

LARYNGOLOGY

# Demographics and coexisting tremor, cervical dystonia and vocal fold disorders in a group of patients with spasmodic dysphonia

## *Dati demografici e presenza di tremore, distonia cervicale e patologie delle corde vocali in un gruppo di pazienti con disfonia spasmodica*

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### SUMMARY

The primary aim of this study is to describe the demographic and clinical characteristics of a group of patients with spasmodic dysphonia (SD). As a secondary aim, we examined associations of age at SD diagnosis and sex with co-existing cervical dystonia and nonvocal tremor; as well as association of vocal tremor with sex and nonvocal tremor. Seventy-four consecutive patients who were treated for SD at the Mayo Clinic in Jacksonville, Florida between October 1, 2015 and March 31, 2018 were included in this retrospective study. Information was collected regarding sex, age at SD diagnosis, BMI, SD diagnosis type, recent history of major stress/depression, recent history of upper respiratory tract infection (URTI), co-existing neurological diseases, and co-existing vocal disorders. The majority of patients were female (75.7%) and median age at SD diagnosis was 61 years (range: 17 – 80 years). The median BMI was 25.7 (range: 16.9 – 63.7). The most common diagnostic combinations were adductor dysphonia only (52.7%), adductor dysphonia and MTD (18.9%), and adductor dysphonia and tremor (17.6%). Co-existing tremor was present in 36.6% of patients and cervical dystonia was present in 15.5%. Co-existing vocal disorders were observed as follows: paresis/paralysis (3.1%), cyst (3.1%), mass (4.7%), polyp (1.6%), and anterior glottis web (1.6%). Sex was not notably associated with either cervical dystonia or nonvocal tremor (all  $P \geq 0.30$ ). Older age at SD diagnosis was significantly associated with cervical dystonia ( $P = 0.049$ ), but not nonvocal tremor ( $P = .22$ ). Other than co-existing tremor, most patients had no co-existing neurological diseases or vocal disorders. Additionally, patients who were older at SD diagnosis were significantly more likely to have co-existing cervical dystonia.

**KEY WORDS:** spasmodic dysphonia, demographics, risk factors, neurologic disorders, vocal fold pathologies

### RIASSUNTO

*L'obiettivo principale di questo studio è quello di descrivere le caratteristiche demografiche e cliniche di un gruppo di pazienti affetti da disfonia spasmodica (SD). Come obiettivo secondario, abbiamo valutato l'età dei pazienti al momento della diagnosi associandola al sesso e tremore non cordale. Sono stati valutati retrospettivamente settantaquattro pazienti consecutivi, trattati per SD alla Mayo Clinic di Jacksonville dall'1 ottobre 2015 al 31 marzo 2018. Sono stati raccolti dati riguardanti sesso, età alla diagnosi, BMI, tipo di SD, storia personale di stress maggiore/depressione, recenti infezioni delle vie aeree superiori (URTI), presenza di patologie neurologiche o delle corde vocali coesistenti. La maggioranza dei pazienti è risultata di sesso femminile con un'età media alla diagnosi di 61 anni (17-80). Il BMI medio è 25,7 (16,9-63,7). le associazioni diagnostiche più comuni sono state disfonia da iperadduzione e MTD (18,9%); disfonia da iperadduzione e tremore (17,6%). La disfonia da iperadduzione isolata è stata trovata nel 52,7% dei casi. Il 36,6% dei pazienti era affetto da tremore mentre il 15,5% da distonia cervicale. Sono state identificate patologie delle corde vocali come paresi/paralisi (3,1%), cisti (3,1%), neoformazioni (4,7%), polipi (1,6%), sinechie glottiche anteriori (1,6%). Non è stata riscontrata alcuna*

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### Conflict of interest

The Authors declare no conflict of interest.

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*associazione fra sesso e distonia o tremore non cordale. L'età avanzata alla diagnosi ha mostrato un'associazione statisticamente significativa con la distonia cervicale ( $P = 0,049$ ) ma non con il tremore non vocale ( $P = 0,22$ ). In questo gruppo di pazienti affetti da SD la maggior parte dei casi non mostra contestuali patologie neurologiche o patologie delle corde vocali. I pazienti più anziani alla diagnosi di SD hanno più probabilità di essere affetti da distonia cervicale.*

PAROLE CHIAVE: *distonia spasmodica, caratteristiche demografiche, fattori di rischio, malattie neurologiche, patologie delle corde vocali*

## Introduction

Spasmodic dysphonia (SD) is a voice disorder with an unknown pathogenesis. SD is considered to be an adult-onset focal dystonia and mainly diagnosed in two forms. Adductor SD is the most common, diagnosed in 90% of patients<sup>1</sup>. Epidemiologic, genetic and neurologic risk factors for SD have been addressed in several studies<sup>2-5</sup>. Most recent evidence suggests that SD is a type of focal dystonia<sup>6,7</sup>. Although the neuropathophysiologic mechanism still remains unclear, three involved neurologic mechanisms are proposed: reduced cortical inhibition, sensory-processing disturbances, and functional neuroanatomic changes in SD<sup>8</sup>.

In a three-center study, 74 of 4,447 (1.7%) patients with dysphonia had SD<sup>9</sup>. In another large study group who sought voice therapy, 21 of 821 (2.6%) patients had SD<sup>10</sup>. Risk factors for SD such as stress, upper respiratory tract infection (URTI) and coexistent neurologic diseases have been investigated in several studies<sup>2,11-15</sup>. Up to date, the relationship between age at SD diagnosis and sex with co-existing cervical dystonia (CD), nonvocal and vocal tremor has not well been studied. SD was reported to be significantly more common in females than in males in a study population who sought voice therapy<sup>10</sup>. In our study, we describe the demographics of SD, examine the associations of age at SD diagnosis and sex with coexisting CD, and evaluate associations of sex and nonvocal tremor with vocal tremor in a small group of SD patients.

We hypothesize that SD is more common in females and is commonly seen in patients with vocal tremor and/or other dystonias.

## Materials and methods

### *Study patients*

A retrospective chart review of 74 consecutive patients who were treated for SD at Mayo Clinic in Jacksonville, Florida, between October 1, 2015 and March 31, 2018 was performed. Diagnosis of SD was made based on patient history, speech examination findings and laryngoscopic examination. This study was approved by the Mayo Clinic Institutional Review Board.

All adult patients who had adductor or abductor SD with

or without any accompanying muscle tension dysphonia (MTD), vocal or non-vocal tremor, and SD were included in this retrospective study. It is not always easy to distinguish SD and MTD since the features are not always black and white and might be overlapping. Diagnosis was made by history, comprehensive speech evaluation and endoscopic visualisation of the larynx during a dynamic voice assessment using a flexible laryngoscope. Information was collected from the medical records regarding patient sex, age at SD diagnosis, body mass index, SD diagnosis type, recent history of major stress/depression, recent history of URTI, coexisting neurologic diseases and coexisting vocal disorders. A relatively large amount of data was unavailable for recent history of major stress/depression ( $n = 38$  missing) and for recent history of URTI ( $n = 41$  missing). Data was missing for fewer than 15 patients for all other variables.

### *Statistical analysis*

Continuous variables were summarised with sample median and range. Categorical variables were summarised with number and percentage of patients. Associations of sex and age at SD diagnosis (dichotomised at the median) with coexisting CD and nonvocal tremor were examined using Fisher's exact test. Associations of sex and nonvocal tremor with vocal tremor were also evaluated using Fisher's exact test. P values of 0.05 or lower were considered statistically significant and all tests were 2-sided. All statistical analyses were performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

## Results

A summary of demographic and clinical features is provided in Table I. The majority of patients were women ( $n = 56$ ; 76%), and the median age at SD diagnosis was 61 years (range, 17-80 years). The median body mass index was 25.7 (range, 16.9-63.7). The most common diagnostic combinations were adductor SD only ( $n = 39$ ; 52.7%), adductor SD and MTD ( $n = 14$ ; 18.9%) and adductor SD and tremor ( $n = 13$ ; 17.6%). Recent history of major stress/depression and URTI were observed in 58% (21/36) and 21% (7/33) of patients, respectively. Coexisting tremor (as a neurologic disease) was present in 36.6% of patients ( $n = 26$ ), and cervical dystonia was present in 15.5%

**Table I.** Demographic and clinical features of the overall cohort.

Variable	Number of records found	Summary <sup>a,b</sup>
<b>Sex (male)</b>	74	18 (24.3)
<b>Age at diagnosis, y</b>	72	61 (17-80)
<b>BMI, kg/m<sup>2</sup></b>	63	25.7 (16.9-63.7)
<b>Diagnosis:</b>	74	
adductor SD only		39 (52.7)
adductor SD and MTD		14 (18.9)
adductor SD and tremor		13 (17.6)
abductor SD only		3 (4.1)
adductor SD, MTD, and tremor		3 (4.1)
adductor SD and abductor SD		1 (1.4)
adductor SD, abductor SD and tremor		1 (1.4)
<b>Recent history of major stress/depression</b>	36	21 (58.3)
<b>Recent URTI</b>	33	7 (21.2)
<b>Coexisting neurologic disease (can have more than one):</b>	71	
Parkinson disease		0 (0.0)
cervical dystonia		11 (15.5)
nonvocal tremor		26 (36.6)
other		0 (0.0)
none		37 (47.9)
<b>Coexisting vocal disorders (can have more than one):</b>	64	
paresis/paralysis		2 (3.1)
polyp		1 (1.6)
cyst		2 (3.1)
anterior glottic web		1 (1.6)
mass		3 (4.7)
none		56 (87.5)

BMI: body mass index; MTD: muscle tension dysphonia; SD: spasmodic dysphonia; URTI: upper respiratory tract infection; <sup>a</sup>: median and range are presented for continuous variables; <sup>b</sup>: number and percentage are presented for categorical variables.

(n = 11). Coexisting vocal disorders were observed during laryngoscopy as follows: vocal mass (n = 3; 4.7%); vocal fold paresis/paralysis (n=2; 3.1%); cyst (n = 2; 3.1%); anterior glottis web (n = 1;1.6%); and polyp (n = 1; 1.6%). Only 1 patient had more than 1 coexisting vocal disorder and had anterior glottis web, right vocal fold paresis and granuloma (mass). Other patients had only 1 coexisting vocal disorder, if any.

Table II displays associations of sex and age at SD diagnosis with coexisting CD and tremor (as a neurologic disease). Diagnosis of 'CD' and 'tremor' were driven from the clinical notes of neurologists in patient charts. Sex was not notably associated with either CD or tremor; CD was present in 3 (16.7%) of men and 8 (14.3%) of women (P = 1.00) and tremor was present in 4 (22.2%) men and 22 (39.3%) women (P = 0.30). CD was significantly associated with age at SD diagnosis, being present in 2 (5.6%) patients with an age at diagnosis 60 years or younger (n = 36) compared to 9 (25.0%) patients diagnosed after age 60 (n = 36) (P = 0.049). Nonvocal tremor was not strongly associated with age at diagnosis, occurring in 10 (27.8%) patients with an age at diagnosis of 60 years or younger (n = 36) and 16 (44.4%) patients diagnosed after age 60 (n = 36) (P = 0.22).

Associations of sex and nonvocal tremor with vocal tremor are shown in Table III. There was no notable association between sex and vocal tremor (P = 1.00), although there was a significant association between nonvocal tremor and vocal tremor (P = 0.001). Specifically, of 26 patients with nonvocal tremor, 12 (46.2%) had vocal tremor compared to only 5 (11.1%) patients in the subgroup without nonvocal tremor (n = 45).

**Table II.** Associations of patient sex and age with coexisting neurologic disease.

Variable	Association with CD		Association with nonvocal tremor	
	No. (%) with CD (n = 74)	P value <sup>a</sup>	No. (%) with nonvocal tremor (n = 74)	P value <sup>a</sup>
<b>Sex:</b>		1.00		0.30
male (n = 18)	3 (16.7)		4 (22.2)	
female (n = 56)	8 (14.3)		22 (39.3)	
<b>Age at diagnosis:</b>		0.049		0.22
≤ 60 (n = 36)	2 (5.6%)		10 (27.8%)	
> 60 (n = 36)	9 (25.0%)		16 (44.4%)	

CD: cervical dystonia; <sup>a</sup>: P values result from Fisher exact test.

**Table III.** Associations of sex and nonvocal tremor with vocal tremor.

Variable	No. (%) with vocal tremor (n = 74)	P value <sup>a</sup>
<b>Sex:</b>		1.00
Male (n = 18)	4 (22.2)	
Female (n = 56)	13 (23.2)	
<b>Nonvocal tremor:</b>		0.001
Yes (n = 26)	12 (46.2)	
No (n = 45)	5 (11.1)	

<sup>a</sup>: P values result from Fisher exact test.

## Discussion

SD, also known lately as laryngeal dystonia, has no known aetiology and cure to date. Risk factors for SD and associations between other neurologic diseases and SD have attracted the interest of laryngologists and neurologists. In our group of SD patients, as well as demographics and risk factors, we examined the relationship between age at diagnosis and sex with CD, nonvocal and vocal tremor.

The majority of our patients were women (76%), in concurrence with the literature. In a review of epidemiology in SD patients by Tanner, the female:male ratio was 3:1<sup>1</sup>. Patel et al reported 77.6% of patients were women in an SD group of 718 patients<sup>15</sup>, and Schweinfurth et al reported 79% female dominance in their study of 168 patients with SD<sup>3</sup>. Female predominance in SD might be attributed to genetic, hormonal, or autoimmune factors, but this remains unknown.

Median age at diagnosis was 61 years in our cohort (range, 17-80 years). In other studies, median age was from 43 to 59 years<sup>2,3,13,15-18</sup>. The older age of onset in our patient cohort might be attributed to delay in diagnosis as well as delay in consulting to a tertiary care clinic. Creighton et. al. reported in their study on 107 patients using a questionnaire that it took 4.43 years to be diagnosed with SD after first going to a physician with vocal symptoms<sup>19</sup>. They concluded that 'objective criteria for the diagnosis of SD and increased clinician education are warranted to address this diagnostic delay.'

The most common diagnostic combinations in our study group were adductor SD alone (53%), adductor SD and MTD (19%) and adductor SD and tremor (18%). Adductor SD incidence among all SD patients is reported to be between 82% and 91.8% in the literature<sup>1,13,15,16,20</sup>. In our study cohort, 95.9% of the patients had adductor SD (alone or combined with abductor SD, MTD and/or tremor). Abductor SD (alone or combined with adductor SD and/or vocal tremor) constituted 6.8% of all patients.

Vocal tremor is not a rare finding in SD patients. Patients with SD were reported to be 12.8 times more likely to have vocal tremor than the control group in a study by White et al.<sup>17</sup> In another study, vocal tremor was confirmed with electromyogram in 29% of SD patients<sup>21</sup>. Vocal tremor prevalence was between 26% and 32% in other studies<sup>13,16,17</sup>. In our study, vocal tremor prevalence was 23.0%; 23.2 % of female patients and 22.2% of male patients had vocal tremor. This is in agreement with, but slightly lower than other studies. The highest vocal tremor incidence among SD patients was reported by Patel et al., being 54.5% in their study group; 60.0% among women, and 32.8% among men<sup>15</sup>. Vocal tremor is a clinical diagnosis. The variety of

incidences in different studies might be attributed to the lack of objective diagnostic measures for vocal tremor.

Recent history of major stress/depression and URTI prior to onset of symptoms was observed in 58% and 21% of patients, respectively, in our SD patients. In 1983, Schaefer documented that SD symptom onset followed URTI in a small group of patients<sup>11</sup>. In 1984, Izdebski et al, comparing 200 SD patients with 200 case-controls, found no statistically significant precipitating factors for SD including URTI, stress, occupation, and voice use patterns<sup>2</sup>. In a chart review of 350 SD patients, Childs et al. identified the most common risk factors for SD as stress (42%), URTI (33%) and pregnancy/parturition (10%)<sup>12</sup>. In 2012, Tanner compared 150 SD patients with 136 patients having other voice disorders using a questionnaire, and reported that SD is uniquely associated with a personal history of sinus and throat illnesses, mumps and rubella<sup>1</sup>. Schweinfurth et al, in their study on 168 SD patients who completed a questionnaire, reported that 30% of patients related the onset of symptoms to URTI and 21% to stress<sup>3</sup>. White and colleagues, in 2012 investigated the prevalence of anxiety and depression in SD, comparing 128 SD patients with 146 case-controls with other voice disorders. The results showed that individuals with SD are no more likely to have anxiety or depression than those with other voice disorders. However, there was association between anxiety and depression and patients with voice disorders<sup>14</sup>.

Coexisting nonvocal tremor in our SD group was present in 37% of patients, and coexisting CD was present in 16%. Schweinfurth et al. reported that essential tremor was found in 26% of their 168 SD patients<sup>3</sup>. In 2011, Tanner et al. compared 150 SD patients with 150 case controls with normal voices, and SD was reported to be related to personal history of tremor, as well as family history of tremor<sup>13</sup>. In contrast, patients with SD were no more likely to have nonvocal tremor than the control group in a study by White et al.<sup>17</sup>. SD patients were more likely to have CD than the patients with other vocal disorders in another study by Tanner et al.<sup>4</sup>. Increased incidence of other dystonias, especially blepharospasm, and writer's cramp was also seen in SD patients<sup>13</sup>. Patel et al. reported that other movement disorders (CD, blepharospasm, limb dystonia, oromandibular dystonia) were found in 5.2 % of their group of 718 SD patients<sup>15</sup>.

Coexisting vocal disorders were observed as follows: vocal mass (5%), vocal fold paresis/paralysis (3%), cyst (3%), anterior glottis web (2%) and polyp (2%). Tanner et al. reported that risk factors for SD included occupational and avocational voice use as well as family history of voice disorders<sup>13</sup>. In another study, a history of frequent,

occupationally intense voice use was prevalent in both SD and voice disorders case-control group. However, those in the SD group had been employed in this type of job for more years<sup>4</sup>. We did not encounter any SD studies in the English literature reporting simultaneous vocal disorders with SD.

Sex was not notably associated with either CD or nonvocal tremor in our SD patient group. In the literature, predictive factors associated with increased nonvocal tremor severity include older age, longer disease duration, presence of vocal tremor and a longer follow-up duration<sup>22</sup>. CD was significantly associated with age at SD diagnosis, with a higher incidence in patients diagnosed after age 60; however, nonvocal tremor did not reveal an association with age at diagnosis.

SD patients with vocal tremor have shown higher associated nonvocal tremor<sup>15</sup>. In our group, there was a significant association between nonvocal tremor and vocal tremor ( $P = 0.001$ ). Specifically, of the patients with nonvocal tremor, 46% had vocal tremor compared to only 11% of patients in the subgroup without nonvocal tremor. White et al. stated that ‘the presence of comorbid nonvocal tremor in patients with vocal tremor is > 50% in both controls and patients with SD’; therefore the authors recommended referral of all patients with SD and/or vocal tremor to a neurologist for a thorough evaluation<sup>17</sup>.

Our study did not fully examine family histories of neurologic disorders and voice disorders, or personal history of infectious disease as identified by Tanner and Schweinfurth, or the gradual or sudden onset as identified by Childs et al.<sup>1,3,12</sup>. Several limitations of this study are important to bear in mind. First, the retrospective design introduces biases into data collection and yielded a large amount of missing data for some variables. Additionally, we did not include a control group of non-SD patients and are therefore unable to properly evaluate risk factors for SD. Finally, the sample size of the study was relatively small, resulting in a lack of precision in the descriptive summaries presented.

In the literature, there are not many studies regarding the risk factors for and co-existence with SD. More prospective studies are needed in order to better understand SD and thus to improve the clinicians’ approach to SD patients. We believe this study will raise more questions and interest on the subject.

## Conclusions

In this group of SD patients, a majority of patients were women and presented with adductor SD. Other than coexisting tremor, most patients had no coexisting

neurologic diseases or vocal disorders. Additionally, patients who were older at SD diagnosis were significantly more likely to have coexisting CD. However, this finding may simply reflect the tendency to experience more coexisting health conditions as patients age. SD patients should be evaluated for coexisting tremor or dystonias, as treating them can improve vocal outcomes.

## Acknowledgements

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