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## **Review of differential diagnosis and management of spasmodic dysphonia**

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### **Abstract**

Purpose of Review: The recent literature on spasmodic dysphonia is reviewed with regard to pathogenesis, differential diagnosis, treatment options, audits, and current methods of management.

Recent Findings: Advances in technology have enabled clinicians to better understand the connection between brain and laryngeal function and dysfunction. Refinements in imaging and genetic investigation techniques have led to advances in the understanding of the underlying mechanism of this neuro-laryngeal disorder. Development of diagnostic assessment tools and measures of Quality of Life hold the potential to improve treatment and care.

Summary: Fifty articles published between 2014 and 2015 were selected for this review. The sources were drawn from several clinical specialties: 54% come under the scope of laryngology, 32% from neurology, and 14% from other areas. It remains poorly understood,

misdiagnosed and under diagnosed. Its identification, diagnosis, treatment selection, and coordination of care require an expert specialist multi-disciplinary team. More training is required to help people who have this chronic and psychosocially disabling voice disorder, which impinges on all aspects of their lives. Spasmodic dysphonia is now classified as a “rare” disease in the USA. This designation will assist in international standards of diagnosis, assessment, treatment, and management.

**Keywords:** spasmodic dysphonia, laryngeal dystonia, botulinum toxin, quality of life

## **Introduction**

The focus of this review is spasmodic dysphonia (SD), also called laryngeal dystonia. It will address differential diagnosis, methods of investigation, treatment, and management of this vocal cord function disorder in adults. It will not consider other laryngeal impairments such as paradoxical vocal fold motion disorder, difficulties pertaining to oromandibular or palatal function, or pulmonary conditions. Genetic aspects of spasmodic dysphonia will be considered, but not research dealing with the genetics of dystonia more generally. We review treatment options including surgery, neuromodulation and intralaryngeal botulinum toxin type A (BoNT-A) injections, however investigations regarding the pharmacological activity of other varieties are not included. Research published in languages other than English has been regrettably omitted.

## **Background**

Laryngoscopic visualization of abnormal spasms of the adductor muscles of the vocal cords during speaking was first described 150 years ago [1]. Years of speculation followed about whether these vocal symptoms were of organic or psychogenic origin. The abnormal vocal cord movements were characterised as dystonic tic in the 1980s [2]. Now, SD is recognised as an idiopathic focal dystonia affecting the intrinsic muscles of the larynx. It is classified as a Rare Disease (RD) by the National Institutes of Health USA, with a prevalence of 14 per 100,000 predominantly affecting women (2.5:1). Peak onset incidence ages are 30-50 years. Vocal symptoms range from occasional difficulty to sustained inability to phonate [3]. SD presents with two main phenotypes: (a) the more common adductor SD (ADSD), and (b) the relatively rare abductor SD (ABSD). Mixed SD (MSD) involves characteristics of both types. Vocal tremor often coexists with SD [4].

## **Pathogenesis**

The central processes underlying the aetiology and pathophysiology of laryngeal dystonia are multifactorial [5]. Traditionally, SD was thought to result from basal ganglia abnormalities. The pathogenesis of SD is currently considered to involve genetic and environmental factors [6]. Advances in imaging techniques using magnetic resonance imaging (MRI) functional magnetic resonance imaging (fMRI), positron emission tomography (PET), transcranial magnetic stimulation (TMS) and transcranial sonography (TCS) have enhanced our understanding of voice and speech production processes and the relationship between brain and laryngeal function.

Bilaterally distributed functional sensorimotor brain networks are imaged on MRI during oral sentence production speech in healthy controls [7]. Speech production preferentially recruited in the inferior parietal lobule and cerebellum into large-scale networks. Interregional connectivity during speaking was stronger in the left hemisphere. The laryngeal motor cortex established a core network overlapping with speech related networks [7]. Imaging abnormal functional networks in patients with SD has been demonstrated using MRI [8, 9], PET [10], TMS [11, 12], TCS [13], and proprioceptive acuity [14]. The consensus points to the involvement of large-scale brain networks for speech production, and thus SD may be a heterogeneous disorder. Brain abnormalities appear to alter central control of voluntary voice production. SD is likely due to a sensory disorder with the muscle spindle playing a central role [13]. The terms used to describe vocal movement impairments are not systematic or standardised. Nomenclature for vocal fold movement impairments which currently apply to paresis or paralysis could be expanded to include other movement variables, such as spasm [15].

## **Diagnosis and Differential Diagnosis**

Although SD is most common, other dystonic laryngeal manifestations can exist: stridor, dis-coordinated breathing, paroxysmal cough, hiccups and sneezing [4]. Focal dystonias have been recently described to selectively impair the cricothyroid [16] and hyoid muscle [17]. There are new descriptions of task-specific laryngeal spasms during singing, but not speaking [18] and in dystonic cough [4]. ADSD and ABSD differ in their acoustic characteristics. In ADSD, hyperactivity of the adductor muscles (thyroarytenoid) result in voice breaks and consequent alterations in phonation and pitch. In ABSD, the spasms occur in the posterior cricoarytenoid muscles resulting in breathy, segmented speech. Patients with ADSD have

greater difficulty with voiced sounds and ABSD with unvoiced sounds [19]. MSD involves characteristics of both. Perceptual voice feature characteristic of ADSD and ABSD are similar. Both show slow, effortful, dysfluent speech, whilst whispering and non-speech vocalization, crying and laughing are normal [19]. High subglottic pressure is associated with sudden adduction followed by high airflow associated with voice breaks. These prominent aerodynamic findings correlate with the perceptual judgements of ADSD [5].

Accurate diagnosis of ADSD is challenging. The perceptual voice characteristics are often misdiagnosed as a functional voice disorder, muscle tension dysphonia (MTD). Due to differences in their aetiology, treatment options are different. People with MTD respond to traditional behavioural voice therapy unlike people with ADSD. Misdiagnosis can lead to ineffective, time-consuming and expensive treatments. ADSD is typically diagnosed on clinical evaluation, and confirmed by videolarngoscopic evidence of excessive spasmodic adduction of the vocal cords [20, 21]. In SD with dysphagia, videofluoroscopic swallowing investigation is used [22]. Voice spectography provides objective measures of sound alterations [20]. Voice onset time in word initial voiceless consonant is found to differ between ADSD, ABSD and controls, and may serve to further quantify SD voice symptoms [23].

### **Assessment, Treatment and Outcome**

More rigorous multidimensional SD rating scales with demonstrated reliability, validity, and responsiveness are needed for accurate diagnosis and clinical evaluation of treatment effectiveness [24]. To ensure differential diagnostic accuracy and appropriate treatment recommendations, voice quality scaling and acoustic analysis should include tasks with various utterance durations including sentence-length items [19]. Expert listeners have been trained to differentiate between SD and tremor over the telephone [3]. This may provide an efficient new differential diagnostic tool. The main computerised software programme used in acoustic analysis is the Multi-Dimensional Voice Programme. The new operaVOX analysis software combines perceptual and acoustic evaluation. Multi-Dimensional Voice Programme and operaVOX compare for reliability on measures of fundamental frequency, jitter and shimmer, but not noise to harmonic ratio [25].

Increased risk of mood disorders is identified in voice-disordered patients [3], with low correlation between the patient's and the clinician's subjective voice analyses. Only the patient can provide real information about their experience [26]. The Voice Handicap Index assesses the impact of voice disorder on the patient's quality of life (QOL). The qualitative questionnaire measures the functional, emotional and psychosocial consequences of voice disorder [20] and is useful for evaluating clinical effectiveness. Inclusion of wellness and/or QOL as an outcome measure is important to establish an evidence base for appropriate patient interventions. The experience of anxiety and situational voice problems can be assessed using the standardised self-report Behaviour Assessment Battery modified for voice to quantify speech-related anxiety and negative speech-associated attitudes [27]. Such a battery may help with diagnosis and designing a tailored multi-dimensional treatment plan for patients with SD [28].

Patients with ADSD and ABSD often complain that speaking is effortful. Vocal effort can be measured in a variety of ways: (a) physical/physiological, (b) aerodynamic, (c) acoustic, and (d) perceptual. A new measure--the Borg-CR10, assesses the experience of vocal effort in voiced disordered patients but is not sensitive to measure the severity of impairment [29]. The perception of vocal effort notably appears to be a trained phenomenon requiring an awareness of the internal sense of effort. Training for perception of effort and control for individual differences in internal awareness may be necessary to obtain valid effort ratings. In healthy individuals, an increased sense of vocal effort is reflected in measures of sub-glottal pressure, trans-laryngeal airflow, and maximum flow declination rate. The acoustic cepstral signal is positively correlated with vocal effort [30]. There is a stronger relationship between aerodynamic and acoustic measures of vocal effort within rather than across individuals [31]. Future work is needed to establish the relationship between these measures in voice disordered individuals.

A qualitative study [32] of expert and everyday listener's perception of ADSD individuals demonstrated that both could appreciate the abnormal vocal quality. Both groups made assumptions about speakers with ADSD based on their voice and described the overall severity for ADSD speech as strongly related to perceived vocal effort. This study highlights the sound and speech characteristics of SD that evoke negative and judgemental reactions from listeners. As a result, individuals with SD experience a social penalty [33]. This emphasises the need for a better understanding of the underlying basis of perceptual judgements of voice in everyday communication [32]. SD also impacts on individuals' QOL

and productivity in the workplace. New standardized work-related QOL assessment scales are needed to determine how SD affects the quality and quantity of their work [34].

Treatment for SD includes alcohol [35], surgery [10, 36, 37], neuromodulation [38] and intra-laryngeal injections of BoNT-A with various injection techniques using electromyography guidance (EMG) [16, 39, 40]. Dosages and titrations of BoNT-A are also being investigated [41-44]. Several audits of long-term outcomes have been carried out. The largest longitudinal group study on 1,300 patients with SD (82% ADSD) has been updated [45]. Retrospective demographic data is also reported from Mayo Clinic, Arizona, USA [46] and Mumbai, India [47]. In the Indian study, 80% of patients were male in contrast to international studies of SD, where the ratio is 80% female. Higher dose titrations were also used for both ADSD and ABSD compared to other centres.

### **Current situation**

Time from onset to diagnosis can be an indicator of the quality of care received during the diagnosis of adult onset dystonia [48]. Although SD diagnosis has improved, it remains unacceptably delayed [49]. Better education in the understanding of the particular signs and symptoms of this voice disorder is required. One limiting factor in arriving at a diagnosis, and a contributing factor to limited therapeutic interventions, is our lack of full understanding of SD phenomenology, aetiology and pathophysiology [35]. Misdiagnosis can lead to ineffective time-consuming and expensive treatments that may not be beneficial. Moreover, there is no available gold standard test for differential diagnosis [50]. A large proportion of the SD population may be un-diagnosed and untreated in the USA [3].

BoNT-A injections is less beneficial for some forms of SD. It is estimated that 90% of ADSD patients receive 90% benefit, while only 10% of ABSD patients receive 70% benefit. Co-occurring vocal tremor has an unpredictable response [35]. However, BoNT-A injections are expensive and typically must be repeated every 3-4 months throughout a patient's life which may lead to both psychological and financial burden [35]. There is a complex relationship between the impact of diagnosis, clinical practice, prescription habits, health insurance rules, and patient compliance. In many countries, health insurance rules determine the maximum amount of intervention or cost which significantly impacts on temporal variables of voice therapy. International consensus is required regarding duration and frequency, and optimal treatment practice [51]. With regard to QOL, patients with SD reported a negative impact on the quantity and quality of their work [34]. The timing of

BoNT-A injections may play an important role in determining the degree to which the symptoms of SD affect a person's job performance.

SD is now classified as a RD by the National Institute of Health, USA. At an international level, it is a category in the "Rare Clinical Disease Network," a part of the Dystonia coalition working to advance the pace of clinical and translational research to find better treatments and a cure. The Strategy for Rare Diseases, NHS England's statement of intent sets out 51 commitments agreed to be achieved by 2020 including: (a) empowering those with RD, (b) identifying and preventing RD, (c) diagnosis and early intervention, (d) coordination of care, and (e) role of research [52].

### **Conclusion**

SD is a heterogeneous, multifaceted, and multifactorial chronic and incurable voice disorder of unknown aetiology. It is still under- or misdiagnosed. There is no gold standard diagnostic test for differential diagnosis. Accurate diagnosis and treatment require a multidisciplinary team of experts. Current treatment options offer symptomatic relief. Intralaryngeal, EMG guided injections of BoNT-A are still the current gold standard treatment modality. On the plus side, advances in imaging techniques have improved the understanding of the neurogenic basis for the disorder. SD is now classified as a RD in the USA. We urgently hope that this recognition can be adopted by other countries to facilitate the empowerment of individuals with SD and develop international standards for diagnosis, treatment, and care.

### **Key Points**

- Brain abnormalities in patients with SD may alter central control of voluntary voice production.
- SD may be due to a sensory disorder, with the muscle spindle playing a central role.
- Diagnosis, treatment, and management needs to be multifactorial and provided by an expert multi-disciplinary team.
- Differential diagnosis can be assisted by new acoustic and perceptual assessment tools.
- SD has a significant impact on QOL and leads to social penalty.

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