Tremor	5.2%	50.5%
Essential Tremor (IFH)	5.2%	51.4%
Other Surgery	5.0%	52.1%
Intense Occupational Voice Use	4.5%	52.9%
Social Anxiety	4.3%	53.2%
Get Hurt Feelings Easily (EFH) (protective)	4.1%	59.2%
Cancer (IFH)	4.0%	61.2%
Blepharospasm	3.1%	62.8%
Neck/Throat Tension	3.0%	63.2%
Meningitis (IFH)	2.8%	63.5%
Essential Tremor	2.7%	63.6%

Income	2.6%	64.9%
SD (IFH)	2.3%	65.0%
Tic Disorder (IFH)	2.2%	65.1%
Compulsive Behaviors (IFH)	2.2%	65.4%
Cancer (EFH)	2.0%	65.6%
Vocal Tremor (EFH)	1.8%	65.7%
Respiratory Allergies (protective)	1.3%	66.0%
Education	1.2%	67.0%
Get Hurt Feelings Easily (IFH) (protective)	1.0%	67.7%
Gender	0.0%	67.8%

* = Recomputed after adding the variables that precede it in the model.

IFH = Immediate Family History

EFH = Extended Family History