Adductor Spasmodic Dysphonia

Ton Langeveld

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Proefschrift

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Aan mijn ouders

Voor Denise

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General introduction

1.1

In 1965, Bloch[1] wrote: "Man is distinguished among the other biological systems by the prodigious extension of his faculty of communication. Homo faber, homo loquens, homo sapiens, are the three essential qualifications that ethnology attributed to him. Man's primary means of communication is speech. He is unique among life forms in his ability to acquire and use speech." It is even more remarkable that he has derived this ability from a physiological apparatus primarily designed for other purposes: the vital functions of breathing and eating.

Communication cannot occur in isolation. It is essentially a dynamic process of interaction between two or more people, in which thoughts, ideas and feelings are exchanged. For the exchange to be effective each participant has to conform to the rules which govern communicative 'competence' and 'performance'.[2] 'Competence' presumes that the speaker 'knows' what he or she wishes to say (i.e. has access to an intact cognitive system). It also presumes that the speaker has access to a means of 'saying it', via intact phonological, lexical, syntactic, and prosodic processes. Successful 'performance' is dependent upon the relay of information in a manner which is intelligible to the listener. This depends on the fine motor coordination of respiration, phonation, and articulation. Non-verbal behavior such as

gesture and facial expression constitutes an integral part of the communication process. Thus, the total communication process consists of a number of modules, both on the speaker's side (initial concept, linguistic processing, and eventual production) and the listener's side (reception, recognition, and comprehension of the message).

As was already pointed out, speech and language functions are of fundamental human significance, both in social interaction and in private intellectual life. When they are disturbed, the resultant functional loss exceeds all others in gravity – even blindness, deafness, and paralysis.[3] Trauma, disease, or defect can have a devastating effect on one or more of the aforementioned modules. For example, aphasia or dysphasia can lead to a loss or impairment of the production and/or the comprehension of spoken or written language due to an acquired lesion of the brain. Another example is dysarthria, a defect in articulation, which is a pure motor disorder of the muscles of articulation and may be due to flaccid or spastic paralysis, rigidity, repetitive spasms, or ataxia. In contrast, articulation in head and neck cancer patients is often largely and irreversibly affected by the tumor and/or treatment.

Similarly, a disorder of the larynx or its innervation can result in aphonia or dysphonia. Articulation and language are unaffected, but the soundsource is. How seriously this can disturb speech, communication, and ultimately one's life, is illustrated most clearly by adductor spasmodic dysphonia (ADSD), in which vocal function becomes both unpredictable and unreliable. The impaired communication of patients with ADSD often results in withdrawal from social life and isolation. On top of this, many patients are initially diagnosed as having a psychogenic voice disorder, with social stigmatization as a consequence. Moreover, due to this misdiagnosis, therapy fails and many patients resort to alternative treatment modalities and "medical shopping". Depression and anxiety, feelings of frustration and negative attitudes towards communication, often accompanied with somatic complaints, are frequently observed in patients with spasmodic dysphonia.

In the late 1980's at the ENT-department of the Leiden University Medical Center a new treatment modality was developed for genuine psychogenic voice disorders: visualization.[4] The favorable results of this newly employed method were spread by word of mouth. As the effect was so spectacular, some cases were reported in the popular press. This media exposure elicited a stream of patients to our department. From 1992 until 1997 about 600 patients with a presumed psychogenic voice disorder were seen for a second opinion. In more than 500

patients the psychogenic nature of their disorder was confirmed. However, 86 patients were diagnosed as having adductor spasmodic dysphonia. Encouraging results were reported in literature on the effect of botulinum toxin treatment for spasmodic dysphonia. These findings initiated the research and treatment of this group in our department. The results of these observations and experiments are reported in this thesis.

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Spasmodic dysphonia: a review

1.2

History

Introduction

Adductor spasmodic dysphonia (ADSD) is primarily a disturbance of phonation. Patients with this bizarre voice disorder produce a strained-strangled, harsh voice with breaks in pitch and phonation (staccato-like catches), loudness bursts, and glottal fry.[1] In this effortful voice quality, volume is reduced and often a tremor can be perceived. Remarkably, these symptoms are reduced or absent during whispering, speaking or singing in falsetto register and nonspeech vocalizations like laughing, crying, and yawning. Spasmodic dysphonia is initially intermittent and task or situation specific. The marked intermittency and functional specificity of the symptoms have suggested a psychological basis for this enigmatic voice disorder.[2]

A Psychogenic Approach

Traube[3] is credited as the first who described a case of SD in 1871:

> *"Die spastische Form der nervösen Heiserkeit beobachtete Professor Traube bei einem hysterischen jungen Mädchen. Die sehr heisere, fast aphonische Patientin vermochte mit grosser Anstrengung nur zuweilen sehr hohe, fistulirende Töne anzuschlagen. Die larygoscopische Untersuchung ergab einen krapfhaften Verschluss der Stimmritze, wobei die linke Cartilago Arythaenoidea sich vor die rechte schob und wahrscheinlich auch die Stimmbänder zum Theil sich deckten. Das verhalten dieser letzteren war deßhalb nicht zu eruiren, weil die Epiglottis stark nach hinten geneigt war. Auch in diesem Falle hatte der electrische inconstante Strom keine Wirkung."*

He based his diagnosis on the short duration of the illness and assumed a hysterical etiology. This was the origin of psychogenic theories on SD. In the following decades a psychogenic etiology of SD was almost universally accepted. In the fifties and sixties this view was still so pervasive that Arnold[122] was moved to write that since the first description, "all authors agreed that spastic dysphonia represented a psychoneurotic disorder of pneumophonic coordination". Specifically, most clinicians[123,41] viewed the SD voice complex as a hysterical conversion reaction wherein some psychic conflict becomes somatized to the laryngeal sphincter. In neuropsychiatric terms, this process was described by Heaver[123] as a "regressive sequence of loss of cortical inhibition as it was replaced by the clinical ascendancy of medullary primitive phonatory mechanisms" (p.23). Working within this psychoanalytic tradition, Brodnitz[53] retrospectively reviewed 130 SD cases seen in the course of his career and reported that 41% could pinpoint SD onset following severe emotional trauma. An additional 22% were said to exhibit many of the symptoms of severe neuroses. Descriptive enumerations of such symptoms in association with SD frequently include anxiety, depression, and hypochondriasis or somatic preoccupation.[123,41] Interestingly, the psychoanalytically oriented researchers also concurred that psychotherapy had in general not proven effective in the treatment of spasmodic dysphonia. This was due, in their view, to the emotional disorder itself, which inhibits insight and leads to a resistive unwillingness by the patient to cooperate appropriately in the psychotherapeutic process.[2,41,53,123]

An organic approach

Synchronically, several reports were published in which an organic etiology was postulated. The first was by Schnitzler[4] in 1875, who described two patients with "cramping of the vocal cords and forced voice". These patients were noted to have synkinesis of facial muscles and abnormal movements of the arms and legs. He called this organic disorder "aphonia spastica" or spastic dysphonia.[5] A more detailed description followed by Critchley[6] in 1939. He described three patients with SD-like symptoms and suggested cerebellar or basal ganglion pathology. He also reviewed several cases reported by Ramsay Hunt (1914), Schuster (1924), and Meige (1928) and concluded that this speech disorder in combination with

various head and neck clonic movements were part of an underlying neurologic disease rather than proof of psychiatric affliction.

In the fifties, Segré[7] described fifteen cases of SD, of which some appeared to be based on a neurological disorder (tabes dorsalis and multiple sclerosis). Many therapeutic options were described. Functional prognosis, however, was not favorable. Therefore, in some cases "recourse to surgery was necessary" (p.155). Segré proposed anaesthetizing the pharynx and the larynx to determine which muscles might be transected to alleviate the symptoms of laryngeal spasm. In some cases this led to the disappearance of symptoms, which was useful for the confirmation of functional causes of aphonia. Segré[7] describes the three operations by Réthi, Chevalier Jackson and King. The first was based on the concept that the hyperadduction of the ventricular bands and supraglottic closure depended above all on the hyperactivity of the stylopharyngeal muscles. Réthi had devised a simple external intervention to cut off those fibers, partly or entirely. A placebo effect, however, was thought of as Segré[7] stated: "This intervention probably acts as suggestive psychotherapy". Chevalier Jackson proposed "the cutting of a central and symmetrical 'cuneus' (wedge) in both ventricular bands in cases of spastic dysphonia". In King's method the arytenoid was fixed laterally, to "neutralize the spasmodic dysphonia without converting it into a paretical dysphonia".

In 1960, Robe[8] published the results of an electroencephalographic study of ten SD patients. Four patients had a positive history of neurologic disease in the family. All patients had signs of central nervous system (CNS) disease and all but one of the electroencephalograms were abnormal. Robe concluded that spastic dysphonia is a "manifestation of disordered function of the central nervous system and is not a disease in sui generis". However, the variability of symptoms, signs, and course from patient to patient precluded a general statement. Besides, the author did not deny the existence of psychiatric abnormalities in spastic dysphonia, or that psychotherapy did not have a place in the treatment.

Although these findings were not duplicated by subsequent investigators, they clearly led the way for future challenges to the concept that all cases of SD were due to psychiatric disturbance.[9]

In 1968, Aronson[10,11] recognized the need for further investigation of both the symptoms and the causes of spastic dysphonia. In the late sixties it was still generally accepted[10] that "spastic dysphonia, being a vocal expression of psychoneurosis, should usually be classified as a conversion reaction. Neurasthenic neurosis

and emotional trauma have been mentioned as causes, as well as, but to a lesser extent, vocal abuse in professional persons who use their voices extensively" (p.205). In this extensive work Aronson[10] described 1. the variations in quality and severity of the symptoms, 2. the neurologic characteristics; and 3. the psychiatric characteristics and results of a standardized psychometric test – Minnesota Multiphasic Personality Inventory (MMPI) in 34 SD patients. Firstly, he found that "their voices showed excessively low pitch, monopitch, harshness, intermittent voice stoppage, and voice tremor occurred in more than 70% of the patients. Secondly, twenty-seven of the patients were examined neurologically and 20 had one or more neurologic signs, including tremor, hyperreflexia, reduced alternate motion rate, and faciolingual asymmetries. These signs occurred with a greater frequency than would be expected in a normal population. From this they hypothesized that spastic dysphonia had a neurologic substrate and might be related to the essential tremor syndrome. Thirdly, on the MMPI, no statistically significant differences occurred between the profiles of the SD patients and those of a large population of normal persons. Of the 29 patients given psychiatric interviews, 18 were judged to have some emotional problems and 11 none. Although as a group they gave the impression of being compulsive, of overcontrolling their anger, and of being quite unaggressive verbally, it is suggested that these traits are not exclusively characteristics of spastic dysphonia but are quite common in patients having a variety of emotional problems" (p.217).

Because of the hypothesized relation between spastic dysphonia and essential tremor, Aronson[11] undertook a consecutive study in which he focussed on the similarities and differences between the voice symptoms of these two disorders. Essential tremor was selected because it appeared to have more of the features of spastic dysphonia than did other neurologic dysphonias. In addition, he compared the voice symptoms of spastic dysphonia and essential tremor with the voice symptoms of pseudobulbar palsy, amyotrophic lateral sclerosis, bulbar palsy, cerebellar ataxia, and parkinsonism. He concluded that pitch lowering, pitch breaks, voice tremor, and strain-strangled dysphonia were not exclusive symptoms of spasmodic dysphonia. He noted that SD symptoms tended to be present from the time of onset, while psychogenic voice disorders were episodic, a point that could be significant in differentiating SD from psychogenic dysphonias.[9,11]

In Aronson's study[11] another interesting issue was touched upon. He proposed a change in the term 'spastic dysphonia'. 'Spastic' is commonly used to imply disease of corticobulbar or corticospinal (pyramidal) pathways. The neurologic evidence in his study was mainly an affection of the extrapyramidal system.

He observed that the strained voice quality in this voice disorder waxes and wanes from moment to moment in a spasmodic fashion. Therefore, he proposed the term 'spasmodic dysphonia', to prevent the confusion that could arise from the use of the term 'spastic'. The many (historical) synonyms of spasmodic dysphonia are listed in the *Addendum*.

In 1971, McCall[12] and coworkers offered substantial evidence for considering spasmodic dysphonia as a neurologic disorder. By means of videofluoroscopic observations they provided evidence that spasmodic dysphonia might be symptomatic of isolated, phonatory-related laryngospasms or might appear in association with a more general problem that affects the behavior of the laryngeal and pharyngeal musculature during quiet respiration as well as during contextual speech. They concluded that patients with spasmodic dysphonia might exhibit atypical movement patterns in the larynx and pharynx that are tremor-related or apparent manifestations of muscular dystonia. They were the first who related spasmodic dysphonia to dystonia.

This view was endorsed by Aminoff[13] in 1978. In a clinical study of 12 patients with spasmodic dysphonia he found that the dysphonia was part of a more widespread neurological disorder (idiopathic torsion dystonia, blepharospasm, postural tremor). He concluded that the voice disorder is probably due to a focal dystonia of the laryngeal musculature. Moreover, it was hypothesized that its pathological basis is related to basal ganglia dysfunction as it is in idiopathic torsion dystonia.

In 1982, Marsden and Sheehy[14] reported the relationship between blepharospasm-oromandibular dystonia (Meige syndrome, cranial dystonia), torsion dystonia, and spasmodic dysphonia. In their series they noted multiple presentations of the voice disturbances in these patients and hypothesized that isolated spasmodic dysphonia may be a sole manifestation of dystonia. These findings were in line with the study of Golper et al.[15] They analyzed the clinical findings and speech characteristics of a group of 10 persons with the diagnosis of Meige syndrome. They found that aside from the blepharospasm and oromandibular involvement, some patients also had involvement of platysma, soft palate, tongue, pharynx, esophagus and respiratory muscles. Half of the subjects had voice abnormalities. These included voice stoppages, inhalation phonation, strain-strangled voice, vocal tremor, and audible grunts at the end of phrases. The authors contended that most of these signs were suggestive of dystonia.

In 1985, Blitzer and coworkers[16] performed an electromyographic study in 14 patients with 'spastic' / spasmodic dysphonia. Their findings were not indicative for spasticity of the laryngeal musculature, as was already suggested by Aronson.[11] Clinical observation and EMG data identified patients with tremor (2/14), pyramidal and extrapyramidal disease (1/14), and myoclonic disorder (1/14). The remaining 10 patients had clinical and EMG findings consistent with dystonia, a neurologic disorder characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms and concluded that these patients had 'focal laryngeal dystonia'. They classified spasmodic dysphonia as a type of dystonia (laryngeal dystonia) that may present focally or in association with other dystonic movements.

Dystonic movements may be either slow and sustained, or rapid turning movements that result in involuntary postures that interfere with smooth functioning. Patients may present with focal dystonia which involves one region or group of muscles. Examples are blepharospasm (forced, involuntary eye closure), oromandibular dystonia (involving facial, jaw, and tongue muscles), torticollis (neck muscles), and writer's cramp (action-induced involvement of hand muscles). When multiple regions are involved, the condition is classified as multifocal, unilateral, or generalized.

Primary (idiopathic) dystonia is typically action-induced. The symptom is enhanced with use of the affected body part, which usually appears normal at rest. According to the etiologic classification, primary or idiopathic disease is found in patients who have no personal history of neurologic illness or exposure to drugs known to cause acquired dystonia, e.g., phenothiazines, and who have normal intellectual, pyramidal, cerebellar, and sensory examinations, and normal diagnostic studies. Patients who have these abnormalities are classified as having secondary dystonia. Clinical phenomenology is often a clue as to etiology. Movement and resulting postures are often unusual and, therefore, dystonias are one of the most frequently misdiagnosed neurological conditions.[17]

Symptoms of dystonia usually begin as focal dystonia involving a single region of the body. Spread to other regions is commonly seen in childhood-onset dystonia, while the disorder tends to remain focal with adult-onset.[18] Some of these conditions were thought to have a psychogenic origin because they were triggered by specific actions, exacerbated during mental and social stress, and might have been associated with psychiatric disability without obvious cause. However, a central nervous system cause is supported in most cases.[16]

Several authors have described tremor activity in patients with spasmodic dysphonia.[11,16,19-23] Blitzer[16] noted that almost 25% had an irregular tremor of 4-8Hz on phonation. Aronson and Hartman[19] studied this tremor more closely in patients with dysphonia and noted that it was similar to that in persons with essential tremor. They also observed that several patients had synchronous pharyngeal, lingual, velar, mandibular, facial, thoracic, or diaphragmatic tremor. Ludlow[20] also observed a vocal tremor that affected vocal amplitude, and wrote of a possible link between essential tremor and spasmodic dysphonia. In a videoendoscopic study of 38 patients with spasmodic dysphonia, Woodson[21] noted tremor of the larynx or pharynx in 29 patients. Rosenfield[22] found essential tremor in 71 of 100 patients with spasmodic dysphonia, involving the larynx or pharynx in 59 subjects. In a recent review on laryngeal dystonia (spasmodic dysphonia) Brin and coworkers[23] found that many patients with spasmodic dysphonia present with a tremulous voice. The differential diagnosis between spasmodic vocal breaks due to essential tremor and those due to a dystonic tremor can be difficult. However, the frequent association between essential tremor and dystonia suggests that these two disorders may de pathogenically linked, or that physiologic mechanisms underlying one disorder predispose these patients to develop the other and vice versa.[24]

In 1992, Izdebski[34] published a physiologic model on the symptomatology of adductor spasmodic dysphonia. He wrote that in dystonia the amplitude, timing and coordination of contraction of groups of muscles are affected, and the pattern strongly suggests faulty coordination of afferent and efferent signals, possibly in the basal ganglia. The basal ganglia are thought to be responsible for automatic execution of motor programs, and influence the weighing and timing of movements. They take into account the desired movement (motor command), current activity and afferent signals, and may compare these in order to calculate the appropriate muscle activation. Giving too much emphasis to the motor command or reduced weight to arriving sensory signals could generate excessive muscle activation. This theory can explain why simple functions may be spared whilst specific and more complex motor programs are impaired. In other dystonias, such as torticollis, the primary involuntary movement may be overpowered by erratic or forceful antagonist contractions, or by the 'geste antagonistique' and sensory tricks. According to the author, in ADSD, the primary over-activity is of the vocalis adductor complex. The brain may misread the adductor state of the glottis and respond with inappropriate sudden efferent discharges. Many of the other features could be compensatory and involve conscious adjustments.

Spasmodic dysphonia: current opinion

Adductor spasmodic dysphonia is an uncommon, often severely disabling chronic voice disorder of unknown etiology. It is supposed that it is a focal (laryngeal) dystonia. Dystonia is a neurological disorder of central motor processing characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms, probably related to basal ganglia dysfunction. Therefore, spasmodic dysphonia can be considered as an action-induced laryngeal movement disorder.

Symptomatology

Introduction

Spasmodic dysphonia, a focal laryngeal dystonia, is a chronic neurological disorder of central motor processing characterized by action-induced spasms of the vocal folds. The vocal folds are normal at rest, but with an action-induced task-specific movement, the muscles contract inappropriately, causing abnormal movements and muscle spasms, typically resulting in dysphonia during speaking.[25] In 1973, Aronson[1] described two major types of spasmodic dysphonia, based on these perceptual voice characteristics: an adductor (ADSD) and an abductor (ABSD) type.

Adductor spasmodic dysphonia

ADSD, the more common form, typically presents insidiously during middle age. Symptom onset is usually gradual, beginning with uncontrolled voice breaks, hoarseness, and increased effort associated with speaking. Like other focal dystonias, it is initially intermittent and task or situation specific, and gradually becomes more intrusive, more frequent and severe. The symptoms typically progress over 1 to 2 years and then remain chronic. Patients report that onset may have been associated with an upper respiratory infection, a stressful period in their life, or no apparent cause.

There is no single characteristic that defines ADSD, and each patient has a different combination of features. Generally, however, the voice is characterized by pitch and/or voice breaks during vowels, difficulties initiating voice, and a harsh, strained-strangled voice quality.[26] Some patients attempt to overcome their speech difficulties by whispering or by raising the pitch of their voice or using inspiratory speech. However, when asked to try to speak 'normally' or without compensating, a typical adductor speech pattern is evident. Many patients find that speaking involves undue physical effort and is very tiring.[27] Moments of improved speech are noted during emotional or physiological states, such as joy, anger or intoxication, or following

yawning, and may occur during ingressive speech, in non-speech vocalization and during paralinguistic utterances, such as 'uh-uh'. Although some patients may improve, shouting and stress usually make the speech worse. Patients may use any of these maneuvers to compensate for, or mask, SD, and it can be difficult to distinguish between compensatory strategies and the primary vocal symptoms.[31]

Abductor spasmodic dysphonia

The less common abductor type is characterized by spasms of the posterior cricoarytenoid muscles, producing a breathy, effortful hypophonic voice with abrupt termination of voicing, causing aphonic or whispered segments of speech.[25] Originally, the term abductor spasmodic dysphonia was used in reference to a perceptually distinctive voice in which normal or hoarse voice is suddenly interrupted by brief moments of breathy or whispered (unphonated) segments. As described to Aronson[28]: "The term abductor spasmodic dysphonia was chosen because it appeared as if the vocal fold physiology responsible for the voice disorder was the opposite of that which occurs in adductor spasmodic dysphonia, i.e. instead of spasmodic hyperadduction of the vocal folds producing moments of strained voice or voice arrest, the vocal folds spasmodically hyperabduct, releasing bursts of unphonated air. Although the disorder has not long been recognized, evidence is beginning to show that, as with the adductor forms, abductor spasmodic dysphonia may not be due to a single cause, but may have either psychogenic or neurologic substrates".

Adductor and abductor spasmodic dysphonia: a continuum disorder?

Both the adductor and abductor type are believed to be due to hypertonia in different sets of laryngeal muscles. Cannito and Johnson[29] proposed that both adductor and abductor abnormalities exist in all patients and that the symptoms depend on whether there is more adductor or abductor activity. Their view was endorsed by the findings of Hanson[30] et al who performed a kinematic analysis of video-documented laryngeal examinations in spasmodic dysphonia patients. They believed that the relative balance of abductor versus adductor on perceptual symptoms results from the relative imbalance of muscle tone between adductor and abductor muscle fibers and that kinematic data do not suggest that adductor and abductor symptoms in SD result from different basic pathophysiologies. Moreover, they supported the view that spasmodic dysphonia is a heterogeneic symptom complex, that may result from a variety of CNS lesions, neuromuscular diseases, and movement disorders when these diseases affect control of laryngeal muscles.

Epidemiology

The incidence and prevalence of adductor spasmodic dysphonia in the general population is unknown.[28] The consensus, however, is that ADSD is rare. The best guess as to its prevalence is based upon a survey of cases at the Mayo Clinic from the records of people residing within the limits of Rochester, Minnesota.[32,33] The prevalence of diagnosed generalized dystonia within this community was estimated at 34 per million and of the various focal dystonias at 296 per million. The total prevalence of all forms of dystonia being 330 per million. The authors commented that the estimates of the incidence and prevalence of focal dystonia might be low. These syndromes are often not brought to medical attention, and if so, are frequently not recognized and documented. Extrapolating these figures for the Netherlands, it would yield an incidence of 45 and a prevalence of approximately 750.

Of 2556 cases of dystonia registered at the Dystonia Clinical Research Center at Columbia-Presbyterian Medical Center, New York City, 562 (22%) had laryngeal involvement.[17] Of these 562 patients, 464 (82.5%) had primary (idiopathic) dystonia and 98 (17.5%) had secondary (acquired) dystonia. Of the group with primary dystonia, 273 (59%) were women and 191 (41%) were men. Of those with primary laryngeal involvement, 15% had involvement of other parts of their body. Twenty percent of patients with primary laryngeal dystonia had a family history of dystonia.

In a recent study of Brin[23] the demographic data of 901 patients with laryngeal dystonia were described (Table 2).

Table 1. Incidence and prevalence of dystonia (Nutt[33]).

	Incidence*	Prevalence†
Generalized dystonia	2	34
Focal dystonia:	25	296
– Cranial dystonia	8	86
– Spasmodic dysphonia	3	52
– Spasmodic torticollis	11	89
– Writer's cramp	3	69
Total	27	330

* crude incidence per 10^6 person-years

† crude prevalence per 10^6 persons

Table 2. Laryngeal dystonia in 910 patients (Brin[23]).

	Dystonia		Number	%
	Primary	Secondary		
N	744	157	901	
Age onset	39	40		
Female	471	109	580	64.4
Focal	492	83	575	63.8
Segmental cranial	161	32	193	21.4
Multi-segmental	51	17	68	7.5
Generalized	40	25	65	7.2
% Adductor	83	73		

Diagnostic assessment

Introduction

Actually, it is not hard to diagnose ADSD: often there is a typical history and voice. However, a number of difficulties are encountered in the diagnostic work-up of patients with spasmodic dysphonia. Objective 'gold-standard' tests are lacking. Dystonic symptoms vary considerably over time, during different tasks and in different situations. Patients may whisper or speak in falsetto in an attempt to escape from the strain-strangled, staccato voice, thus masking their dystonia and hampering diagnosis. Finally, spasmodic dysphonia is a relatively rare voice disorder that is not familiar to many clinicians.

For adequate evaluation of patients with spasmodic dysphonia a team consisting of an otolaryngologist, neurologist, and speech-language pathologist is necessary to exclude pathologies other than spasmodic dysphonia. Team evaluation rests on the identification of characteristic clinical phenomenology.[35] The diagnosis is based on history, physical examination, perceptual evaluation of voice, laryngological and general neurologic examination.

Medical history

The history of a patient with ADSD is rather typical. With rare exception, adductor spasmodic dysphonia begins insidiously as a non-specific hoarseness, at first fluctuating in severity, with intervening periods of normal voice. Then, gradually, the strained adductor laryngospasms intrude, breaking up the hoarseness. The

disorder may plateau or continue to worsen until phonation during speech is all but impossible.[28] Moments of improved speech may be triggered by either intoxication (e.g. alcohol) or, by different psychologic states such as anger or joy.[34] Improved speech has also been observed during choral reading, ingressive speech, during or immediately following yawning, and in non-speech vocalizations.[31,34,40] Many patients have an acceptable singing voice. Poor symptom control and exacerbation of symptom severity by stress has also been reported as typical in ADSD patients.[41,42]

Perceptual analysis

The analysis of perceptual symptoms is one of the mainstays in the diagnostic work-up of spasmodic dysphonia. There is universal agreement that the strained-strangled (overpressured) voice quality is characteristic of ADSD. An impressive body of descriptions is used to characterize ADSD perceptually (Addendum).

Already in the late 1970's overpressure was defined as the main ADSD symptom. Systematic studies of ADSD voice quality followed and revealed tremor, aperiodicity, breathiness and vocal arrests in addition to overpressure.[39,71] Based on the physiologic assessment of ADSD symptoms Izdebski[34] et al designed a symptomatologic model of ADSD. This was the first objective modeling of the symptoms and a diagnostic test battery was derived from this work.

A purely perceptual taxonomy of ADSD symptoms was also compiled into the Unified Spasmodic Dysphonia Rating Scale (USDRS), quantifying fourteen perceptual symptoms in conversational speech and six voice tasks that improve or worsen perceptual symptoms.[35]

In this clinic diagnostic criteria are based on a set of elementary phonatory tasks capable of generating or eliminating ADSD symptoms and differentiating between related voice disorders. These criteria are derived from the 'minimal diagnostic vocal test battery' described by Izdebski.[34] The original protocol of Izdebski was adapted to fit our needs. Consequently, the following subtests are now employed:

1. Sustained phonation at varied frequency and intensity levels,
2. All-voiced and voiced-voiceless speech,
3. Modal, falsetto, and whisper modes,
4. Vegetative tasks (coughing, in- and expiration).

A number of these tasks elicit ADSD symptoms in a predictable and systematic fashion: predominantly in loud modal phonation. Symptoms will be significantly

diminished or even absent at high F_0 levels and while whispering, regardless of loudness levels. Because symptoms occur more frequently during a fully approximated glottis, speech containing all-voiced segments will more readily display overpressure than will speech containing voiced-voiceless segments. When overpressure leads to generation of vocal arrests, these will be irregular. In contrast, tremor tends to be more regular and remains present throughout both modal and falsetto range, as well as in whisper mode. Tremor of laryngeal musculature will also be present in vegetative tasks, including inspiration and expiration, while SD type vocal arrests and overpressure will be absent in these vegetative tasks.

Laryngological and neurological examination

Fiberlaryngoscopy is performed to observe the glottal function and exclude structural lesions of the larynx and vocal fold paralysis. The symmetry, range, speed, and control of vocal fold adduction and abduction can be observed during speech and non-speech tasks (e.g. at rest, quiet breathing, sniffing, and coughing). Abnormalities (disruptions, spasms, breathy breaks, and tremor) appear particularly in vowels and in voiced sentences. Blitzer[25] describes a variation of the staging system proposed by Koufman[43] and Morrison and Rammage.[44] Type 1 hyperadduction is forceful overcontraction at the vocal fold level with tight compression of the vocal processes and arytenoids. Type 2 is forceful contraction including contact of the false cords. In type 3 the thyroarytenoid muscle pulls the arytenoids anteriorly, narrowing the supraglottic airway. Type 4 is sphincteric closure, where by the arytenoids are pulled so far anteriorly that they tightly close against the epiglottis. Although these classifications are not obligatory for the diagnostic assessment, they can be useful in describing the pretreatment phenomenology of the larynx. A comprehensive neurologic history and examination has to be performed, with particular attention for any spasms, dysfunction, or tremor of an other area in the head and neck.

Laryngeal electromyography

Laryngeal EMG, although not diagnostic, may be very useful in defining the EMG characteristics of the laryngeal abnormality.[17] In 1946 Tarrasch[46] performed the first study where muscle activity in SD patients was sampled. She found a consistent marked increase in muscle activity during phonation in SD patients as compared with levels obtained in 4 control subjects. In 1985, spasmodic dysphonia was linked to dystonia through a clinical and EMG evaluation of SD patients and patients with multifocal or generalized dystonia.[16] The same group (Blitzer and Brin[47]) performed an analysis of laryngeal electromyograms in 110 patients with spasmodic dysphonia. This revealed 23% of cases with an irregular tremor activity

(4-8Hz), while only 6% were found to have a regular tremor (similar to essential tremor). Seventeen percent of cases had enlarged potentials, while 4% had small potentials, and 6% had reduced numbers of motor units.

Schaefer[48] performed EMG suggesting involvement beyond the vagal nerve. When the EMG signal is simultaneously analyzed with a voice spectrogram, a greater than normal delay in onset of sound production is observed, especially in the adductor type. Ludlow et al[49] found abnormally high resting activity levels in both the thyroarytenoid (TA) and cricothyroid (CT) muscles. They demonstrated an imbalance between the TA and CT muscles resulting in excessive adductor and shortening tension on the vocal cords during quiet respiration, speech and swallowing. Moreover, uncontrolled spasmodic bursts of muscle activity in the TA and CT muscles were observed during speech and phonation. By measuring muscle activity only during symptom production, Nash[50] concluded that the voice breaks in ADSD are due to an intrusion of spasmodic bursts upon an otherwise normal muscle activation pattern. Therefore, laryngeal EMG is a valuable tool for a better understanding of the pathophysiology of this disorder. However, according to Rosenfield[45] detecting such abnormalities requires complicated analysis techniques and offers minimal practical use for routine diagnostic investigation.

Several other tests have been used to evaluate ADSD. However, most of these are used to measure the effect of treatment. The most relevant tests will be discussed in the next paragraph on treatment of spasmodic dysphonia. Some diseases with vocal symptoms and signs which might encompass spasmodic dysphonia, are listed in table 3.

Table 3. Differential diagnosis: some neurological disorders with spasmodic dysphonia (Whurr[31]).

Dystonia, with or without tremor	
Essential tremor	
Other tremor:	(druginduced - cerebellar - rubral)
Psychogenic disorders	
Tics / stuttering	
Degenerative disorders:	(Parkinson's disease, Wilson's disease, motor neuron disease, progressive supranuclear palsies, olivopontocerebellar atrophy)
Inflammatory disease	
Myoclonus	
Chorea	
Tardive dyskinesia	
Cerebral palsies	

Treatment options

Introduction

There is no known cure for adductor spasmodic dysphonia. Authors who have written about spasmodic dysphonia agree on the poor results of any form of therapy. For many decades, ADSD had been considered as a psychogenic voice disorder. Therefore, treatment was directed along psychological lines for many years. With few exceptions, however, psychotherapy (in the widest sense of the word), hypnotism, acupuncture, homeopathy, and biofeedback relaxation techniques have consistently failed, and speech therapy was rarely helpful. Treatment of dystonia with medications (muscle relaxants, tranquilizers, etc.) usually resulted in an incomplete response and was frequently unsuccessful. Moreover, some of them caused intolerable side effects. These experiences were already put into words at the beginning of the twentieth century by Moll[54]:

> *"Over de therapie kan Spreker kort zijn, daar patiënt nog slechts zeer kort onder zijn observatie is. Veel stelt Spreker zich van de behandeling, welke ook, niet voor, wegens de ervaring van Semon en Mackenzie, die zeggen, dat noch een psychische, noch een physische behandeling, noch de strengste, langdurige rust der stem, noch methodische spreek- en ademoefeningen, noch locale aanwending van electriciteit aan en in de hals, noch inwendige middelen en koudwaterkuur, in één woord dat niets een blijvend resultaat heeft opgeleverd en de aandoening dus zoo goed als ongeneeslijk is."*

In 1976, more than hundred years after the first description of spasmodic dysphonia by Traube in 1871, no progress had been made towards its treatment. As Brodnitz[53] pointed out: "Until newer research can achieve a more thorough understanding of the etiology of the disease, and thereby provide a rationale for more successful therapy, the combination of voice therapy with psychotherapy still offers the best chances for ameliorating this disorder" (p.214).

Recurrent laryngeal nerve section

Therapy for spasmodic dysphonia underwent a significant advance with the introduction of recurrent laryngeal nerve sectioning (RLNS) by Dedo[55] in 1976. He hypothesized that "if a recurrent laryngeal nerve was paralyzed in a patient with spastic dysphonia, the other vocal cord might prove to be 'precompensated' so that its excessively strong adduction would carry it across the midline to the deliberately paralyzed cord, giving a relatively normal phonation" (p.452). For the first patient, he chose a woman with a 17-year history of spasmodic dysphonia who had been seen by more than 29 doctors of varying specialties without improvement of her voice and who yet persisted in her willingness to seek help. Temporary paralysis of the recurrent laryngeal nerve by lidocaine injection left the patient with a husky phonation without obvious spasm. The huskiness of her voice was then corrected by teaching the patient to raise the pitch and bringing the sound "up in front of her mouth" (p.453). After five trials of lidocaine injections, with paralysis of the vocal cord confirmed each time by indirect laryngoscopy, the patient underwent sectioning of her right recurrent laryngeal nerve. Postoperatively, with the help of speech therapy, she developed "essentially normal voice" within weeks. Moreover, she resumed her political, radio, and television career after an 18-year hiatus (p.453). Subsequently, 33 additional patients underwent similar treatment. These 33 patients were selected from a group of 41 patients who had temporary lidocaine-induced paralysis of their right recurrent laryngeal nerves. Placebo injection did not change the voice in any of these patients. Dedo stated all patients were pleased with the improvement of their voices and noted a decrease in associated head and neck tics and grimaces. Two of the patients had breathy but phonatory voice when tired or competing with environmental noise.

In the following years, several institutions reported their results of RLNS with initially good results.[56-66] Some modifications of Dedo's original technique were investiga-

ted in the hope of reducing the breathy and weak voice, which usually followed ablation. Amongst them were crushing and avulsion of the nerve, and the selective section of the adductor branch.[57,64,65] Once again, almost all patients had initial improvement. Subsequent experiences indicated, however, that the voice sometimes was excessively breathy and that, after a while, the spasmodic symptoms recurred in a significant number of patients. Recurrence was often worse than the original presentation.[57,59,66]

Particularly Aronson[66] objected to RLNS on the grounds of long-term results. He reviewed 33 patients treated with surgery. By three years, only 36% of patients had some persistent improvement and only 1 of 33 achieved a persistent normal voice. Adverse effects included breathiness, hoarseness, diplophonia, and falsetto. Of the 64% with failed voices at 3 years, 48% were worse than before surgery. Failures were more common among women (77%) than men (36%). He found that the return of symptoms was not produced by reactivation of the paralyzed vocal cord but by intensification of normal fold adduction either alone or together with hyperreactivity of the supraglottic constrictors, along with elevation of the larynx from hypercontraction of the extrinsic laryngeal musculature.[66] Comparable unsatisfactory long-term results were reported by other authors.[57,59,67]

Recurrence of spasmodic closure has been attributed to increased function of the opposite vocal fold. Blitzer et al[51] postulated that the return of symptoms in these patients was due to stressing the remaining functioning vocal cord, thereby intensifying the dystonic symptoms. This experience is shared with the nerve section of branches of the facial nerve for therapy of blepharospasm, and cervical rhizotomies for torticollis. Often these procedures result in only temporary relief and may have unacceptable complications.[52]

An EMG study performed by Ludlow[69] indicated, however, that patients who had recurrent spasms often had measurable activity in the supposedly paralyzed muscle. This was probably due to regeneration of the recurrent laryngeal nerve. An experimental study in dogs demonstrated that this nerve rapidly regenerated after transection, although not accurately.[70] Netterville and colleagues[64] re-operated on patients with recurrent symptoms and confirmed that the previously divided recurrent laryngeal nerve had indeed become intact once more.

Adjunctive procedures have been described in an effort to improve the results of recurrent laryngeal nerve section.[71] Teflon injection has been used in patients

who had persistent significant breathiness or aspiration. This had to be performed cautiously and conservatively, because too much closure would result in a return of vocal tightness. In patients who had recurrent or persistent tightness, 'thinning' of the paralyzed vocal fold with a CO_2 laser was advocated.[68]

In summary, recurrent laryngeal nerve section originally seemed to be the treatment of choice for spasmodic dysphonia because of the excellent immediate results. However, on long-term follow-up many failures were found leaving a poor voice and the consequences of a paralyzed vocal cord. At about the time that these surgical limitations were becoming apparent, botulinum toxin A became available and is now the treatment of choice.[27]

Botulinum toxin

The concept of using this potent neurotoxin to treat patients with disorders of muscle function is credited to Dr Alan B. Scott, from the Smith-Kettlewell Eye Research Foundation in San Francisco. In 1970-71, in an effort to develop a non-surgical treatment for strabismus, he developed an elegant EMG-guided technique to inject small doses of botulinum toxin type A into extraocular muscles, with the aim of weakening them.[72] By 1973, he demonstrated in animal experiments that it appeared suitable for treatment of strabismus, and also suggested that it may be beneficial in blepharospasm.[73] In 1977, Scott injected the first strabismus patient, and, in 1980, published the results of the first clinical trial botulinum toxin type A for strabismus.[74]

In 1984, the Food and Drug Administration (FDA) licensed botulinum toxin type A in the USA as the 'orphan' drug Oculinum, manufactured by Allergan. In December 1989, after extensive laboratory and clinical testing of botulinum toxin type A, the FDA approved this biologic agent for therapeutic use in patients with strabismus, blepharospasm, and other facial nerve disorders, including hemifacial spasm. Oculinum was renamed as Botox®.[72]

The neurotoxins produced by Clostridium botulinum are the most potent acute toxins known and are the causative agents of the neuroparalytic disease botulism. There are seven immunologically distinct toxins (A-G). Type A has been studied most intensively and is used most widely, but the clinical applications of the other types are also being explored. All are polypeptides of a molecular weight of about 150 kDa that have a similar structure and pharmacological action. In their most active forms the toxins exist as dichain molecules in which a heavy (H) chain is

linked by disulphide bonding to a light (L) chain associated with a single atom of zinc.[76] The heavy chain is responsible for targeting the toxin to cholinergic neurons. The light chain is the toxic portion of the molecule.[79]

Botulinum toxin - mode of action

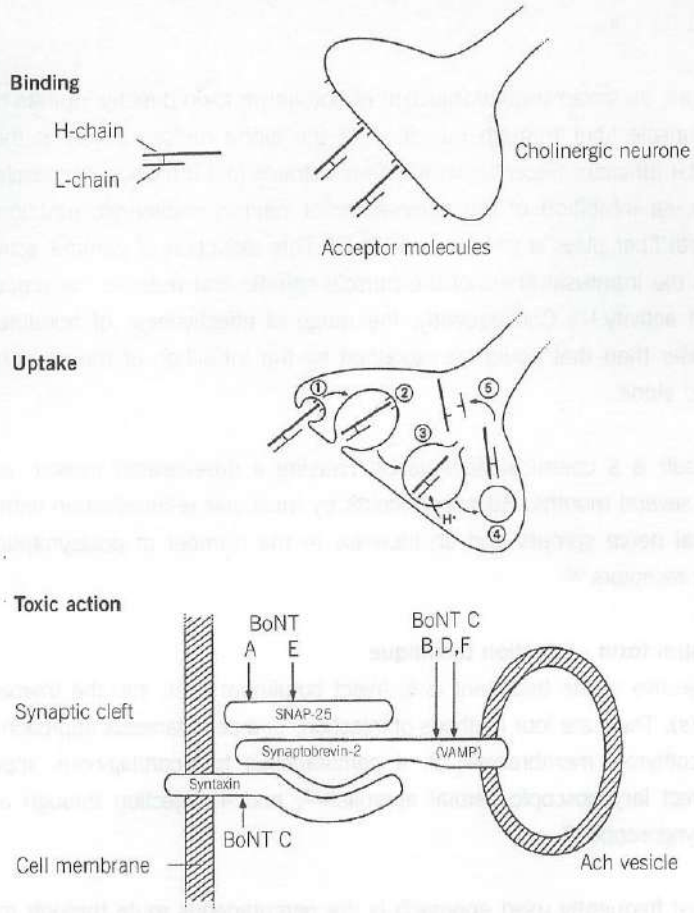
The botulinum neurotoxins are extremely potent agents having specific toxicities ranging from $2x10^7$ to $2x10^8$ mouse LD_{50} doses mg^{-1} protein. They act presynaptically by blocking the release of the neurotransmitter acetylcholine at the neuromuscular junction.[76] Three stages may be involved in inhibition (Figure 1,[79]):

1. Toxin binding. In this primary step the toxin binds rapidly and irreversibly to acceptors on the presynaptic membrane. The H-chain of the toxin is responsible for the highly selective targeting of the toxin to peripheral cholinergic nerve terminals. It binds selectively and irreversibly to a small pool of high affinity acceptor molecules at the presynaptic surface.

2. Internalization. During the next stage the toxin crosses the cell membrane (plasmalemma) and enters the nerve terminus. Following binding to the acceptor on the nerve surface the neurotoxin is internalized by an energy-dependent process. This probably resembles receptor-mediated endocytosis with the toxin-acceptor complex becoming encapsulated in endosomes that migrate into the cytosol.[77] Before it can act, the toxin must penetrate the endosomal membrane and escape into the cytosol. The endosome contents are actively acidified by a proton pump in its membrane. At low pH, the toxin changes conformation (channel formation) and can insert into the lipid bilayer of the vesicle and translocate the 50kDa L-chain into the cytosol.[78]

3. Toxic activity. In the final stage the acetylcholine-release mechanism is disabled. It is the L-chain that is the toxic portion of the botulinum neurotoxins.[79] Inside the cytosol, the L-chain catalyses the Zn^{2+}-dependent proteolysis of one of the components of the neuroexocytosis apparatus.[78] Normally, the arrival of an action potential at the nerve ending triggers an influx of calcium ions which promotes the exocytosis of acetylcholine from vesicles at active zones on the plasmalemma.[76] In the neuroexocytosis process three proteins play a crucial role: vesicle-associated membrane protein (VAMP) also known as synaptobrevin, which is an integral protein of the synaptic vesicle membrane. The synaptosomal-associated protein (SNAP-25) and syntaxin are both proteins of the cytosolic face of the presynaptic membrane. Botulinum neurotoxin B, D, F, and G attack VAMP, whereas botulinum neurotoxin A and E cleave SNAP-25 and C cleaves both SNAP-25

Figure 1. Mechanisms of binding and uptake and the toxic actions of the botulinum neurotoxins within the cholineric nerve terminal (Hambleton and Moore[79]).



Binding: The heavy (H) chain is responsible for binding and uptake of the toxin, and the light (L) chain is the toxin portion.

Uptake: is an active, energy-dependent process using endocytosis (1,2), and escape of toxin into the cytoplasm (3,4). It is not clear whether the two chains become dissociated in vivo before the L-chain produces its toxic effect (5).

Toxic action: Syntaxin is a protein that is embedded in the cell surface plasma membrane, and SNAP-25 is a cytoplasmic protein that transiently associates with the membrane. Synaptobrevin-2 (VAMP) is embedded within the membrane of the synaptic vesicles. Damage to these proteins by the botulinum neurotoxins blocks fushion of the vesicle with the cell membrane and release of acetylcholine (Ach) into the synaptic cleft. The sites of action of the botulinum toxins (A-F) are indicated.

and syntaxin. The result of the cytosolic catalytic activity of the L-chain is a persistent blockade of acetylcholine release and hence an impairment of muscular contraction because the muscle acetylcholine receptors are not activated by acetylcholine.[75,78,79]

Therefore, an intramuscular injection of botulinum toxin directly inhibits the extrafusal muscle fiber through inhibition of the alpha motor neuron at the neuromuscular junction. Recent research demonstrates that inhibition of muscle spindle activity via inhibition of the gamma motor neuron cholinergic junction on the intrafusal fiber plays a role as well.[124,125] This reduction of gamma activity then relaxes the intrafusal fibers of the muscle spindle and reduces the amount of Ia afferent activity.[126] Consequently, the range of effectiveness of botulinum toxin is broader than that could be explained by the inhibition of the neuromuscular junction alone.

The result is a chemical denervation causing a dose-related muscle weakness lasting several months. Recovery occurs by muscular re-innervation with smaller collateral nerve sprouts and an increase in the number of postsynaptic acetylcholine receptors.[90]

Botulinum toxin - injection technique

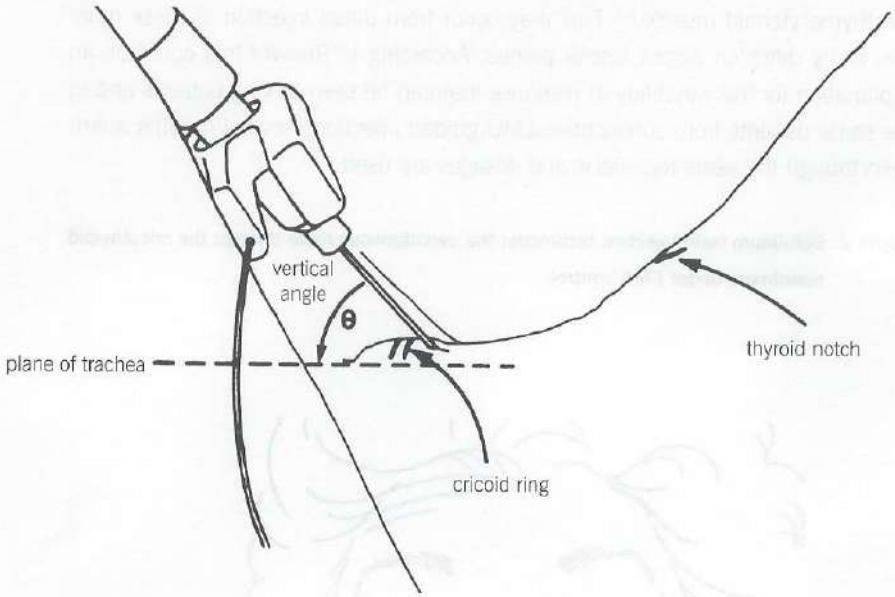
The objective of the treatment is to inject botulinum toxin into the thyroarytenoid muscle(s). There are four methods of injection: 1. a percutaneous approach through the cricothyroid membrane[80]; 2. a percutaneous transcartilaginous approach[81]; 3. indirect laryngoscopic peroral approach[82]; and 4. injection through a flexible nasolaryngoscope.[83]

The most frequently used approach is the percutaneous route through the cricothyroid membrane under EMG control (Figure 2), as described by Blitzer et al.[25,80,85] The patient is in supine position with the neck extended. A modified 1½-inch 27-gauge Teflon-coated needle is used both as a monopolar electrode to locate the thyroarytenoid muscle and as a port for injection of the botulinum toxin. The needle is placed through the skin and cricothyroid membrane and angled superiorly and slightly laterally into the thyroarytenoid muscle. Correct position of the needle tip is confirmed by the presence of crisp action potentials on phonation. The botulinum toxin is then injected into the muscle. Topical anesthesia is usually not necessary. The main disadvantage of this approach is that the needle tip can easily be placed more posteriorly than intended. In this position, injections denervate portions of the lateral cricoarytenoid and cricothyroid muscles, in addition to

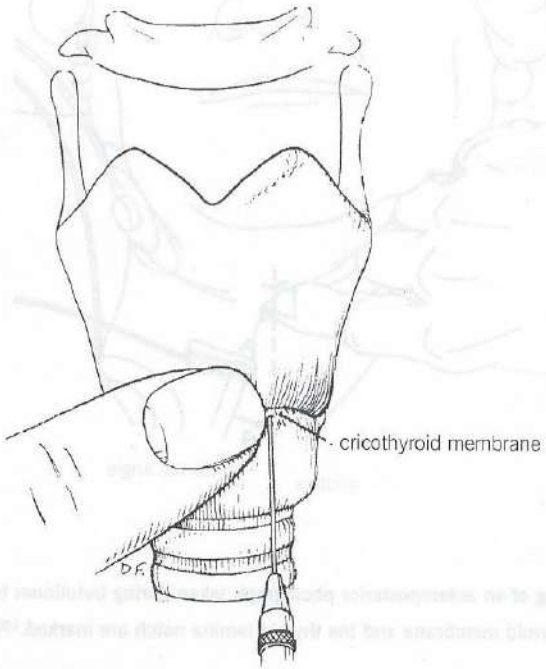
the thyroarytenoid muscle.[83] This may occur from direct injection of these muscles or by diffusion across fascial planes. According to Rhew[83] this could be an explanation for the variability in response that can be seen among patients and in the same patients from consecutive EMG guided injections several months apart, even though the same technique and dosages are used.

Figure 2. Botulinum toxin injection technique: the percutaneous route through the cricothyroid membrane under EMG control.

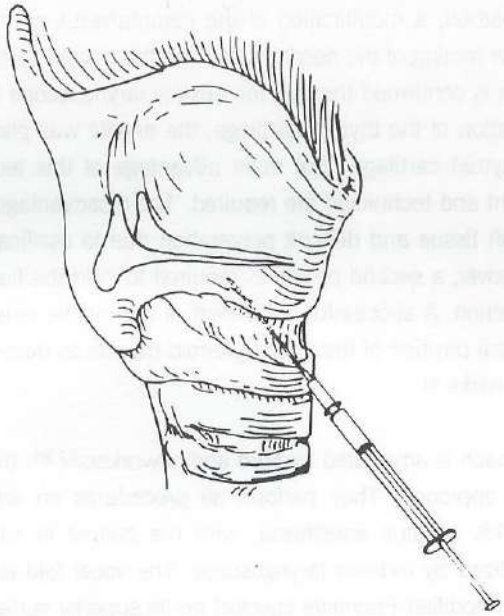
A. Line drawing of an anteroposterior photograph taken during butulinum toxin injection. The cricothyroid membrane and the thyroid lamina notch are marked.[103]



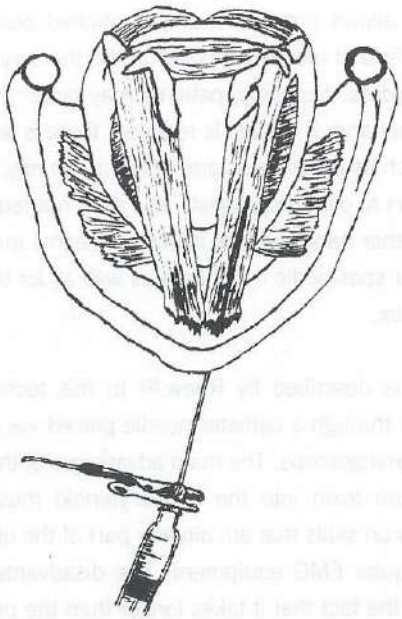
B. Lateral view of the same injection session.[103]



C. Location of the needle placement.[81]



D. Direction of the needle placement.[81]



E. Needle in place in the vocal fold.[88]

The second method, a modification of the percutaneous approach, is described by Green.[81] The routing of the needle is through the thyroid cartilage and adequate needle position is confirmed through the flexible laryngoscope before injection. In case of ossification of the thyroid cartilage, the needle was placed just under the edge of the thyroid cartilage. The main advantage of this technique is that no EMG equipment and technician are required. The disadvantage is sludging of the needle with soft tissue and difficult penetration due to ossification of the thyroid cartilage. Moreover, a second person is required to hold the flexible laryngoscope during the injection. A successful placement of the needle requires knowledge of the intralaryngeal position of the thyroarytenoid muscle as discerned from external laryngeal landmarks.[81]

The third approach is advocated by Ford and coworkers[82,84]: the indirect laryngoscopic peroral approach. They perform all procedures on an outpatient basis, using topical 4% cocaine anesthesia, with the patient in sitting position. The larynx is visualized by indirect laryngoscopy. The vocal fold is penetrated by an injector device (modified Phonagel injector) on its superior surface. The botulinum toxin is delivered to at least two sites in the anterior-to-posterior axis. The depth of injection is adjusted at each site to achieve maximum dispersion in the superior-to-inferior axis. The rationale for this technique is based on three assumptions. Firstly, this approach allows precise visually controlled placement of botulinum toxin so that a diffuse field of motor end-plates in the thyroarytenoid muscle can be affected with minimal dose. Secondly, patients may prefer this technique since it is well tolerated by most and, if dosage is reduced, there is less likelihood of dose-related side effects such as breathiness and choking. Thirdly, it is a technique that relies on skills common to otolaryngologists and does not require EMG equipment or expertise. On the other hand, peroral injections seems inadvisable for patients with mixed or abductor spasmodic dysphonia as well as for those patients with an uncontrollable gag reflex.

The fourth approach is described by Rhew.[83] In this technique the botulinum toxin injection is given through a catheter needle placed via an operative channel of a flexible fiberoptic laryngoscope. The main advantages of this method are precise placement of botulinum toxin into the thyroarytenoid muscle. This alternative injection method relies on skills that are already part of the otolarygologist's repertoire and does not require EMG equipment. The disadvantages are that special equipment is needed, the fact that it takes longer than the percutaneous method, that it requires an assistant, and filling the catheter needle increases the amount of botulinum toxin needed for injection.

In just two studies the percutaneous and transoral approach were compared.[83,86] Rhew[83] found no differences in efficacy and side effects between both methods. In a retrospective study, García Ruiz and coworkers[86] globally judged the transoral technique superior to the percutaneous technique in terms of effectiveness (48 of 48 responses with transoral technique versus 61 of 76 responses with the percutaneous approach). On the other hand, dosage of botulinum toxin, duration, and side effects were similar with both techniques.

Botulinum toxin - unilateral / bilateral

Blitzer and coworkers[80] at Columbia University, New York, were the first who injected botulinum toxin in the vocal folds in 1984. They had already investigated ADSD patients with percutaneous EMG of the vocalis muscles.[16] In this technique, impaling the muscle through the cricothyroid membrane, they used a monopolar Teflon-coated EMG needle with an exposed tip. Their first injection consisted of 2.5 units botulinum toxin in one vocal fold, with little effect, however. An additional 7.5 units were given, which caused a vocal fold paresis, a period of breathy dysphonia, and eventually a 90% improvement of vocal function.[25] Trying to reduce the occurrence and duration of breathy dysphonia and minimizing the total exposure to botulinum toxin, they explored bilateral, low-dose injections.[51] This strategy paralleled their theory that weakening or paralyzing one vocal fold stresses the remaining vocal fold and exaggerates the dystonic symptoms, leading to poor voicing. They initiated a first-treatment program of injecting both vocalis muscles with 3.75 units botulinum toxin. Patients received benefit within 24 to 72 hours, with sustained improvement for 2 to 9 months with an average of 4 months. Patients improved to an average of 90% of normal function. Clinically significant adverse effects included extended breathy dysphonia and mild choking on fluids. They concluded that botulinum toxin had become their treatment of choice for dystonic conditions of the larynx.[51] Since their first report on this subject[80], this group has published several detailed accounts of their technique and results.[16,17,23,25,47,51,52,87,88]

Soon after the first publication by Blitzer et al,[80] two other groups reported their results using much larger quantities (15-30 units botulinum toxin) injected into one vocal fold.[85,89] Their intention was to produce complete unilateral vocal cord paralysis, to simulate the effects of recurrent laryngeal nerve section. In 1987, the Houston group[85] published the results of botulinum toxin injections in two ADSD patients. Twenty-four hours after the injection, indirect laryngoscopy revealed a marked paresis of the injected vocal fold, with normal movement of the opposite side. Three months after the injection, there was an almost complete return of

function. This correlated well with the time course of the patient's clinical status. No side effects were reported.

In 1988, Ludlow et al[89] reported comparable beneficial effect of unilateral botulinum toxin injections in 16 patients. However, they noted reduced swallowing speed (13 out of 16 patients, 6 days on average) and reduced voice volume (14 out of 16, two weeks on average). They concluded that objective comparisons across methods were needed to determine which techniques produce the greatest improvement in speech function with fewer side effects.

Since then, three studies have been reported in which the efficacy of unilateral and bilateral botulinum toxin injections in the treatment of ADSD were compared.[92,93,94] The results were not unequivocal. In 1993 Adams[92] concluded that unilateral botulinum toxin injections provided both superior and longer lasting benefits than bilateral injections. In the comparative study of Zwirner[93] in 1993 no significant differences could be found. Both injection modes resulted in the reduction of laryngeal spasms within 48 hours after injection. In 1994, Maloney and co-workers[94] recommended that botulinum toxin injections for spasmodic dysphonia should be initiated using a bilateral protocol. If the patient experienced severe side effects, a unilateral injection was offered with the understanding that both vocal benefit and duration of effect would be reduced. An explanation for the different results in these studies could be that uni- and bilateral injection were compared in two different, relatively small groups using different doses of botulinum toxin.

Indirectly, five other studies have touched on this subject.[95-99] In 1992, Ludlow[95] found that women had longer benefits following unilateral than bilateral injections and men were more susceptible to side effects and required smaller dosages than women did, particularly with the unilateral injection type. The results of Adams[96] suggested that standard unilateral and bilateral botulinum toxin injections provided equivalent degrees of improvement in the symptoms of spasmodic dysphonia. However, bilateral injections appeared to be associated with a longer period of excessive phonatory airflow than did unilateral injections. In a subsequent study the same research group (Liu[97]) substantiated their earlier conclusions. Thus, unilateral injections, though as effective in relieving vocal spasms, caused less volume and swallowing problems then did bilateral injections. Using the peroral, indirect laryngoscopic-guided injection technique, Inagi[98] found no significant differences between results of unilateral single, bilateral single, or bilateral multiple injections, provided the botulinum toxin was delivered to both the thyroarytenoid

and lateral cricoarytenoid muscles. He recommended that initial botulinum toxin therapy for spasmodic dysphonia patients should be a single unilateral injection placed strategically at the posterior portion of the thyroarytenoid and directed toward the lateral cricoarytenoid muscles so that both muscle groups are affected.

In tailoring efficacy and side effects, Koriwchak and coworkers[99] tried to reduce the duration and severity of the breathy interval following bilateral injection, by designing an alternating unilateral injection protocol. They hypothesized that at any given point the patient always had one strong and one weak vocal fold. They concluded that alternating unilateral injections offered a viable alternative to bilateral injections in patients who find the breathy interval that follows bilateral injections troublesome. These patients must tolerate more frequent injections and a slightly higher failure rate. Thus, patients may choose between bilateral injections, which offer a longer duration of action and more side effects, and alternating unilateral injections, which offer shorter lasting side effects but a shorter duration of action. Factors affecting this choice may include the distance the patient resides from the treatment center, the occupation of the patient, and patient/physician preferences and/or prior experience.

Botulinum toxin - dosage and placement

Botulinum toxin type A is obtained as Botox® from Allergan, Inc., Irvine, California. It is received as frozen, lyophilized toxin. It is reconstituted with normal saline (without preservative) generally to a final concentration of 2.5 units per 0.1 ml. In literature, generally, dosages range from 15 to 60 units unilaterally[A] to 1.25 to 3.5 units bilaterally[B]. However, decisions regarding placement of the botulinum toxin to be injected are generally based on the experience and empirical judgment of the otolaryngologist. There is hardly any scientifically rational basis for choosing which muscle group to inject, how many sites should be addressed, and which side(s) should be injected to optimize results.[98]

The primary goal of the procedure is to inject the botulinum toxin in one or both thyroarytenoid muscle(s). Some authors[26,82,83] advocate multiple injection sites per muscle to increase diffusion throughout the muscle because of the even dispersion of the end plates in this muscle and to prevent the accumulation of excessive fluid in one location.[100] Most authors, however, suffice with one single bolus per muscle. Once injected into the thyroarytenoid muscle, the toxin can be identified in the lateral cricoarytenoid muscle (a strong adductor) as well, due to diffusion across facial planes, even at doses less than 10 units.[98,101] In an anatomical study of Castellanos[103] it was found that the fibers of the two muscle

groups interdigitated along their common border, making a clear distinction between them difficult.

Botulinum toxin - therapy assessment

Several modalities have been used to assess the success of botulinum toxin treatment: patient's self-evaluation of voice quality and performance[C], perceptual voice ratings[D], acoustic analysis[E], (flexible) videolaryngoscopy[F], aerodynamic[G] , and laryngeal resistance[H] measurements, neuro-physiological[I] and psychological testing[J]. In general, these modalities were used for evaluation of voice improvement and side effects, comparing uni- and bilateral procedures and/or comparing injection techniques. For all of these modalities significant improvement was found after treatment with botulinum toxin.

Probably the most important evaluation procedure for determining the success of treatment is the patient's judgement of his/her voice quality and performance. As was already pointed out by Woodson[102]: "The patient's perception of his/her problem is, of course, the 'bottom line' in determining patient satisfaction with treatment. These ratings are essential to validate the relevance of objective measures" (p.342).

Perceptual evaluation of the voice can be a reliable tool in the hands of experienced judges (high intra/interobserver agreement). After training and with the use of anchor stimuli good reliability for less experienced listeners can be obtained. Nevertheless, there are several drawbacks of perceptual scaling. Numerous scales have been developed, but there is still no uniformity or standardization and validity testing is not always performed. However, voice perception is a complex process and is probably determined by more information than we are capable of analyzing acoustically. As pointed out by Kreiman,[117] perceptual evaluation is the standard against which other measures are evaluated. Moreover, as long as the relationship between the perceived voice and acoustic analysis fails, we have to depend on our ears.

Until now, no systematic perceptual rating of the pre- and posttreatment ADSD voices has been reported. In fact, until the work of Stewart[35] (see Diagnostic assessment - perceptual analysis p.27) there were no studies in which the (pretreatment) perceptual characteristics of ADSD were systematically investigated. Most studies dealing with evaluation of botulinum toxin treatment only used the overall voice quality or rate some features of the 'typical' ADSD voice, e.g. strain, fluency, effort of speaking, spasm severity etc. and mostly include the well-

known side effects of botulinum toxin treatment like breathiness and hoarseness. Unfortunately, Stewart's Unified Spasmodic Dysphonia Rating Scale (USDRS) has not been widely introduced nor applied for assessment of the posttreatment ADSD voice.

For reliable assessment of voice quality one needs reproducible measurements and parameters that can objectively monitor changes in voice quality following treatment. These measurements should preferably be relevant to the clinical symptoms. In the last decade several papers have been published dealing with ADSD and acoustic analysis. A wide range of acoustic parameters has been employed in the assessment of this voice disorder. Summarizing current opinion, quoting Woodson[102]: "Since acoustic changes are insufficiently specific to separate spasmodic dysphonia from other neurological voice disorders, they should not be regarded as diagnostic tests, but as indicators of function. In patients with spasmodic dysphonia, acoustic analysis is useful in documenting severity and monitoring response to treatment" (p.340).

Although acoustic analysis of the voice can provide objective and reproducible measures of phonation, there are no specific parameters that can acoustically characterize ADSD. The clinical relevance of these objective measures could be demonstrated if a strong association existed with the more subjective measurements of vocal function and performance, both by the patient and 'observer/listener'. However, these have never been found. The same holds true for (flexible) videolaryngoscopy, aerodynamic and laryngeal resistance measurements, and neuro-physiological testing. All of these are objective methods of monitoring patients undergoing botulinum toxin injections for treatment of spasmodic dysphonia. All of these methods showed statistically significant differences before and after treatment. However, in spasmodic dysphonia the situation is complicated by the fact that in dystonias, symptoms vary considerably over time, during different tasks, and in different situations. Many patients are more symptomatic when under stress. The testing environment is artificial and may be stressful, and its relevance to everyday life situations may be minimal.[104] The clinical relevance, therefore, is limited.

Botulinum toxin - side effects

In general, the main adverse effects of botulinum toxin treatment in adductor spasmodic dysphonia are two-fold and transient: breathy dysphonia and swallowing problems, regardless the injection technique. Typically, breathiness starts after 3 days and lasts for 2 to 3 weeks. Once the breathiness has resolved, the impro-

vement of the voice becomes greatest around 3 weeks and lasts between 2 and 5 months. Swallowing difficulties, i.e. mild choking on fluids, appear as early as the breathy voice. If needed, patients are instructed to swallow carefully, and to change head posture by tilting the chin towards the chest ("chintuck") while swallowing.[26] The swallowing problems, which are usually resolved within two weeks, probably arise from spread of the botulinum toxin to the pharyngeal musculature.[119] Another possible explanation for the transient difficulty in swallowing liquids were the findings of Sedory Holzer et al.[120] They found a significant increase in the duration of the laryngeal elevation following botulinum toxin injection. Less common complications include hyperventilation, a 'sore throat' feeling, and diplophonia. In literature, there are no reports of major complications like (aspiration) pneumonia.[23]

Until now, there is no explanation for the discrepancy between the duration of voice improvement and side effects. A challenging theory is given by Castellanos et al,[103] who argue that closure of the glottic sphincter and vocal fold adduction are due to the actions of both the thyroarytenoid (TA) and the lateral cricoarytenoid muscles (LCA). Both muscles contain a high proportion of fast-twitch fibers, which are more important in sphincteric function than in the slow-tension forces used in phonation. The authors postulate that the transient side effects after intralaryngeal botulinum toxin administration (breathiness and mild aspiration) may be the result of a differential effect on the fast-muscle fibers in both the TA and LCA muscles. Axonal sprouting has been demonstrated to occur in animals after botulinum toxin injection. If it is the case that fast-twitch fibers are innervated more rapidly and to a greater degree by axonal sprouting than slow-twitch fibers in the human, it would provide a physiologic basis for the earlier return of sphincteric actions of TA and LCA muscles than the tensor and abductory actions. This would help explain the rapid resolution of the breathiness and aspiration in the face of persistent blockage of the dystonic symptoms.

Botulinum toxin - immunoresistance

In literature no cases are reported who have developed resistance to botulinum toxin type A due to antibody formation at the low doses used for laryngeal injection in spasmodic dysphonia. Other disorders treated with botulinum toxin require repeated injections over many years as well. Some of the patients who initially respond well develop tolerance to treatment with botulinum toxin type A. Several centers have investigated the possible development of immunoresistance due to the production of blocking anti-botulinum toxin antibodies.[75] There is considerable variation in the reported frequency of antibodies after botulinum toxin type A

treatment, probably because the various studies have used different assays.[79] Greene[121] identified three potential risk factors for the development of botulinum toxin resistance: 1. frequent injections; 2. 'booster' injections (given within 2 to 3 weeks after the initial injection); and 3. high doses of botulinum toxin per treatment.

Botulinum toxin - voice therapy

For many years voice therapy has been a treatment modality for spasmodic dysphonia. The consensus has been that patients may achieve temporary improvement under limited speaking situations (falsetto, whispering, speech on inspiration) during treatment, but little lasting carryover is obtained.[109] Nowadays, voice therapy is regarded as supportive to botulinum toxin injections.

In a preliminary study Murry and Woodson[109] demonstrated a prolonged duration of benefit when speech therapy was added to the botulinum toxin treatment program. The voice therapy was designed to target aspects of the presumed underlying pathophysiology that remained after botulinum toxin injection. This included extrinsic muscle hyperfunction and regulation of breath flow during phonation. The authors toned down their results stating that other factors could have influenced the favorable outcome. Factors such as increased attention of the voice, personal motivation, and secondary gain from improved speaking might have played a role in prolonged control of the voice. They therefore concluded, that further studies of the relationship between spasmodic dysphonia variables and voice therapy are needed to determine who may benefit most by this therapy.

Botulinum toxin - summary

Localized injections of botulinum toxin have become the treatment of choice for controlling symptoms in patients with spasmodic dysphonia. In treating ADSD, the thyroarytenoid muscle on one or both sides is injected. Short-term complications are usually mild and consist of transient breathy phonation and dysphagia. No long-term complications have been reported.[91] Symptoms usually return at 2 to 5 months, when re-injection is required.

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C. Ref: 25,26,51,52,82-86,88,89,93-95,97-99,105,110,112
D. Ref: 25,36,51,84,88,92,96,107
E. Ref: 36,81,83,84,89,92,93,96,104,110,112,113
F. Ref: 21,81,83,89,104,108,112
G. Ref: 82,93,104,106,112
H. Ref: 81,111
I. Ref: 51,108
J. Ref: 2,114-116

Addendum

Die spastische Form der nervösen Heiserkeit	Traube	1871
Funktioneller Larynxkrampf	Gerhardt	1873
Aphonia spastica	Schnitzler	1875
Phonatorischer Krampf der falschen Stimmbänder	Heymann	1878
Phonischer Stimmritzenkrampf	Schech	1879
Stammering of the vocal cords	Prosser James	1879
Spasm of the tensors of the vocal cords	Morell Mackenzie	1880
Koordinatorischer Stimmritzenkrampf	Nothnagel	1881
A rare form of laryngeal neurosis	MacBride	1884
Spasmus glottidis phonatorius	Helbing	1886
Lalophobia	Coen	1886
Aphonie und Dyspnoea spastica	Michael	1886
Die spastische Form der Mogiphonie	Fraenkel	1887
Le spasme phonique de la glotte	Koch	1888
Laryngeal cramp of musicians and speakers	Foster	1890
Aphonie et dyspnée spasmodique	Onodi	1892
Aphtongia laryngea spastica	Gottstein	1893
Phonic spasm	Daniel	1896
Aphonia et dysphonia spastica	Barth	1911
Aphonia (Dysphonia) spastica	Arnoldi	1915
Dysphonia spastica	Amersbach	1929
Die spastische Form der Phonasthenie	Stein	1937
Psychophonasthenia	Greene	1938
Spasmodic aphonia	Segré	1951
Cramps of professional voice	Pradillo	1957
Dysphonia spastica of the character of vocal stuttering	Kiml	1963
Spasmodic dysphonia	Aronson	1968
Ad- and Abductor spasmodic dysphonia	Aronson	1973

Adapted from Kiml[5] and modified.

Outline of the thesis

1.3

Spasmodic dysphonia is an uncommon, often severely disabling chronic voice disorder of unknown etiology. Until recently it was believed that spasmodic dysphonia was psychogenic in origin. Now it is supposed to be a focal (laryngeal) dystonia. Dystonia is a neurological disorder of central motor processing characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms, probably related to basal ganglia dysfunction. Therefore, spasmodic dysphonia can be considered as an action-induced laryngeal movement disorder. The vocal symptoms of adductor spasmodic dysphonia (ADSD) are characterized by difficulty with voice initiation, a strain-strangled, effortful phonation with voice breaks and glottal fry. The current treatment of choice for ADSD is botulinum toxin injections in the vocal folds.

Nevertheless, we encountered several problems both in the diagnostic work-up of these patients and in their treatment with botulinum toxin. Therefore, we focused on some of these non-explored diagnostic and therapeutic issues of this voice disorder.

The aims of the study were:

> to define diagnostic perceptual characteristics of ADSD
> to assess the optimal voice quality and performance through botulinum toxin injections
> to determine the effect of botulinum toxin injections on the quality of life
> to assess the pathophysiology of ADSD

Diagnosing spasmodic dysphonia can be difficult. Objective 'gold-standard' tests are lacking and dystonic symptoms can vary considerably over time, during different tasks and in different situations. Patients may whisper or speak in falsetto in an attempt to escape from the strain-strangled, staccato voice, masking their dystonia and hampering diagnosis. Finally, spasmodic dysphonia is a relatively rare voice disorder with which many clinicians are not familiar. One of the mainstays in the diagnostic work-up of ADSD is the evaluation of the perceptual symptoms. In **Chapter 2** ADSD is characterized perceptually through a rating system based on the GRBAS scales. Therefore, three experienced observers independently scored seventy-seven patients, quantifying the voice profiles. Moreover, the reproducibility of the "Extended" GRBAS system was assessed in eight less-experienced observers.

A substantial amount of literature is available about the efficacy of botulinum toxin injections in ADSD. Nevertheless, an important issue remained unsolved: is a unilateral injection superior to a bilateral injection, or vice versa? This question was addressed in **Chapter 3** where both procedures (unilateral and bilateral) were compared using equal doses of botulinum toxin in the same patient. In this way we tried to reduce the interpatient variability, as this is probably one of the main methodological drawbacks of earlier research, leading to contradictory results. The patients' subjective responses to botulinum toxin injections were used for assessment of the efficacy and of possible adverse effects.

Several modalities have been used to evaluate the success of botulinum toxin treatment. Among these are patient's self-evaluation of voice quality and performance, perceptual voice ratings, acoustic analysis, flexible videolaryngoscopy, aerodynamic measurements, and neuro-physiological and psychosocial testing. For all of these modalities significant improvement was found. Most studies assessed the voice at some arbitrary interval after injection and tended to concentrate on only one modality to appraise the effectiveness of this therapy. In **Chapter 4** the efficacy of botulinum toxin injections in ADSD was assessed by comparing patient's pretreatment values to posttreatment values and comparing both pre- and posttreatment values with those of normal controls. Perceptual ratings, (temporal) acoustic analysis, and self-assessment scores were used to achieve this. The posttreatment condition was defined as the moment the patient experienced his or her voice as normal or "optimal" after at least three consecutive injections.

For decades, (adductor) spasmodic dysphonia has been considered predominantly as a psychogenic voice disorder. The characteristic ADSD symptoms are reduced or absent during whispering, speaking or singing in a falsetto register and nonspeech

vocalizations (laughing, yawning). Spasmodic dysphonia is initially intermittent and task or situation specific. The marked intermittency and functional specificity of the symptoms have suggested a psychological basis for this unusual disorder. At present, it is generally accepted that ADSD has a neurologic, although undetermined cause. Nevertheless, it is accompanied with much mental and physical distress. In **Chapter 5** standardized psychometric tests were used to assess personality characteristics and psychological and somatic well-being of the patients. Moreover, the effect of botulinum toxin treatment on their well-being was evaluated.

As was already pointed out in the previous chapter, ADSD is regarded currently as a focal dystonia. This view is partly based on characteristic EMG patterns. The association of spasmodic dysphonia with other focal and generalized dystonias or involuntary movements, such as myoclonus and tremor supports this hypothesis. There is strong evidence that a generalized disorder is responsible for (focal) dystonias. Lack of inhibition or hyperreactivity of motor brain structures characterizes this. Transcranial magnetic stimulation (TMS) allows the evaluation of excitability of corticospinal pathways. If generalized hyperexcitability is a feature of focal dystonias, then studies of muscles other than laryngeal ones, which are not accessible to TMS, may show abnormalities. In **Chapter 6** we investigated if TMS indeed showed evidence of cortical hyperexcitability.

In **Chapter 7**, the main conclusions of this research project are summarized and discussed, and some suggestions for further research are given.

In **Chapter 8**, the final comments, several striking features of adductor spasmodic dysphonia and its treatment are discussed.

Perceptual characteristics of adductor spasmodic dysphonia

APM Langeveld, HA Drost, AH Zwinderman, JHM Frijns, RJ Baatenburg de Jong. *Perceptual characteristics of adductor spasmodic dysphonia*. Ann Otol Rhinol Laryngol 2000;109:741-8

2

Introduction

Adductor spasmodic dysphonia (ADSD) is a voice disorder that is probably due to laryngeal dystonia. Dystonia is a neurologic disorder of central motor processing, probably related to basal ganglia dysfunction, and is characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms. Spasmodic dysphonia can be associated with other focal (blepharospasm, oromandibular dystonia [Meige syndrome], torticollis and writer's cramp) or generalized dystonias or involuntary movements, such as myoclonus and tremor[1]. The cause of dystonia is usually idiopathic, but it can be secondary to other disorders.

Aronson[2] defined 2 main types of spasmodic dysphonia: the adductor and abductor types. The former is characterized by difficulty with voice initiation, a strained-strangled, effortful phonation with voice breaks and glottal fry.[3] The abductor type, less common, is characterized by intermittent hyperabduction of the vocal cords leading to a whispering voice, hypophonia, and possible aphonic breaks.

A number of difficulties are encountered in the diagnostic workup of patients with spasmodic dysphonia. Objective gold standard tests are lacking. Dystonic symptoms vary considerably over time, during different tasks and in different situations. Patients may whisper or speak in falsetto in an attempt to escape from

the strained-strangled, staccato voice, thus masking their dystonia and hampering diagnosis. Finally, spasmodic dysphonia is a relatively rare voice disorder that is not familiar to many clinicians.

For adequate evaluation of patients with spasmodic dysphonia, a team consisting of an otolaryngologist, a neurologist, and a speech-language pathologist is necessary. The diagnosis is based on history, physical examination, perceptual evaluation of speech, and laryngological and general neurologic examination. The analysis of perceptual symptoms is one of the mainstays in the diagnostic workup of spasmodic dysphonia.

Much research has been done to find acoustic parameters of voice quality. Although acoustic analysis of the voice provides objective measures of phonation, there are no specific parameters that can acoustically characterize ADSD. In 1997, Leinonen et al[4] stated, "The correspondence of the current acoustic measures with what is perceived by the ear is still too poor to allow the substitution of acoustic tests for perceptual ones".

Several perceptual systems have been developed for evaluation of voice disorders in general.[5-9] Some of these not only describe perceptual characteristics of voice quality, but also include nonlaryngeal parameters.[5,9] The complexity of these systems could be the reason they were not widely introduced. Perhaps another reason for the lack of a universally acceptable system is that there is not one that has shown itself to be broad enough to effectively capture the categories necessary for all pathological voices.

The GRBAS system, based on the work of Isshiki et al,[6] was originally designed for quantifying the auditory impression of hoarseness for early detection of laryngeal cancer. It contains 5 well-defined parameters: "G" (overall grade of hoarseness); "R" (roughness); "B" (breathiness); "A" (asthenia); and "S" (strained quality). A four-point scale, from 0 to 3, was used to quantify each parameter.[10] In a multicenter study on perceptual evaluation of dysphonia, the GRBAS system appeared to be reliable and of clinical relevance, based on low intraobserver and interobserver variability. Moreover, the GRBAS profiles could discriminate quite well between different pathological groups.[11]

In the past 10 years, we routinely used the GRBAS system and found that not all pathological voices could be described with it. Therefore, in course of time, we extended the GRBAS system (Table 1), appending the parameters aphonia (eg,

psychogenic whispering), diplophonia (eg, nodules, cyst), staccato (eg, spasmodic dysphonia), tremor (eg, essential voice tremor), falsetto (eg, mutational voice disorder), and vocal fry (eg, spasmodic dysphonia). We feel that these characteristics of voice quality add relevant information to the original GRBAS system.

The extended GRBAS system highly agrees with the voice quality parameters proposed for perceptual evaluation of pathological voices by the Swedish authors Hammarberg and Gauffin.[8] This system was based on the results of perceptual-acoustic correlations and on consensual validations of defining terminology. These voice quality parameters were suggested as clinically relevant and were proposed for routine voice evaluation. However, indicators for overall grade ("G" in GRBAS) and tremor ("extended" GRBAS) are lacking in the "Hammarberg system". Grade is a common description of overall severity of a voice disorder, and it reflects a global measure of voice production.[12] Voice tremor is present in several neurological voice disorders, and cannot be described in the Hammarberg system. However, in contrast to the GRBAS scale, the Swedish system has not been widely adopted in the English-language literature.

Until the work of Stewart et al[13] (1997), there were no studies in which the perceptual characteristics of ADSD were systematically investigated. Most studies dealing with this subject only used some general descriptions of the "typical" ADSD voice, eg, strained, groaning, staccato, effortful voice.[2] Perceptual ratings, defined or otherwise, such as overall grade, strained-strangled voice quality, overpressure, vocal spasms, phonatory effort, aperiodicity, breathiness, and tremor, were mostly used for evaluation of therapy outcome after recurrent laryngeal nerve section or botulinum toxin injections and/or for determination of the relationship with acoustic features of spasmodic dysphonia. Moreover, just a few studies subjected the ratings to statistical analysis for evaluating intraobserver and interobserver reliability.[12,14-16] In general, good reliability was obtained. However, comparing the results among these studies seems unjustified, because different symptoms were investigated and/or different statistics were used. Stewart et al[13] designed the Unified Spasmodic Dysphonia Rating Scale (USDRS), a standardized measure for evaluation of symptoms and severity of ADSD. This was the first study in which signs and symptoms of ADSD were investigated systematically. The voices of patients with ADSD were quantified with good reliability for 14 perceptual symptoms in conversational speech and 6 voice tasks that improve or worsen perceptual symptoms.

Whereas the USDRS was purely designed for ADSD, the extended GRBAS system was designed for voice disorders in general. The aim of the present study was assessment of the perceptual characteristics of ADSD with the extended GRBAS system and evaluation of its reproducibility.

Patients and methods

Between 1993 and 1997, we evaluated 77 patients with a clinical diagnosis of ADSD. Among them were 61 women with a mean age of 56.2 years (19 to 87 years) and 16 men with a mean age of 55.5 years (31 to 74 years). The average duration of symptoms was 8 and 7.6 years, respectively. The diagnosis of ADSD was made independently by a speech-language pathologist (H.A.D.) and an otolaryngologist (T.P.M.L.). In addition, the patients had no history of psychiatric or neurologic disorders, particularly, no other dystonias or familial tremors. All patients had symptoms of ADSD for more than one year and had undergone no previous treatment with botulinum toxin. The diagnosis was corroborated in all patients by improvement of voice quality after treatment with local injections of botulinum toxin.

All voice samples were taken before treatment and recorded in a sound-treated room with a Sony Hi-8 videocassette camera recorder and a JVC HiFi stereo videocassette recorder. The patients were seated comfortably on a chair with the microphone (Kennet ET 2100) positioned approximately 30 cm in front of the patient's mouth. Because symptoms of ADSD are markedly manifest in the habitual pitch range of the speaking voice during normal speech, spontaneous speech was used for perceptual evaluation. Spontaneous speech was recorded during history-taking, and the entire recording (on average, 3 minutes) was evaluated.

The voice quality parameters and their definitions are listed in Table 1. The ratings were performed on a visual analog (VA) scale using the extended GRBAS system. A VA scale is an undifferentiated line on which listeners rate voices by making a mark on the line to indicate the extent to which a voice possesses a given characteristic. On the score form, each parameter was scored on a continuous horizontal line of 10 cm from normal or minimal or none on the left side to extremely pathological or maximal or continuous on the right side. The distance in centimeters from the left side measured the score. Originally, in the GRBAS system a 4-point equal-appearing interval (EAI) scale was used for each parameter. "0" equaled normal, "1" slight, "2" moderate, and "3" severe. However, we preferred

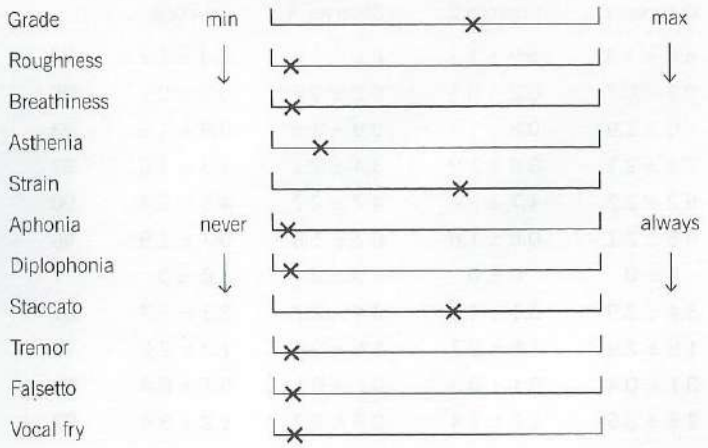
the VA scale, because pilot studies suggested it was more reliable than the EAI scale (G.B. Kempster, unpublished observations, 1987). Kreiman et al[17] found that EAI ratings drifted significantly in a consistent direction within a listening session, in contrast to the VA ratings. Figure 1 shows an example of the perceptual evaluation of a patient with ADSD using the extended GRBAS system and the VA scales.

Table 1. Voice quality parameters and definitions of the extended GRBAS system.

GRBAS	
Grade	Overall degree of impairment
Roughness	Low-frequency aperiodic noise; random fluctuations of glottal pulse
Breathiness	Audible turbulent noise generated at glottis
Asthenia	Weak, powerless voice; no carrying power
Strain	Excessive tension in vocal cords
EXTENSION	
Aphonia	Voice lacking in phonation; a whispering voice
Diplophonia	Two different pitches that can be simultaneously perceived
Staccato	Abrupt voice initiation and arrest; irregular interruption of voice
Tremor	Rapidly occurring fluctuations in pitch and/or loudness; quavering voice
Falsetto	Mode of phonation
Vocal fry	Low-frequency periodic vibration

All patients were scored independently by three experienced observers (one speech-language pathologist and two otolaryngologists) familiar with both spasmodic dysphonia and the extended GRBAS system. The voice sound profile of ADSD was quantified with the mean scores, the standard deviations, and the associated 95% confidence intervals of the different voice characteristics. For each patient, the scores of the three observers were averaged, and these patient means were averaged to obtain the voice sound profile. The observer agreement was quantified with the intraclass correlations. Because the distributions of most scales were skewed, we also calculated the geometric means. The association between the different voice characteristics was quantified with correlation coefficients. The association between the overall grade and the different voice characteristics was quantified with correlation coefficients as well, and modeled with multiple regression analysis. The results of these analyses were reported with the estimated regression coefficients (b) and their standard errors (SE). To assess whether in our sample different voice types of ADSD existed, we performed cluster analysis.

Figure 1. Example of perceptual evaluation of a patient with ADSD using our extended GRBAS system on visual analog scales.



To assess the reproducibility[18] of the extended GRBAS system for ADSD, 8 less-experienced listeners scored the voices of a random subset of 58 patients. The listening procedure was performed twice (with a 4-week interval) by each listener to obtain test-retest reliability for each of the listeners on each perceptual parameter. The group consisted of 4 speech therapists and 4 otolaryngologists. To improve the interobserver rating, a training session was held with presentations of taped reference voice samples of the different parameters of the extended GRBAS system. The data were analyzed with a mixed-model ANOVA to estimate the different variance components involved. Throughout, a p value of .05 or less was considered statistically significant.

Table 2a. Visual analog scores of three experienced observers, with interobserver agreement.

	Visual Analog Scores (cm; mean ± SD)				R_{IC}
	Observer 1	Observer 2	Observer 3	Average	
Grade	6.6 ± 1.9	5.9 ± 1.7	6.6 ± 1.8	6.3 ± 1.7	.79
Roughness	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.6	0.2 ± 0.7	.96
Breathiness	1.0 ± 1.9	0.8 ± 1.4	0.9 ± 1.5	0.9 ± 1.6	.93
Asthenia	3.4 ± 2.1	3.0 ± 1.9	3.4 ± 2.1	3.3 ± 1.9	.82
Strain	5.2 ± 2.7	4.7 ± 2.4	4.7 ± 2.3	4.9 ± 2.4	.90
Aphonia	0.8 ± 2.1	0.6 ± 1.8	0.7 ± 1.8	0.7 ± 1.9	.96
Diplophonia	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
Staccato	3.4 ± 2.9	3.1 ± 2.8	3.4 ± 2.7	3.3 ± 2.7	.91
Tremor	1.8 ± 2.9	1.8 ± 2.7	1.6 ± 2.4	1.7 ± 2.7	.95
Falsetto	0.1 ± 0.4	0.1 ± 0.3	0.1 ± 0.5	0.1 ± 0.4	.88
Vocal Fry	2.3 ± 3.6	2.2 ± 3.4	2.0 ± 3.2	2.2 ± 3.4	.97

R_{IC} - intraclass correlation

Table 2b. Distribution of the visual analog scores of the three experienced observers.

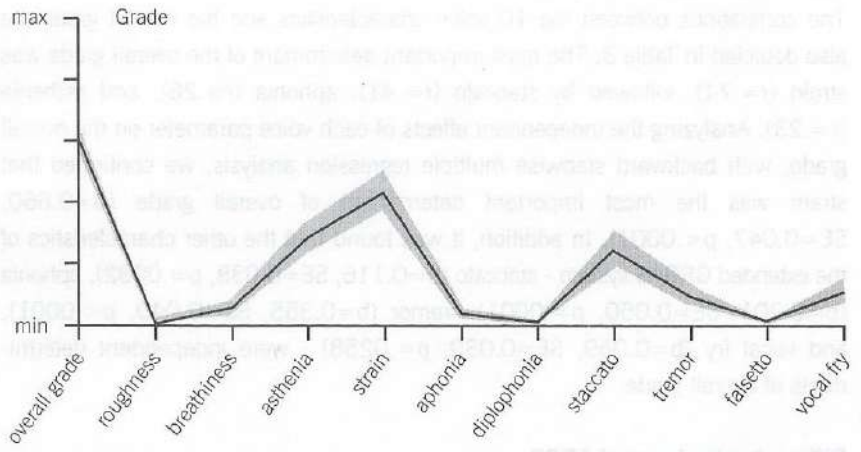
	Distribution of Scores							
	0 cm		0-3 cm		3-7 cm		>7 cm	
	No.	%	No.	%	No.	%	No.	%
Grade	0	0	4	5	34	44	39	51
Roughness	69	90	7	9	1	1		
Breathiness	51	66	16	21	10	13		
Asthenia	11	14	23	30	42	55	1	1
Strain	3	4	17	22	35	45	22	29
Aphonia	63	81	6	8	5	7	3	4
Diplophonia	77	100						
Staccato	16	21	23	30	26	34	12	15
Tremor	44	57	17	22	9	12	7	9
Falsetto	74	96	3	4				
Vocal Fry	47	61	10	13	7	9	13	17

Results

Voice sound profile of ADSD

The mean scores and standard deviations of each experienced observer are given in Table 2. The distribution of the scores was skewed. For example, on the VA tremor scale, 44 patients were scored 0, 17 patients lower than 3 cm, 9 patients between 3 and 7 cm, and 7 patients above 7 cm. Because of the skewed distribution, the geometric means and their associated 95% confidence intervals were calculated as well. The geometric means were comparable with the mean scores. Therefore, only the latter were used for analysis. The mean overall grade was 6.3. Prevalent characteristics were strain (mean, 4.9), staccato (mean, 3.3), asthenia (mean, 3.3), vocal fry (mean, 2.2), and tremor (mean, 1.7). Diplophonia was not encountered, whereas roughness, breathiness, aphonia, and falsetto were rarely scored. The averages and 95% confidence intervals of the 3 observers are depicted in Figure 2. The 3 experienced observers agreed quite well: the intraclass correlations varied from .79 for the overall grade to .97 for vocal fry.

Figure 2. Voice sound profile of adductor spasmodic dysphonia. Black line – mean; shaded area – 95% confidence interval.



Intercorrelations

To assess whether the parameters that are not in the original GRBAS system (aphonia, staccato, diplophonia, tremor, falsetto, and vocal fry) were independent voice characteristics, we calculated the correlation coefficients between these parameters (Table 3). Although aphonia and asthenia had a correlation of .56, and tremor cor-

related negatively (-.52) with strain, all other correlations were .3 or less, indicating that the appended perceptual characteristics were independent parameters.

Table 3. Intercorrelations between the 10 voice parameters.

	R	B	A	S	Aph	Di	St	T	F	VF
Roughness	1.00									
Breathiness	0.02	1.00								
Asthenia	-0.01	0.23	1.00							
Strain	0.15	0.06	0.17	1.00						
Aphonia	0.04	0.23	0.56	0.14	1.00					
Diplophonia						1.00				
Staccato	0.11	-0.21	- 0.21	0.31	- 0.11		1.00			
Tremor	-0.15	-0.10	- 0.05	- 0.52	- 0.08		0.03	1.00		
Falsetto	-0.06	0.04	0.20	0.16	0.12		- 0.04	-0.12	1.00	
Vocal Fry	-0.17	-0.16	- 0.08	0.18	- 0.20		- 0.31	-0.32	0.11	1.00
Grade	0.13	0.03	0.23	0.74	0.26		0.41	0.02	0.13	0.02

Determinants of overall grade

The correlations between the 10 voice characteristics and the overall grade are also depicted in Table 3. The most important determinant of the overall grade was strain (r=.74), followed by staccato (r=.41), aphonia (r=.26), and asthenia (r=.23). Analyzing the independent effects of each voice parameter on the overall grade, with backward stepwise multiple regression analysis, we confirmed that strain was the most important determinant of overall grade (b=0.660, SE=0.047, p<.0001). In addition, it was found that the other characteristics of the extended GRBAS system - staccato (b=0.116, SE=0.038, p=.0032), aphonia (b=0.201, SE=0.050, p=.0001), tremor (b=0.355, SE=0.040, p<.0001), and vocal fry (b=0.069, SE=0.030, p=.0258) - were independent determinants of overall grade.

Different voice types of ADSD

Cluster analysis of the 10 voice characteristics revealed 4 different voice types of ADSD. The averages of the voice characteristics in the 4 clusters are given in Table 4 (see also Figure 3). Cluster I consisted of 17 patients and was mainly characterized by vocal fry and strain with some asthenia and staccato. Cluster II consisted of 15 patients and was mainly characterized by strain and asthenia with some breathiness, aphonia, and staccato. Cluster III consisted of 23 patients

and was mainly characterized by strain and staccato with some asthenia and tremor. Finally, cluster IV consisted of 22 patients and was primarily characterized by tremor with some asthenia, strain, and staccato. On average, the overall grade was most severe in cluster III (mean, 7.1) and least severe in cluster IV (mean, 5.0). Men and women were equally distributed among the 4 different clusters.

Table 4. Visual analog scores of voice parameters in four clusters of adductor spasmodic dysphonia.

	Cluster I (n=17)	Cluster II (n=15)	Cluster III (n=23)	Cluster IV (n=22)	p*
Grade	6.6 ± 1.4	6.9 ± 1.2	7.1 ± 1.6	5.0 ± 1.7	<.001
Roughness	0.1 ± 0.2	0.5 ± 1.0	0.3 ± 0.8	0.1 ± 0.3	.23
Breathiness	0.6 ± 1.4	2.6 ± 2.2	0.6 ± 1.0	0.4 ± 1.0	<.001
Asthenia	3.2 ± 1.4	5.1 ± 1.4	2.3 ± 2.0	3.1 ± 1.7	<.001
Strain	5.9 ± 1.9	6.1 ± 1.6	6.0 ± 1.7	2.0 ± 1.2	<.001
Aphonia	0.0 ± 0.0	2.8 ± 3.0	0.2 ± 0.9	0.3 ± 1.2	<.001
Diplophonia	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Staccato	1.9 ± 2.1	2.0 ± 2.0	6.2 ± 2.1	2.2 ± 1.7	<.001
Tremor	0.3 ± 0.8	0.3 ± 0.6	1.1 ± 1.7	4.4 ± 3.3	<.001
Falsetto	0.2 ± 0.5	0.2 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	.27
Vocal Fry	8.1 ± 1.3	0.2 ± 0.6	0.5 ± 1.1	0.7 ± 1.1	<.001
Number of men	4 (24%)	5 (33%)	4 (17%)	3 (14%)	.50
Age (years)	45 ± 10	54 ± 15	59 ± 14	63 ± 19	<.005
Median duration of ADSD in months (range)	24 (3-144)	96 (8-216)	120 (7-372)	90 (8-240)	<.0001

Data are mean ± SD in centimeters, except as indicated

* p value of 1-way analysis of variance, χ^2 test, or Kruskal-Wallis test, where appropriate

However, patient's age and duration of the spasmodic dysphonic symptoms differed significantly (p values of .005 and .0001, respectively). Cluster I consisted of the youngest patients (45 years) with shortest median duration of symptoms (2 years). The patients with the longest duration of symptoms (10 years) were grouped in cluster III. Cluster II represented an intermediate group with respect to age and duration of symptoms. The oldest patients were found in Cluster IV, in which vocal tremor was the most dominant feature. Strain was considerably less in cluster IV compared to the other clusters.

Figure 3a. Voice sound profile Cluster I (black line) and general profile of ADSD (shaded area).

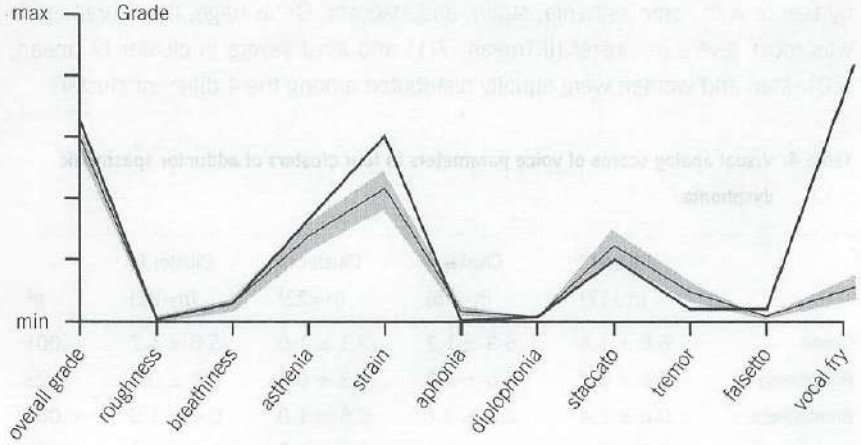


Figure 3b. Voice sound profile Cluster II (black line) and general profile of ADSD (shaded area).

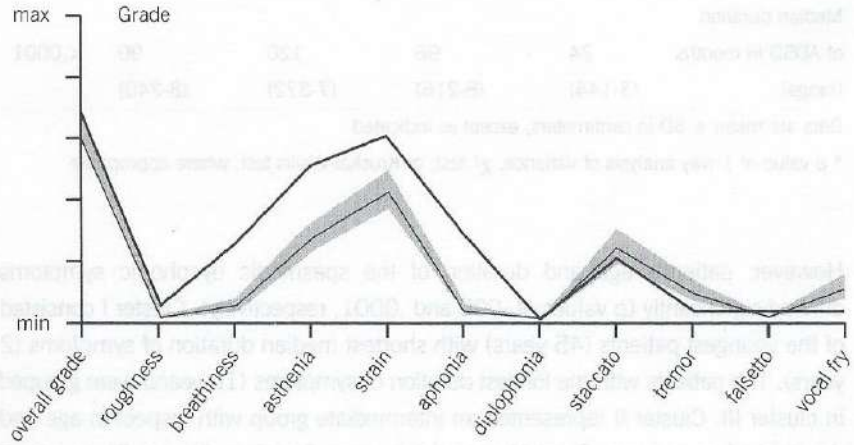


Figure 3c. Voice sound profile Cluster III (black line) and general profile of ADSD (shaded area).

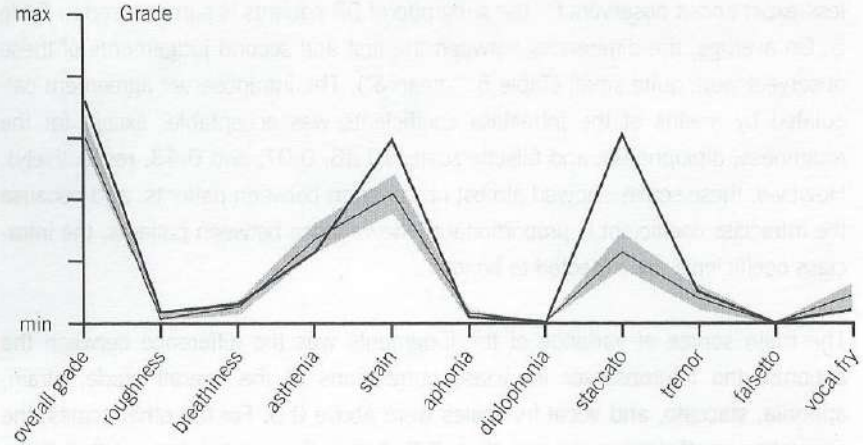
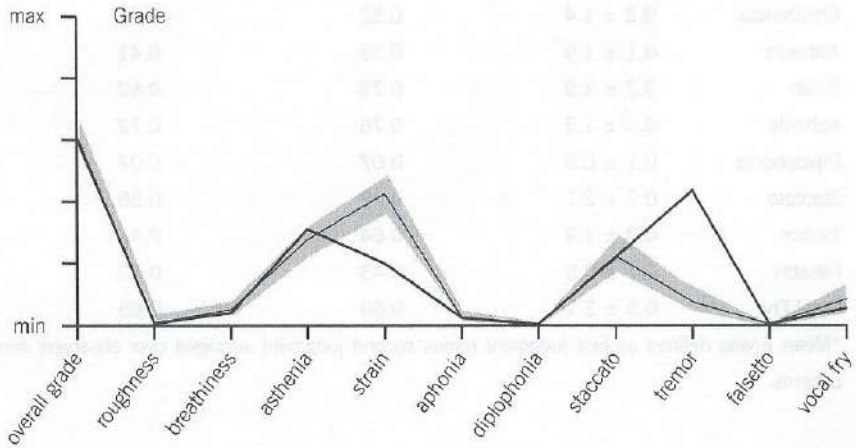


Figure 3d. Voice sound profile Cluster IV (black line) and general profile of ADSD (shaded area).



Intra- and interobserver agreement in eight less-experienced observers

Intraobserver and interobserver agreement between the 2 observations of the 8 less-experienced observers for the subgroup of 58 patients is summarized in Table 5. On average, the differences between the first and second judgements of these observers were quite small (Table 5, "mean δ"). The intraobserver agreement calculated by means of the intraclass coefficients was acceptable, except for the roughness, diplophonia, and falsetto scales (0.36, 0.07, and 0.43, respectively). However, these scales showed almost no variation between patients, and because the intraclass coefficient is proportional to the variance between patients, the intraclass coefficients are expected to be low.

The main source of variance of the judgments was the difference between the patients: the interobserver intraclass correlations of the overall grade, strain, aphonia, staccato, and vocal fry scales were above 0.5. For the other scales, the correlation coefficients were less than 0.5. Again, it must be stressed that these scales had little variance.

Table 5. Variance components in the judgments of eight less-experienced observers.

	Intra-observer Agreement	Intraclass correlation	
	mean δ* ± SD	Intraobserver Agreement	Interobserver Agreement
Grade	0.1 ± 1.3	0.77	0.58
Roughness	0.0 ± 0.8	0.36	0.30
Breathiness	0.3 ± 1.4	0.52	0.41
Asthenia	0.1 ± 1.9	0.59	0.41
Strain	0.2 ± 1.9	0.75	0.52
Aphonia	0.3 ± 1.3	0.76	0.72
Diplophonia	0.1 ± 0.5	0.07	0.07
Staccato	0.7 ± 2.1	0.72	0.56
Tremor	0.2 ± 1.9	0.64	0.41
Falsetto	0.1 ± 0.6	0.43	0.30
Vocal Fry	0.5 ± 2.1	0.69	0.65

*Mean δ was defined as first judgment minus second judgment averaged over observers and patients.

Discussion

Perceptual evaluation of the voice is a reliable tool in the hands of experienced judges (high intraobserver and interobserver agreement). After training and with the use of anchor stimuli, good reliability for less-experienced listeners can be obtained as well. Nevertheless, there are several drawbacks to perceptual scaling. Numerous scales have been developed, but there is still no uniformity or standardization, and validity testing is not always performed. However, voice perception is a complex process and is probably determined by more acoustic information than we are capable of analyzing. As pointed out by Kreiman et al,[17] perceptual evaluation is the standard against which other measures are evaluated. Moreover, as long as the relationship between the perceived voice and acoustic analysis is unclear, we have to depend on our ears.

One of the best-investigated perceptual rating scales is the GRBAS system. In a multicenter study on perceptual evaluation of dysphonia, the GRBAS system appeared to be reliable and of clinical relevance, on the basis of low intraobserver and interobserver variability. In addition, the GRBAS profiles could significantly discriminate between the different pathological groups.[4,11] Compared to other systems, De Bodt et al[10] recommended the use of the GRBAS scale for clinical practice, because of its simplicity, and because it enables a relatively consistent description of voice quality, making it an effective tool for communication between disciplines.

However, not all features of pathological voices can be described with the GRBAS system. Therefore, we appended 6 parameters (aphonia, diplophonia, staccato, tremor, falsetto, and vocal fry) that were partly based on our own experience and partly derived from Hammarberg and Gauffin.[8] In contrast to other scaling methods of voice disorders,[5,9] the extended GRBAS system only describes vocal quality or laryngeal (dys)function. As no other features of the voice or speech tract are determined, clinical usefulness is enhanced.

Stewart et al[13] were the first who systematically investigated the signs and symptoms of ADSD and designed the USDRS. The perceptual parameters or voice characteristics of the USDRS highly correspond with the extended GRBAS system. In Table 6, the resemblances between the rating scales are depicted. Falsetto and diplophonia were not described in the USDRS. Indeed, these perceptual parameters were not significant in our study.

The main aim of the present study was to assess the perceptual characteristics of ADSD with the extended GRBAS system. The most prevalent characteristics of ADSD were strain, staccato, asthenia, vocal fry, and tremor. The most important parameter of the overall grade was strain (r=.74). This is in line with the findings of Zwirner et al.[12] They found that the strained-strangled voice quality correlated significantly with the more global parameter of overall severity, so that this specific perceptual parameter is indeed suitable for the perceptual characterization of the severity of the ADSD. They concluded that this parameter could provide the initial cue as to the presence of this disorder in clinical situations.

In the present study, there was high agreement among the experienced observers: the mean intraclass correlation was .91 (SD, .06; minimum, .79; maximum, .97). The correlations between the scores of the 10 voice characteristics demonstrated that all parameters were independent voice characteristics, the extension of the GRBAS system included.

Interestingly, cluster analysis of the 10 voice characteristics revealed 4 different voice types of ADSD (Table 4 and Figure 3). The sexes were equally distributed among the 4 clusters. However, the patients' ages and durations of symptoms differed significantly. The meaning of these findings is not clear. One can hypothesize that the 4 clusters represent different manifestations of the same disease related to the age of onset, or reflect compensatory strategies. On the other hand, these data could also suggest a shift in symptoms that occurs as the disease progresses. However, this could only be proven in a longitudinal study. The Clusters I, II, and III all have strain as the dominant feature in combination with another characteristic voice quality parameter (vocal fry, asthenia-aphonia, and staccato, respectively). On the other hand, patients having a vocal tremor as the most dominant feature combined with a little strain possibly represent a different type of spasmodic dysphonia, which was already described by Aronson in 1981.[19] According to Aronson and Lagerlund,[20] essential voice tremor and dystonia are the 2 extrapyramidal neurologic syndromes that are responsible for most neurologic forms of spasmodic dysphonia. With respect to our study, dystonia appeared to be responsible for the perceptual characteristics of clusters I, II, and III, and essential voice tremor for cluster IV.

Table 6. Resemblances between USDRS and extended GRBAS system.

USDRS	extended GRBAS system
Overall severity	Grade
Rough voice quality	Roughness
Breathy voice quality	Breathiness
Strained-strangled voice quality	Strain
Abrupt voice initiation	≈ Staccato
Voice arrest	≈ Staccato
Aphonia	Aphonia
Voice loudness	Asthenia
Burst of loudness	≈ Staccato
Voice tremor	Tremor
Expiratory effort	≈ Strain
Speech rate*	
Speech intelligibility reduced*	
Related movements and grimaces†	

USDRS - Unified Spasmodic Dysphonia Rating Scale[13]

≈ approximately equivalent to

* not specific to laryngeal function

† not applicable to laryngeal function

In regard to the intraobserver and interobserver agreements in the 8 less-experienced observers, it can be concluded that the differences between the first and second judgments of these observers were quite small. The interobserver agreement can be considered fair-to-good,[21] if we take into account that the main source of variance of the judgments was the difference between the patients. The main determinants of ADSD (overall grade, strain, aphonia, staccato, and vocal fry) all showed intraclass correlations above .5. This means that even less-trained listeners are able to describe the ADSD voice with the extended GRBAS system.

Conclusions

The findings of this study demonstrate that the extended GRBAS system can be used for accurate and reproducible perceptual characterization of ADSD. Moreover, this system identified 4 voice clusters of ADSD with significant differences in voice and demographic characteristics. The relevance of this finding is not clear and requires further investigation.

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Unilateral versus bilateral botulinum toxin injections in adductor spasmodic dysphonia

APM Langeveld, HA Drost, RJ Baatenburg de Jong. *Unilateral versus bilateral botulinum toxin injections in Adductor Spasmodic Dysphonia*. Ann Otol Rhinol Laryngol 1998;107:280-4.

3

Introduction

Spasmodic dysphonia is a voice disorder of unknown cause. Until recently, it was believed that spasmodic dysphonia had a psychogenic origin. However, now it is generally accepted that spasmodic dysphonia has a neurologic, although undetermined, cause. In 1985, Blitzer et al[1] linked spasmodic dysphonia to dystonia through a clinical and electromyographic evaluation of 'spastic' dysphonic patients and patients with multifocal or generalized dystonia. Dystonia is a neurologic disorder of central motor processing, characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms, probably related to dysfunction of the basal ganglia. Symptoms usually begin as focal dystonia involving a single region of the body. Spread to other regions is commonly seen in childhood-onset dystonia, while adult-onset dystonia tends to remain focal.[2] Spasmodic dysphonia can be associated with other focal (blepharospasm, oromandibular dystonia [Meige syndrome], torticollis and writer's cramp) or generalized dystonias or involuntary movements, such as myoclonus and tremor.[3] The cause of dystonia is usually idiopathic, but it can be secondary to other disorders. Aronson[4] defined two main types: adductor and abductor. The adductor type was already described by Von Traube in 1871. It is characterized by difficulty with voice initiation, a strained-strangled, effortful phonation with voice breaks, and glottal fry.[5] The abductor type, the less common form, is characterized by intermittent hyperabduction of the vocal cords leading to a whispering voice, hypophonia, and possible aphonic breaks.

In the past 100 years many different treatments have been applied to spasmodic dysphonia, including psychotherapy, speech therapy, systemic drugs and recurrent laryngeal nerve surgery. In general, these treatments were ineffective. After the introduction of botulinum toxin type A in ophthalmology by Scott[6] in 1980, botulinum toxin has been used in the treatment of a wide range of dystonias. In 1986 Blitzer et al[7] published the first results of the treatment of spasmodic dysphonia with a local injection in the thyroarytenoid muscle. Botulinum toxin prevents the release of acetylcholine at the motor end plates, resulting in a partial or complete muscle paralysis. The effect is temporary, because of axonal sprouting at the motor end plate that results in reinnervation of the muscle. Therefore, repeated injections of botulinum toxin are necessary. The side effects depend on the dose, the volume injected, and the patient's sensitivity to the toxin. They are transient and related to the site of injection: vocal breathiness and aspiration. These side effects probably result from diffusion of the botulinum toxin into the adjacent muscles.[8]

In the past 10 years, the efficacy of this symptomatic therapy has been described in more than 25 papers in the otolaryngology literature. These studies indicate that relief of symptoms is provided for approximately 4 months.[9] Moreover, in a double-blind controlled study in 1991, Truong et al[10] proved that botulinum toxin acts as more than a placebo. However, two important questions remain: 1) What is the optimal dose of botulinum toxin? and 2) Is a unilateral injection superior to a bilateral injection? In the present study, the attention was focused on the second question.

In 1993, Adams et al[11] reported a study in which the unilateral and bilateral procedures were compared. On the basis of acoustic measurements, they concluded that unilateral botulinum toxin injections provided superior and longer-lasting benefits as compared to bilateral injections. In the comparative study of Zwirner et al[12] in 1993, no significant differences could be found. Both injection modes resulted in the reduction of laryngeal spasms within 48 hours after injection. In 1994, Maloney and Morrison[13] recommended that botulinum toxin injections for spasmodic dysphonia should be initiated with a bilateral protocol. If the patient experienced severe side effects, a unilateral injection was offered with the understanding that both vocal benefit and duration of effect would be reduced. An explanation for the different results in these studies could be that unilateral and bilater-

al injections were compared in two different, relatively small groups with different doses of botulinum toxin.

The aim of this study was to compare the efficacy and side effects of unilateral versus bilateral botulinum toxin injections in patients with adductor spasmodic dysphonia. By comparing both procedures (unilateral and bilateral) using equal doses (5 units and 2 x 2.5 units, respectively) of botulinum toxin in the same patient, we tried to reduce the interpatient variability. The patient's subjective responses to botulinum toxin injections were used for assessment of the efficacy and adverse effects.

Patients and methods

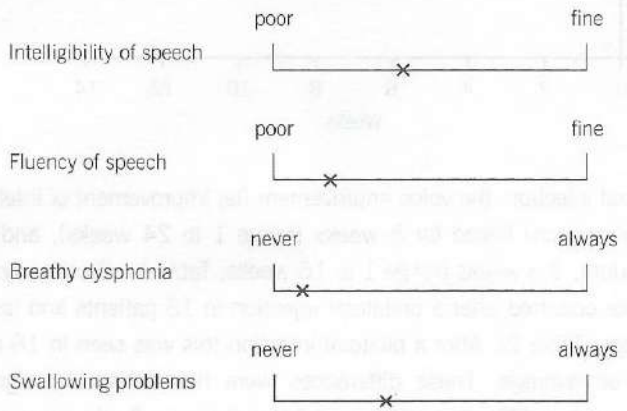
Twenty-seven patients with adductor spasmodic dysphonia were included in this prospective study. Among them were 20 women with a mean age of 57 years (19 to 85 years) and 7 men with a mean age of 58 years (41 to 69 years). The average durations of symptoms were 11 and 12 years, respectively. Diagnosis of adductor spasmodic dysphonia was made independently by the speech-language pathologist (H.A.D.) and the otolaryngologists (T.P.M.L, R.J.B.d.J.). None of the patients had been treated surgically or with botulinum toxin injections. All patients signed informed consent forms.

All patients underwent both treatments. During the first procedure 5 units (1.25 units per 0.1 ml) of botulinum toxin (Botox®, Allergan) were injected in the left thyroarytenoid muscle only. This side was chosen for practical reasons: for a right-handed surgeon it is easier to insert the needle in the left thyroarytenoid muscle. The second treatment was performed after the voice quality had returned to the preinjection level (established by the patient and by audio and video registrations). During this procedure, both thyroarytenoid muscles were injected, each with 2.5 units (1.25 units per 0.1 ml) of botulinum toxin. Those patients who did not respond at all after the first treatment received their second treatment after at least 3 months.

Under electromyographic guidance, a monopolar 27-gauge, 30 mm Teflon®-coated needle was inserted percutaneously, through the cricothyroid membrane into the left thyroarytenoid muscle during the first procedure, and into both thyroarytenoid muscles during the second procedure. For safety, we used the lowest efficacious dose reported in literature: 5 units in total.

The pretreatment and posttreatment conditions (intelligibility of speech and fluency of speech) were assessed by means of self-rating scales (Figure 1). A similar scale was used for assessment of side effects: breathy dysphonia and swallowing problems. During the first week after the injection, the patient had to rate the effect and side effects daily. Thereafter, the rating was weekly for at least 3 months. From these self-rating scales, the occurrence and duration of effects and side effects could be determined (Figure 2).

Figure 1. Self-rating scales for assessment of effects and side effects before and after injection of botulinum toxin. 'Poor' and 'never' were scored as 0%, and 'fine' and 'always' as 100%.

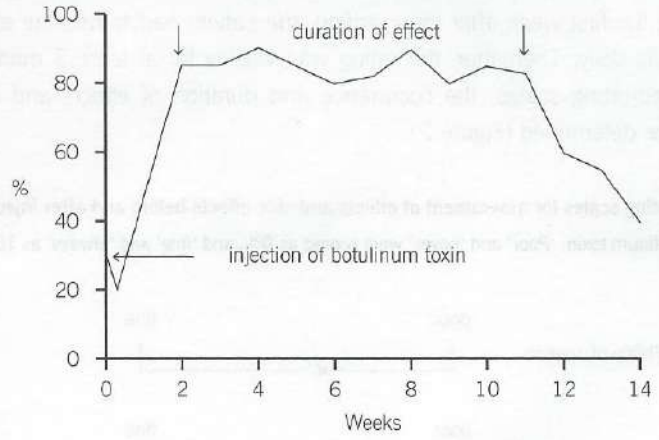


At the end of the study, all patients were asked which treatment they preferred, taking into account both voice quality and side effects. The McNemar $\chi 2$ test was used for statistical analysis. Test results with $p < .05$ were considered statistically significant.

Results

Twenty-three (85%) of the 27 patients experienced a positive effect of the botulinum toxin injection after both procedures. Usually, it took 48 to 72 hours until an optimal effect was established. Four patients did not notice any improvement at all, either after a unilateral or after a bilateral injection. After the dose was raised to 3.75 units bilaterally, 3 of them had an improvement of voice quality. Including these patients, the overall success rate was 96%. The remaining patient withdrew after the second procedure because of the side effects.

Figure 2. Graph depicting changes in intelligibility of speech, derived from self-rating scales. In this example, voice improvement lasted for 9 weeks.



After a unilateral injection, the voice improvement (ie, improvement of intelligibility and fluency of speech) lasted for 8 weeks (range 1 to 24 weeks), and after a bilateral procedure, 9.3 weeks (range 1 to 16 weeks; Table 1). Breathy dysphonia or a weak voice occurred after a unilateral injection in 13 patients and lasted 15 days on average (Table 2). After a bilateral injection this was seen in 16 patients for 15 days on average. These differences were not statistically significant. However, swallowing difficulties, that is, mild choking on fluids, were rated as statistically significantly more frequent after the bilateral procedure (McNemar $\chi 2$ test, $p < .05$). This side effect lasted for 15 days in 15 patients, compared to 11 days in 9 patients after a unilateral injection.

One of the 4 patients who had no beneficial effect after a dose of 5 units had severe swallowing problems after the bilateral injection, and she withdrew from further treatment.

Table 1. Duration of voice improvement in weeks.

	Unilateral	Bilateral	McNemar $\chi 2$ test
Mean	8	9.3	NS
SD	5.4	4.7	
Range	1-24	1-16	

Four patients did not respond and are excluded, so that n=23.
NS - not significant.

At the end of the study, the patients were asked which treatment they preferred concerning voice quality and duration of benefit in relation to duration and severity of side effects. Fourteen patients (61%) of the 23 preferred a bilateral injection, 5 (22%) a unilateral injection, and 4 (17%) patients had no preference.

Table 2. Side effects after unilateral and bilateral injections of botulinum toxin.

	Unilateral	Bilateral	McNemar $\chi 2$ test
Breathy dysphonia			
No. of patients	13	16	NS
Mean duration in days ±SD	15±8.8	15±8.6	NS
Swallowing problems			
No. of patients	9	15	$p<.05$
Mean duration in days ±SD	11±5.8	15±6.9	NS

n=27

Discussion

Concerning the overall improvement of vocal function, our results are in line with those of other studies.[11-13] Both unilateral and bilateral injections resulted in a better voice. In regard to the duration of voice improvement, no significant differences could be found between the unilateral and bilateral procedures in this study. After both procedures, 85% of the patients reported a better voice for approximately 8 to 9 weeks. With regard to the adverse effects of the injections, no differences were found between the procedures in the occurrence and duration of breathy dysphonia or a weak voice. On the other hand, significantly more patients rated swallowing problems after the bilateral injection.

The present study was focused on the question of whether unilateral or bilateral injections are to be preferred. Our results differ from those of the previously mentioned reports.[11-13] Adams et al[11] advocate a unilateral injection. A superior and longer-lasting benefit of this procedure was found on the basis of acoustic measurements. Perceptually, no significant differences could be detected. No differences in the occurrence of side effects between both procedures were found, although swallowing problems were not mentioned. In our view, two important methodological problems are encountered in this study. First, the two procedures used different doses of botulinum toxin. In the unilateral procedure, 15 units were injected, and in the bilateral procedure, 5 units. When more botulinum toxin is

injected, a longer-lasting effect can be expected. Therefore, we cannot support their conclusion that a unilateral injection is superior. In our study, 5 units were injected in both unilateral and bilateral procedures, and no significant differences in duration of benefit were found. Second, there is a wide variety in the expression and severity of spasmodic dysphonia. Therefore, in their study, with relatively few patients, interpatient variability may play a considerable role.

In the study of Zwirner et al,[12] the same methodological problems are encountered. In addition, various doses were used. Moreover, it was indicated that the patients who were injected bilaterally were affected more severely. Therefore, this study does not allow conclusions concerning unilateral and bilateral injection, either.

The third comparative study was performed by Maloney and Morrison[13] in 1994. They recommended that botulinum toxin injections for spasmodic dysphonia should be initiated on a bilateral protocol. Although more side effects were encountered after the bilateral treatment, improvement of vocal quality was better and duration of the benefit longer. In this study too, different and various doses of botulinum toxin were used. Moreover, there was a wide range in the number of treatments. The range of bilateral treatments was 1 to 6, and unilateral, 1 to 4, injecting 1 to 7 units and 3 to 7 units, respectively. It is not clear at which moment in the study (or after how many treatments) the effect and side effects were evaluated, and how many units of botulinum toxin had been injected.

In our study, the above-mentioned methodological drawbacks were avoided by performing the unilateral and bilateral procedures in the same patient, to exclude interpatient variability. By using the same dose of botulinum toxin in both procedures, a second disturbing factor was eliminated. It is remarkable that there was no difference in the average duration of effect. However, most patients preferred a bilateral injection, even at the cost of more and longer-lasting adverse effects. From the results of this study, we designed a treatment protocol that we apply to each new patient. The first treatment is a unilateral injection of 5 units in the left thyroarytenoid muscle, minimizing the occurrence of undesirable side effects. When the effect has ceased, 2.5 units in each thyroarytenoid muscle is injected during the second procedure. The choice for the next treatment depends on the patient's preference. If necessary, the dose can be changed to adjust efficacy and adverse effects.

Conclusions

A unilateral injection of 5 units botulinum toxin provides the same duration of voice improvement as a bilateral injection. In addition, the unilateral procedure carries less swallowing morbidity. On the other hand, most patients prefer a bilateral injection, in spite of more and longer-lasting side effects.

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Evaluation of voice quality in adductor spasmodic dysphonia before and after botulinum toxin treatment

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4

Introduction

Adductor spasmodic dysphonia (ADSD) is an uncommon and poorly understood voice disorder that is probably due to laryngeal dystonia. The vocal symptoms are characterized by difficulty with voice initiation, a strain-strangled, effortful phonation with voice breaks, and glottal fry. The current treatment of choice for ADSD is botulinum toxin (Botox®) injections in the vocal folds.[1] Most papers dealing with ADSD and Botox® treatment conclude that these patients, as a group, have benefited.

Several modalities have been used to evaluate the success of Botox® treatment: patient's self-evaluation of voice quality and performance, perceptual voice ratings, acoustic analysis, flexible videolaryngoscopy, aerodynamic measurements, and neurophysiological, and psychosocial testing.[2] For all of these modalities significant improvement was found. Efficacy was evaluated either by comparing patients' pretreatment and posttreatment conditions or by comparing the pretreatment or posttreatment values with those of normal controls. Available studies in the literature tend to concentrate on only one modality in appraising the effectiveness of this therapy. For example, some studies report improvement on the basis of patient self-rating scales, while others only rely on aerodynamic or acoustic measurements. Moreover, the frequency of recordings, and moments in time at which the voice was recorded after Botox® injection, varied considerably among clinical

investigators. Most studies assessed the voice at some arbitrary interval (eg, 2, 4 or 6 weeks) after injection. What is lacking is research focussing on "optimal" voice quality and performance after Botox® treatment and in which different modalities are combined.

Therefore, the aim of the present study was to assess to what extent voice quality and performance actually improve through injection with Botox®. This was done by comparing patients' pretreatment voice with the optimal voice (as judged by the patient), as well as comparing both pretreatment and optimal voice with normal control voices. The most frequently used testing modalities were applied: perceptual ratings, (temporal) acoustic analysis, and self-assessment scores.

Patients and methods

Subjects

Two groups participated in this study. One group consisted of 46 patients with ADSD. Diagnosis of ADSD was made independently by a speech-language pathologist and two otorhinolaryngologists.[3] Fourteen of these subjects were men with a mean age of 47 years (range, 32 to 72 years) and 32 were women with a mean age of 49 years (range, 19 to 82 years). The second (control) group consisted of 46 normal subjects with no known speech, hearing, or neurologic disorders. The 2 groups were matched for age (± 1 year) and sex.

Time schedule of recordings

This study was part of a larger prospective clinical trial, in which different procedures of Botox® injection were compared in ADSD patients. All 46 patients underwent unilateral and bilateral injections. During the first procedure, 5 units (1.25 U/0.1mL) of Botox® was injected in the left thyroarytenoid muscle only. The second treatment was performed after the voice quality had returned to the pre-injection level (as established by the patient and by audio and video registrations). During this procedure, both thyroarytenoid muscles were injected, each with 2.5 units (1.25 U/0.1 mL) of Botox®. Using electromyographic guidance, a monopolar 27-gauge, 30 mm Teflon®-coated needle was inserted percutaneously, through the cricothyroid membrane into the left thyroarytenoid muscle, during the first procedure, or into both thyroarytenoid muscles, during the second procedure.

The choice for the next treatment depended on the patient's preference. The dose was adjusted by titrating efficacy and side effects. The endpoint of the study was

the moment at which the patient experienced an optimal voice quality and performance. This was obtained after 3 Botox® injections in 26 patients, after 4 injections in 18 patients, and after 5 injections in 2 patients. Thirty-five patients were most satisfied after a bilateral injection, 11 after a unilateral injection. The dosages varied: 5, 7.5, and 10 units in 20, 23 and 3 patients, respectively.

The moment the patients entered the study (pretreatment), they were asked to complete a self-rating questionnaire for judgment of the voice. At that time, recordings were made for perceptual and acoustic evaluation of the voice quality. The moment the patients judged their voices to be optimal, all tests and recordings were repeated. Recordings of the normal control group were obtained over a period of 4 weeks. The following within- and between-group comparisons could therefore be made: 1) within the ADSD group, differences between pretreatment and posttreatment voices; 2) between groups, differences between the ADSD pretreatment group and normal controls; and 3) between groups, differences between the ADSD posttreatment group and normal controls.

Perceptual analysis

The most widely used perceptual rating system is the GRBAS scale, based on the work of Isshiki et al.[4] However, with this system not all audible features of ADSD can be described. Therefore, in a previous study,[5] we extended the GRBAS system with 6 relevant parameters. It was demonstrated that the extended GRBAS system could be used for accurate and reproducible perceptual characterization of ADSD. Since symptoms of ADSD are markedly manifest during conversational speech, spontaneous speech was recorded for perceptual evaluation (see section on acoustic analysis data collection, below). The voice quality parameters and their definitions are listed in Table 1. The ratings were performed on visual analog scales. On the score form, each parameter was scored on a continuous horizontal line of 10 cm, from normal on the left side to extremely pathological on the right side. The distance in centimeters from the left side determined the score. All voice samples were evaluated and scored by 3 experienced observers who were familiar with both spasmodic dysphonia and the extended GRBAS system. In those instances in which the judges rated voice quality differently, a consensus was reached through reevaluation and discussion.

Table 1. Voice quality parameters and definitions of the extended GRBAS system.

GRBAS	
Grade	Overall degree of impairment
Roughness	Low-frequency aperiodic noise; random fluctuations of glottal pulse
Breathiness	Audible turbulent noise generated at glottis
Asthenia	Weak, powerless voice; no carrying power
Strain	Excessive tension in vocal cords
EXTENSION	
Aphonia	Voice lacking in phonation; a whispering voice
Diplophonia	Two different pitches that can be simultaneously perceived
Staccato	Abrupt voice initiation and arrest; irregular interruption of voice
Tremor	Rapidly occurring fluctuations in pitch and/or loudness; quavering voice
Falsetto	Mode of phonation
Vocal fry	Low-frequency periodic vibration

Subjective voice evaluation

For the subjective evaluation of vocal function, a questionnaire was designed that consisted of several aspects of voice quality and function. These included the intelligibility of speech (conversational speech, during a party, in a public gathering), fatigue (tiring and shortness of breath), loudness, mode of phonation (fluency and strain), and known side effects of Botox® treatment such as hoarseness or a breathy voice and choking on fluids. The ratings were performed on visual analog scales (10 cm) from severe or poor on the left side to normal or good on the right side. The distance in centimeters from the left side determined the score. During the first week after the injection, rating was on a daily basis. Thereafter, the rating was weekly for at least 3 months.

Acoustic analysis

Data Collection. All the speech material was recorded in a sound-treated room, using a Kennet ET 2100 electret microphone, a Sony Hi-8 videocassette camera recorder, and a JVC HiFi stereo videocassette recorder. The recording level was adjusted for each subject to optimize the signal-to-noise ratio and was then kept constant for the remainder of the recording. The mouth-to-microphone distance was kept at approximately 30 cm.

The subjects were asked to produce a number of sustained vowels /a/ (as in the Dutch word aap) at a comfortable pitch and loudness level. They also had to repeat a standard Dutch sentence (Adam at altijd een appel op; "Adam always ate an apple") at a normal conversational level. For each subject, the vowel and sentence that sounded most like the subject's habitual voice were analog-to-digital converted (sampling frequency, 44.1 kHz) and digitally filtered with a 16th-order bandpass Butterworth filter (80 Hz to 15 kHz). The signal was stored on a computer system and used for subsequent acoustic analyses. A total of 92 vowels and sentences (46 ADSD patients and 46 matched controls) were therefore stored in separate files.

All acoustic analyses were done with PRAAT, a software package for processing speech signals.[6] A number of acoustic parameters were evaluated to give a more complete description of the voice and speech quality of the ADSD patients.

Temporal Acoustics. As the involuntary disruption of phonation seen in ADSD also interferes with fluent speech, the following temporal aspects of speech production were evaluated for the standard sentence.[7] The total speaking time (TST) was the total duration of a sentence measured from the onset of the first word to the offset of the last word in a sentence. The onset and offset of acoustic energy were determined perceptually and through visual assessment of oscillographic and spectrographic information. The total interword interval time (TIIT) was the total of the durations of all interword silences exceeding 10 ms. The total articulation time (TAT) was the total duration of the sentence minus the interword interval time (TST minus TIIT).

Vowel Onset Times (VOT). Patients with ADSD are known to have particular difficulty with the initiation of speech.[8] It is, however, not known whether the time it takes for the vocal folds to enter a stable mode of vibration is affected by the laryngeal spasms seen in these patients. It is, furthermore, unclear whether vowel onset times are task-related - in other words, whether it is more difficult to initiate a sustained vowel in isolation than to initiate a vowel in running speech. To obtain some insight in vowel onset times, we manually measured the durations of vowel onsets (of both the sustained vowel and the first /a/ in the sentence: Adam at altijd een appel op; "Adam always ate an apple"). Vowel onset was defined as the duration from the beginning of the vowel to the point at which the signal becomes regular in terms of periodicity.[9] Within- and between-group comparisons were made.

Proportion of Aperiodicity and Silence per Vowel. Sapienza et al[10] found aperiodicity, frequency shifts, and phonatory breaks to be useful in classifying phonatory behavior associated with ADSD. The (autocorrelation) algorithm for periodicity detection was used to determine episodes of aperiodicity and silence within the sustained vowel.[11] This algorithm is a short-term analysis method; therefore, the analysis is performed for small segments (frames) that are taken from the (voice) signal in steps of 0.01 second. The appropriate arguments of the pitch detection algorithm were adjusted so that the number of aperiodic frames and silent frames per vowel could be assessed.

The proportion of aperiodicity was determined as follows. If a time frame did not contain an autocorrelation peak above 0.8 relative to the maximum possible autocorrelation, the frame was classified as unvoiced (aperiodic). This value was chosen because it corresponded with aperiodicity as judged through visual inspection of the oscillogram (nonrepetitiveness of cycles) and perceptual judgment of the voice quality. The number of unvoiced frames was then divided by the total number of frames (total duration of vowel), resulting in a value between 0 and 1.

The proportion of silence was determined as follows. Frames that did not contain amplitudes above 0.1 (relative to the global maximum amplitude) were considered silent. The number of silent frames was then divided by the total number of frames, resulting in a proportional value between 0 and 1. This was considered as representative of the proportion of voice breaks.

Instability of Phonation. Laryngeal instability associated with ADSD has a profound influence on the ability to maintain steady phonation, as well as on the voice quality. Several acoustic parameters have been employed as objective measurements of severity, of which those parameters dealing with the stability of phonation seem to be the most useful, eg, fundamental frequency (F_0) SD.[8,12-15] Therefore, the following acoustic analyses were performed on 2 separate segments of the sustained vowel: the initial 2 seconds (including the vowel onset) and a 2-second segment extracted from the middle, stable part of the sustained vowel. All vowel segments were provided with a linear ramped offset of 10 ms to avoid abrupt audible signal transitions. We analyzed 1) F_0 SD: standard deviation of the F_0 in hertz (F_0 was determined with an autocorrelation pitch detection algorithm[11]); 2) MAS: mean absolute slope in hertz per second; 3) PNR: periodicity-to-noise ratio in decibels, representing the periodicity of the signal; 4) PNR SD: standard deviation of the PNR in decibels; 5) Intensity SD: standard deviation

of the intensity in decibels; and 6) intensity range: difference in decibels between the minimum and maximum intensity within a segment.

Statistical analysis

The perceptual voice characteristics, the subjective voice assessment scores, and the acoustic parameters were summarized with means and standard deviations when the distribution was approximately normal. In case of extremely skewed distri-butions, the median and the interquartile range (IQR) were used. Treatment efficacy was assessed by comparing pretreatment and posttreatment scores by the Wilcoxon matched-pairs signed ranks test. Temporal and acoustic parameters were compared with the matched-control group (pretreatment and posttreatment) by the Mann-Whitney test. Throughout this study, a p value of .05 or less was considered statistically significant.

Results

The changes in the perceptual voice quality parameters are given in Table 2. The average pretreatment score of the overall grade of the voice quality was 6.3 (SD, 1.7), and the posttreatment score was 0.7 (SD, 0.9; $p<.001$). The predominant characteristics of the pretreatment voice quality were strain (5.5), asthenia (3.3), staccato (3.1), and vocal fry (2.6). After treatment, all 4 predominant characteristics diminished significantly. However, on average, the voices were not judged as normal (overall grade, 0.7). Some breathiness and asthenia remained. Moreover, after treatment roughness had increased.

Table 3 shows the correlations between the overall perceptual grade and the other voice quality parameters of the extended GRBAS system. Before Botox® treatment, the overall grade was predominantly determined by strain (correlation, r= .92). Staccato and asthenia correlated weakly but significantly with the overall grade (r= .36 and r= .30, respectively). Only strain and staccato appeared as independent determinants of the overall perceptual grade. After treatment the most important determinants of the overall grade were roughness (r= .72), asthenia (r= .56), and breathiness (r= .51). Remarkably, strain, the most predominant perceptual characteristic before treatment, still correlated moderately with the overall grade (r= .40) after treatment.

Table 2. Parameters of the extended GRBAS system before and after Botox® treatment.

	Pretreatment	Posttreatment	P*
Grade	6.3 ± 1.7	0.7 ± 0.9	<.001
Roughness	0.2 ± 0.7	0.4 ± 0.9	.14
Breathiness	1.0 ± 1.7	0.4 ± 0.7	.21
Asthenia	3.3 ± 1.7	0.5 ± 0.8	<.001
Strain	5.5 ± 2.1	0.2 ± 0.4	<.001
Aphonia	0.6 ± 1.8	0 ± 0	.018
Diplophonia	0 ± 0	0 ± 0	-
Staccato	3.1 ± 2.8	0.1 ± 0.3	<.001
Tremor	0.6 ± 1.1	0.2 ± 0.6	.028
Falsetto	0.1 ± 0.3	0 ± 0	.18
Vocal Fry	2.6 ± 3.4	0.2 ± 0.8	<.001

Data are mean ± SD; 0 represents "normal" and 10 "extremely pathological" voice quality.

*Wilcoxon matched-pairs signed ranks test.

Table 3. Correlations between the overall perceptual Grade and parameters of the extended GRBAS system.

	Overall Grade	
	Pretreatment	Posttreatment
Roughness	.08	0.72§
Breathiness	-.00	0.51§
Asthenia	.30*	0.56§
Strain	0.92§	0.40†
Aphonia	0.20	-
Staccato	0.36*	0.25
Tremor	-0.15	0.15
Falsetto	0.12	-
Vocal Fry	0.18	-0.03

* $p<.05$; † $p<.01$; § $p<.001$.

Correspondingly, the self-assessment scores concerning voice quality and performance all improved significantly after treatment (Table 4). However, on average, the patients did not judge their voices as normal, especially with respect to loudness (score, 6.7), intelligibility of the voice in public gatherings (6.8), and hoarseness (7.6).

Table 4. Self-assessment scales before and after Botox® treatment.

		Pretreatment	Posttreatment	p*
Intelligibility	conversation	3.7 ± 2.7	9.0 ± 1.0	<.001
	party	1.7 ± 1.8	7.6 ± 2.5	<.001
	gathering	1.3 ± 1.7	6.8 ± 2.9	<.001
Tiring		2.3 ± 2.4	8.8 ± 1.5	<.001
Loudness		3.2 ± 2.8	6.7 ± 2.4	<.001
Fluency		2.9 ± 2.1	8.7 ± 1.2	<.001
Strain		2.3 ± 2.3	8.9 ± 1.3	<.001
Shortness of breath		4.4 ± 3.2	8.7 ± 1.6	<.001
Hoarseness		3.6 ± 3.2	7.6 ± 2.5	<.001
Choking		8.4 ± 2.3	9.0 ± 1.8	.089

Data are mean ± SD; 0 represents "severe or poor" and 10 "normal or good" voice quality or performance.

*Wilcoxon matched-pairs signed ranks test.

Table 5 provides the results of the acoustic analyses. Fluency of speaking improved significantly as reflected by the reduced total speaking ($p < .001$), interword interval ($p < .001$), and articulation ($p < .001$) times. However, when pretreatment and posttreatment values were compared with values of normal controls, only the interword interval time had improved to such an extent (posttreatment) that it no longer differed significantly from normal control values. Remarkably, the vowel onset time measured in both sustained and running speech did not show a significant improvement. On the other hand, the proportion of aperiodicity and silence (voice breaks) were significantly reduced after treatment. Again, when one compares these values to those of normal controls, the differences remain significant.

In comparing the initial 2-second segment of the sustained vowel to the middle 2-second segment, significant differences were measured in ADSD patients and normal controls for all parameters, except for the average F_0 (all comparisons) and PNR (pretreatment and posttreatment; Table 6). However, in considering all acoustic parameters in the pretreatment-posttreatment comparison, as well as the pretreatment-control and posttreatment-control comparisons, the p values for all medial segments were very similar to the p values for the initial segment (Table 5). The results for the initial and medial segments will therefore not be given separately.

Table 5. Temporal and acoustic characteristics in patients before and after Botox® treatment and controls.

		Pretreatment		Posttreatment		Controls		pre / post	pre / control	post / control
		Mean	IQR	Mean	IQR	Mean	IQR	P*	P†	P§
TST AA (s)		3.25	1.43	2.45	0.65	2.06	0.49	<.001	<.001	<.001
TIIT AA (s)		0.75	0.60	0.18	0.37	0.24	0.24	<.001	<.001	.14
TAT AA (s)		2.56	0.90	2.12	0.59	1.74	0.31	<.001	<.001	<.001
VOT (vowel) (s)		0.099	0.169	0.097	0.112	0.033	0.029	.30	<.001	<.001
VOT (word) (s)		0.062	0.112	0.069	0.048	0.034	0.023	.60	<.001	<.001
MPT (s)		10.2	11.4	9.3	7.7	15.1	9.7	.038	.029	<.001
Voice breaks (proportion)		4.65	10.3	1.05	3.8	0.31	1.2	.001	<.001	.002
Aperiodicity (proportion)		33.7	70	4.5	15	1.0	3.8	<.001	<.001	<.001
F_0 average (Hz)	i	169.7	43.3	176.0	61.4	171.9	64.3	.49	.79	.75
	m	166.7	46.8	174.6	62.4	175.7	63.7	.67	.96	.95
F_0 SD (Hz)	i	9.6	10.4	5.5	5.6	2.8	2.0	.001	<.001	<.001
	m	6.6	6.9	2.0	2.1	1.4	0.9	<.001	<.001	.003
MAS (Hz/s)	i	162.5	138.7	94.4	79.3	52.1	20.8	<.001	<.001	<.001
	m	132.4	122.4	44.2	44.3	42.0	22.8	<.001	<.001	.097
PNR average (dB)	i	11.3	10.2	13.3	7.3	16.6	4.4	.26	<.001	.001
	m	11.1	12.6	14.0	7.4	15.8	5.3	.13	.052	.59
PNR SD (dB)	i	4.2	2.0	3.8	1.5	3.1	1.4	.18	.001	.059
	m	3.2	1.9	2.0	1.6	2.2	2.1	<.001	.003	.32
Intensity average (dB)	i	71.1	8.0	72.1	7.1	73.3	5.2	.99	.36	.53
	m	70.1	8.4	72.5	8.2	68.4	7.2	.77	.26	.092
Intensity SD (dB)	i	3.0	2.0	2.4	1.7	2.1	1.3	.029	.001	.17
	m	1.8	1.8	0.9	0.6	0.9	0.6	.002	.001	.21
Intensity range (dB)	i	15.8	11.6	13.3	10.0	10.8	5.5	.30	<.001	.006
	m	9.1	8.9	4.0	2.8	4.0	2.4	<.001	<.001	.68

i - initial 2-second segment; m - medial 2-second segment. For explanation of other abbreviations, see text.

*Wilcoxon matched-pairs signed ranks test comparing pretreatment and posttreatment values.

†Mann-Whitney test comparing pretreatment values of patients with values of controls.

§Mann-Whitney test comparing posttreatment values of patients with values of controls.

All parameters except the average F_0 , PNR, and intensity improved significantly following Botox® treatment. Before treatment, only the average F_0 and intensity did not differ significantly from normal control values. After treatment, the PNR SD and intensity SD could be added to this list. Therefore, the majority of acoustic parameters measured in this study remained significantly different from those of normal controls.

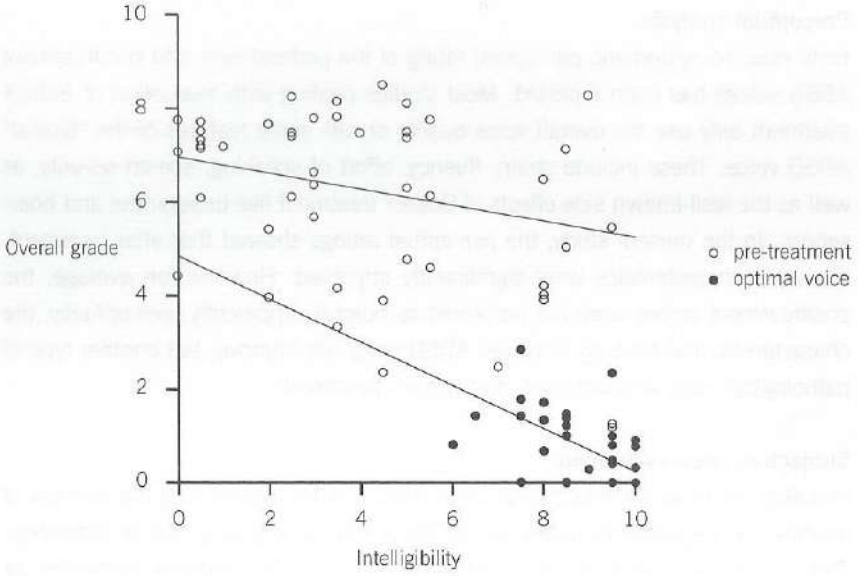
Table 6. Vowel characteristics of initial two-second segment versus medial two-second segment.

	Pretreatment	Posttreatment	Controls
F_0 average	.427	.085	.856
F_0 SD	.002	<.0001	<.0001
MAS	<.0001	<.0001	.002
PNR average	.161	.056	.019
PNR SD	.001	<.0001	<.0001
Intensity average	.002	<.0001	<.0001
Intensity SD	<.0001	<.0001	<.0001
Intensity range	<.0001	<.0001	<.0001

Data are p values of Wilcoxon matched-pairs signed ranks test. For explanation of abbreviations, see text.

Last, a possible relationship between the 3 modalities was assessed, but no strong correlations were detected among the perceptual ratings, acoustic parameters, and self-assessment scores. The highest correlations were found between the pretreatment and posttreatment scores of overall perceptual grade and the patient's self-assessment intelligibility in conversational speech, as is depicted in Figure 1 (pretreatment, r= -.36, p=.014; posttreatment, r= -.51, p<.001; Spearman's rank correlation coefficient test for nonparametric data).

Figure 1. Correlation between the overall perceptual grade and the patients' self-assessment of intelligibility before and after Botox® treatment.



Discussion

In this prospective study, the actual efficacy of Botox® injections in ADSD was assessed by comparing patient's pretreatment values to posttreatment values and comparing both pretreatment and posttreatment values with those of normal controls. Perceptual ratings, (temporal) acoustic analysis, and self-assessment scores were used to achieve this. The posttreatment condition (end point) was defined as the moment the patient experienced his or her voice as normal or as optimal after at least 3 consecutive injections.

The methodological design of this study significantly differs from those of previous studies of ADSD and Botox® treatment. Most studies focus on the duration of benefit and side effects, on comparisons of injection techniques (unilateral versus bilateral, peroral versus percutaneous injections), and/or on searching for the lowest efficacious dose. Efficacy is generally evaluated by either comparing patient's pretreatment and posttreatment conditions or comparing the posttreatment situation with that of normal controls. Moreover, objective tests (often 1 modality) are applied at arbitrary intervals, varying from 1 to 6 weeks, after Botox® treatment. In this study, the efficacy of

Botox® treatment was assessed by concentrating on the optimal voice quality. Therefore, it is hard to compare our results with those available from the literature.

Perceptual analysis

Until now, no systematic perceptual rating of the pretreatment and posttreatment ADSD voices has been reported. Most studies dealing with evaluation of Botox® treatment only use the overall voice quality or rate some features of the "typical" ADSD voice. These include strain, fluency, effort of speaking, spasm severity, as well as the well-known side effects of Botox® treatment like breathiness and hoarseness. In the present study, the perceptual ratings showed that after treatment, the voice characteristics were significantly improved. However, on average, the posttreatment voices were not perceived as normal. Apparently, perceptually, the characteristic and severely impaired ADSD voice did improve, but another type of pathological voice was detected after Botox® treatment.

Subjective voice evaluation

Probably the most important evaluation procedure for determining the success of treatment is the patient's judgement of his or her voice quality and performance. This was already pointed out by Woodson et al[13]: "The patient's perception of his/her problem is, of course, the 'bottom line' in determining patient satisfaction with treatment. These ratings are essential to validate the relevance of objective measures". In our study, the moment the patient perceived his or her voice as normal or optimal determined the end of the trial. In several other studies, patients' diaries were used to assess the efficacy of Botox® treatment and determine the duration of benefit and side effects. However, available reports on the magnitude of improvement of the investigated subjective parameters are limited.[16,17] Therefore, we know that ADSD patients, as a group, have benefited from Botox® treatment, but not to what extent. For example, what does a success rate of 97%, as reported by Inagi et al,[18] really mean - relief of symptoms or achievement of a normal voice? In the current study, patients rated a significant improvement after treatment, but some hoarseness and difficulty with loudness level persisted. Thus, from the patient's perspective, voice quality and performance improved, but were never judged as normal. This outcome is in line with the perceptual ratings: a much better, but still abnormal voice is being perceived after Botox® treatment.

Acoustic analysis

For reliable assessment of voice quality, one needs reproducible measurements and parameters that can objectively monitor changes in voice quality after treatment. These measurements should, preferably, be relevant to the clinical symptoms. In

the past decade, several publications have dealt with ADSD and acoustic analysis. Woodson et al[13] summarize the value of acoustic analysis in this way: "Since acoustic changes are insufficiently specific to separate spasmodic dysphonia from other neurological voice disorders, they should not be regarded as diagnostic tests, but as indicators of function. In patients with spasmodic dysphonia, acoustic analysis is useful in documenting severity and monitoring response to treatment".

Acoustic evidence of temporal disorganization of ADSD speech has already been reported. In 1997, Cannito et al[7] found that although dysfluency was not a defining feature of spasmodic dysphonia, it did contribute significantly to the overall impression of the severity of the disorder. In a noninterventional study, they found significant differences between normal control subjects and ADSD subjects for the total speaking time, total interword interval, and total articulation time. This is in line with our findings: before treatment, all 3 parameters for the patients significantly differed from those of the normal controls. However, although these parameters improved after treatment, they still remained significantly different from those of the normal controls. Until now, only Ludlow et al[19] and Ford et al[20] demonstrated that the "mean sentence length" and "time required to read" decreased after Botox® intervention. Unfortunately, in both studies, the total interword interval times were not assessed. Therefore, an increase in sentence duration could also have been the result of a longer pause time between the words.

The following acoustic parameters are routinely used to quantify changes in voice quality: F_0, F_0 SD, perturbation parameters (jitter, shimmer), harmonics-to-noise ratio, and measurements of voice breaks ("voice break factor," "voice break index," "degree of voice breaks").[21] It was found that these parameters in ADSD patients differed significantly from those of normal controls. After Botox® treatment, however, a statistically significant reduction was found only for F_0 SD and measurements of voice breaks.[22] Jitter and shimmer were not assessed in our study because, as Bielamowicz et al[23] stated: "... as measures of perturbation apparently cannot be reliably applied to voices that are even mildly aperiodic, we question their utility in quantifying vocal quality, especially in pathological voices". This is in line with the work of Titze and Liang,[24] who found that for frequency variations above 6% per cycle, no statements about accuracy could be made.

In 1997, Zwirner et al[8] found significant differences between the initial and middle segments in normal control subjects for the F_0 SD. Before treatment, no significant differences in the ADSD group could be detected. The difference between the initial second and the middle second was statistically significant. They therefore

concluded that a "normal" pattern of laryngeal stability was achieved during sustained phonation. In the current study, the initial 2 seconds differed significantly from the medial 2-second segment extracted from the sustained vowel for all acoustic parameters (including F_0 SD) for both the pretreatment and posttreatment conditions, except for the average F_0 and PNR (pretreatment; Table 6). The fact that our results already differed significantly in the pretreatment condition is in contrast to the results of Zwirner et al. However, only 16 subjects participated in their study. Moreover, it is unclear which pitch extraction algorithm was used, or whether the extracted segments were provided with linear ramped offsets to avoid abrupt audible signal transition.

In this study, (temporal) acoustic analysis revealed that there was a significant improvement after Botox® treatment. Nevertheless, the "optimally" treated ADSD voice still remained deviant as compared to normal voice quality. Acoustically, the typical ADSD characteristics persisted, although they were present to a lesser extent.

Relationship between modalities

Although acoustic analysis of the voice can provide objective and reproducible measures of phonation, there are no specific parameters that can acoustically characterize ADSD. The clinical relevance of these objective measures could be demonstrated if a strong association existed with the more subjective measurements of vocal function and performance, both by the patient and the observer/listener. In this study, however, no strong correlations were found among the perceptual ratings, acoustic parameters, and self-assessment scores. Zwirner et al[12] could not detect specific relationships among any of the acoustic parameters and/or airflow rate and/or the videoendoscopic findings.

Conclusion

Currently, Botox® injection is the therapy of first choice for ADSD. Although significant improvement is measured perceptually, subjectively, and acoustically, in general, the optimal voice obtained with Botox® never fully equals normal voice quality or function.

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Adductor spasmodic dysphonia and botulinum toxin treatment: the effect on well-being

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5

Introduction

Adductor spasmodic dysphonia (ADSD) is an uncommon and poorly understood voice disorder, which was first described by Traube in 1871. The vocal symptoms are characterized by difficulty with voice initiation, a strain-strangled, effortful phonation with voice breaks and glottal fry. Remarkably, these symptoms are reduced or absent during whispering, speaking or singing in a falsetto register, and non-speech vocalizations (laughing, yawning). Spasmodic dysphonia is initially intermittent and task or situation specific. The marked intermittency and functional specificity of the symptoms have suggested a psychological basis for this unusual disorder.

Initially, (adductor) spasmodic dysphonia was considered predominantly as a conversion symptom of an hysterical illness affecting the coordination of speaking and breathing.[1-3] Heaver[4] argued that spasmodic dysphonia especially affected persons with a hysterical and narcissistic personality structure. Berendes[5] analyzed several psychological factors in 23 patients with spasmodic dysphonia. He concluded that this voice disorder had to be considered as a neurosis without hysterical characteristics. However, these ideas could offer no objective support for the hypothesized contribution of psychological factors in the ontogeny of spasmodic dysphonia, because they were based on case histories or patient descriptions.

To by-pass the questionable validity and reliability of interviewers and observers, psychometric tests were applied to assess the psychological phenomena related to this enigmatic voice disorder.[6-9] These studies showed elevated levels of depression and anxiety and negative attitudes toward communication in ADSD patients when compared to matched normal controls. In one study elevated levels of somatic complaints were also found.[7] Treatment with botulinum toxin injections generally reduced the levels of depression and anxiety and significant attitudinal improvement was observed. Whether these differences could be explained as a reaction to a chronic disorder or as being related to a possible psychogenic origin of spasmodic dysphonia remained unsolved.

Nowadays, spasmodic dysphonia is thought to be a physical disorder, an idea already proposed by Schnitzler[10] in 1874. This is supported by the association of spasmodic dysphonia with other focal and generalized dystonias or involuntary movements, such as myoclonus and tremor. It is now assumed that ADSD has a neurologic (undetermined) cause, and is characterized as a disorder of central motor processing resulting in focal laryngeal dystonia. As well as the abnormal voice, a variety of other abnormalities have been found using objective tests including electroencephalography, evoked potentials, blink reflexes, vocal reaction times, and responses to vagal stimuli.[11]

In summary, ADSD is generally accepted as a physical voice disorder associated with several psychological and somatic complaints. Some studies on the psychological impact of ADSD have been performed. The results of these studies supported the need for further research into the role of emotional aspects of spasmodic dysphonia prior to intervention, their relation to objective and subjective voice changes, and how therapeutic management affects the long-term outcome of patients with spasmodic dysphonia.[9] At present, the role of general personality variables in relation to ADSD is unknown.

The aim of this prospective study was twofold: 1) To investigate the hypothesis that personality variables might underlie spasmodic dysphonia; and 2) To determine whether symptoms of negative affectivity (depression and anxiety) and somatic complaints are consequences of the disease.

Subjects and methods

Forty-six consecutive patients (32 female and 14 male) with adductor spasmodic dysphonia were included in this study. The demographic data are summarized in Table 1. Based on their medical history none of the patients appeared to have psychiatric or neurologic disorders, particularly, no other dystonias or familial tremors. All patients had symptoms of adductor spasmodic dysphonia for more than one year and had no previous treatment with botulinum toxin.

Table 1. Demographic data.

		Age (yrs)		Duration of symptoms (yrs)	
	No.	mean	range	mean	range
women	32	47.9	19-80	8.9	1-29
men	14	53.7	31-68	7.9	1-31

The personality characteristics of the patients were assessed using the Dutch Personality Questionnaire (DPQ).[12] This questionnaire was developed in the beginning of the seventies in The Netherlands, adapted from the California Psychological Inventory.[13] Extensive validational data is available on this inventory. The reliability and validity of the DPQ has been proven to be satisfactory.[12,14-18] The 132 items of the DPQ, answered on a three-point scale (True - ? - False), are non-overlappingly keyed in the following scales: 1. Neuroticism (21 items); 2. Social Anxiety (15 items); 3. Rigidity (25 items); 4. Hostility (19 items); 5. Egoism (16 items); 6. Dominance (17 items); 7. Self-esteem (19 items). The seven scales are not independent: highest scale intercorrelations are approximately .45. Usually three second order factors are found: emotional stability versus neuroticism (high loadings of scale 7 and with opposite sign scale 1), introversion versus extraversion (high loadings of scale 2 and with opposite sign scale 6), and dogmatism versus friendliness (high loadings of scale 3,4 and 5).[19] The raw scores on the seven DPQ-scales were used in this study.

The Hopkins Symptom Checklist[20] (HSCL) was applied to assess and monitor the psychological and somatic complaints before and during botulinum toxin treatment. This checklist is a self-report symptom rating scale which a subject answers on a four-point scale of distress ("not at all" – "extreme"). In answering the HSCL an explicit temporal referent is provided in terms of "How have you felt during the past seven days including today?" This makes the HSCL suitable for

measuring changes, eg, measuring the effect of therapy. The Dutch version of the HSCL consists of 57 symptoms and complaints and has the following scales: somatic well-being (HSCL-Somat, 8 items), psychological well-being (HSCL-Psych, 17 items), and a total score (HSCL-Total, 57 items). In this study the normgroup of the general population was used as a reference. There is ample support for the reliability and validity of the HSCL.[20]

To substantiate the effect of botulinum toxin treatment on the changes in psychological and somatic complaints, the changes in vocal function were also determined. This was achieved through subjective (patient) and objective (observers) rating. The subjective rating consisted of statements concerning the patients' experience of their voice quality and performance (intelligibility, effort, and fluency of speech). Perceptual evaluation of spontaneous speech was used to rate voice quality objectively. All voice samples were judged by three experienced observers, who were familiar both with spasmodic dysphonia and a perceptual evaluation rating system, derived from the GRBAS system.[21] For the purpose of this study we only used the "G" -parameter (Grade) to quantify the overall impression of severity of the dysphonia. Assessment of the degree of dysphonia was achieved by calculating the means of the scores of the three observers. Both subjective and objective ratings were performed on visual analogue scales (VAS). On the score form, each parameter was scored on a continuous horizontal line of 10 cm from bad / extremely pathological on the left side to good / normal on the right side. The distance in centimeters from the left side measured the score.

Procedure and time schedule

This study was part of a larger prospective clinical trial, in which different procedures of botulinum toxin (Botox®) injections were compared in ADSD patients.[22] All 46 patients underwent unilateral and bilateral injections. During the first procedure 5 units (1.25 units per 0.1 mL) of Botox® were injected in the left thyroarytenoid muscle only. The second treatment was performed after the voice quality had returned to the preinjection level (established by the patient and by audio and video registrations). During this procedure both thyroarytenoid muscles were injected, each with 2.5 units (1.25 units per 0.1 mL) of Botox®. Using electromyographic guidance, a monopolar 27-gauge, 30 mm Teflon®-coated needle was inserted percutaneously, through the cricothyroid membrane into the left thyroarytenoid muscle during the first procedure, or into both thyroarytenoid muscles, during the second procedure. The choice for the next treatment depended on the patient's preference. Titrating efficacy and side effects the dose was adjusted. The end of the study was the moment at which the patient experienced his or her former

"normal" voice. However, a normal voice could not always be established. In those cases the endpoint was the optimal voice that could be achieved.

The questionnaires were administered at the following instances. The moment the patients entered the study (pretreatment) they were asked to complete the DPQ, the HSCL and the self-rating questionnaire for (subjective) judgment of the voice. At that time recordings were made for perceptual (objective) evaluation of the voice quality. During the follow-up period, i.e. one month after the unilateral injection, one month after the bilateral injection, and at the moment of the optimal voice (posttreatment) all tests, except for the DPQ, were performed again.

Results

Descriptive statistics for the Dutch Personality Questionnaire scores of the 46 ADSD patients before treatment with Botox® are provided in Table 2. There were no significant differences between the patients and the representative normgroup of the Dutch population in the raw scores of the seven scales of the DPQ.

Table 2. The Dutch Personality Questionnaire (DPQ): mean scores and standard deviations of the ADSD patients and normative data.

	ADSD patients (n=46)	Dutch normgroup (n=5686)
Neuroticism	13.2 ± 9.4	12.0 ± 7.9
Social Anxiety	10.2 ± 8.7	10.9 ± 6.9
Rigidity	26.9 ± 9.9	28.4 ± 7.8
Hostility	16.5 ± 7.8	18.2 ± 6.7
Egoism	11.2 ± 5.0	12.6 ± 5.0
Dominance	14.6 ± 6.7	13.8 ± 5.8
Self-esteem	27.8 ± 6.3	28.0 ± 5.6

None of the scales differed significantly, one-sample t-test, df=45

On the other hand, the Hopkins Symptom Checklist showed differences across all three scales, patients having significantly elevated mean scores compared to the representative normgroup (Table 3).

Table 3. The Hopkins Symptom Checklist (HSCL): pretreatment mean scores and standard deviations of the ADSD patients and normative data.

	ADSD patients (n=46)	Dutch normgroup (n=406)	p*
HSCL-Psych	12.6 ± 8.6	7.9 ± 6.2	.0005
HSCL-Somat	3.5 ± 2.6	2.1 ± 2.3	.0005
HSCL-Total	36.8 ± 20.0	22.3 ± 16.5	< .0001

p*: one-sample t-test, df=45

Table 4. The Hopkins Symptom Checklist (HSCL), the patients' and observers' ratings of the voice quality: pretreatment and posttreatment mean scores and standard deviations.

	Pretreatment	Posttreatment	p*
Patient†	3.4 ± 1.4	8.1 ± 1.5	< .001
Observer†	3.7 ± 1.7	9.2 ± 0.9	< .001
H-Psych	12.6 ± 8.6	6.1 ± 6.4	< .001
H-Somat	3.5 ± 2.6	2.2 ± 2.6	.005
H-Total	36.8 ± 20.0	18.6 ± 18.4	< .001

p*: paired t-test

† : 0 represents a "very bad or extremely pathological" voice and 10 a "good or normal" voice.

In Figure 1 the changes of the patients' and observers' voice ratings and HSCL-total scores in course of time are shown. Both VAS-scores of vocal function and HSCL-scores showed continuous improvement during Botox® treatment. These findings are reflected in Table 4 as well. Compared to the mean pretreatment scores of the HSCL, there was a significant decrease following treatment. In fact, the mean scores of all three scales reached values within the normal range. Comparing the scores of the ADSD patients after treatment with the representative normgroup there were no significant differences (Table 5).

Figure 1. Changes of the patients' and observers' voice ratings (VAS-scores) and HSCL-Total scores in course of time. Given are the means and their associated 95% confidence intervals.

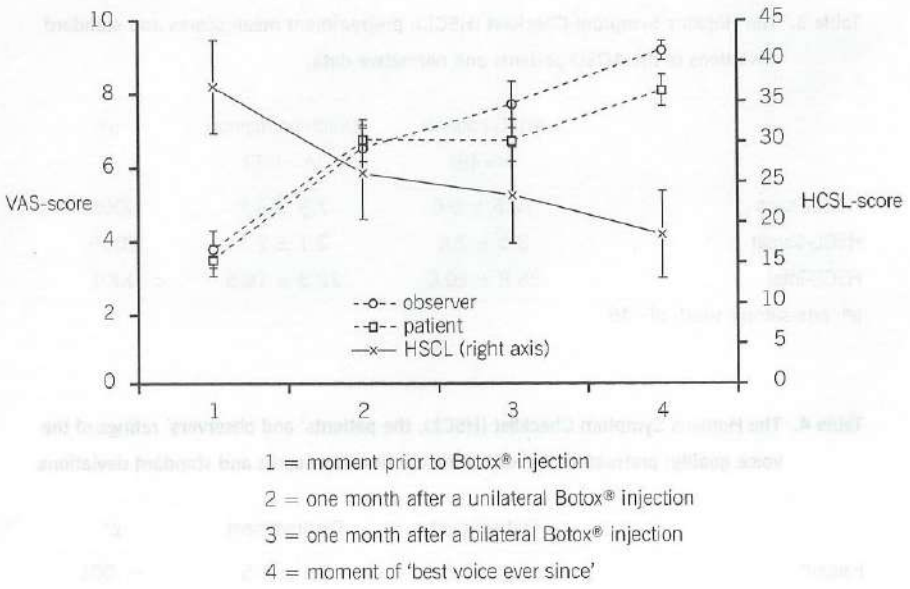

Table 5. The Hopkins Symptom Checklist (HSCL): posttreatment mean scores and standard deviations of the ADSD patients and normative data.

	ADSD patients (n=46)	Dutch normgroup (n=406)	p*
HSCL-Psych	6.1 ± 6.4	7.9 ± 6.2	.06
HSCL-Somat	2.2 ± 2.6	2.1 ± 2.3	.60
HSCL-Total	18.6 ± 18.4	22.3 ± 16.5	.18

p* none of the scales differed significantly, one-sample t-test, df=45

Discussion

The first goal of this study was to investigate the hypothesis that personality variables might underlie adductor spasmodic dysphonia. Using the Dutch Personality Questionnaire (DPQ), no significant differences were found between the ADSD patients and the representative normgroup of the Dutch population. Based on the DPQ results, no distinction could be made between normal and ADSD subjects. This either means that there are no typical personality traits associated with ADSD or that the DPQ could not detect those personality attributes. As the DPQ is accepted as an accurate, comprehensive tool, it would seem that the first hypothesis (ADSD is not associated with typical personality traits) seems justifiable.

Our findings parallel the early work of Aronson[6] who applied the MMPI to 33 patients with spasmodic dysphonia. None of the 10 clinical scales of the MMPI could differentiate between the spasmodic dysphonia patients and a general medical outpatient population. Based on the MMPI they argued that patients with spasmodic dysphonia had to be a remarkably heterogeneous group.

The second aim was to determine whether symptoms of negative affectivity (depression and anxiety) and somatic complaints were consequences of the disease. Research on patients with physical symptoms or disorders underlines the changeability of psychological and somatic complaints in relation to medical treatment.[23] In 1991, Cannito et al[7] already found elevated scores of depression and anxiety among 18 patients with spasmodic dysphonia compared to matched normal controls. In addition, patients showed abnormally elevated levels of somatic complaints. Whether these differences could be explained on the basis of reaction to a chronic disorder or if they were related to a possible psychogenic origin of spasmodic dysphonia remained unsolved.

Prior to intervention we also found statistically significant elevated levels of psychological and somatic complaints. These complaints decreased systematically during the course of the treatment. Compared to the pretreatment scores of the HSCL, a significant reduction was found posttreatment (Table 5). Moreover, they all reached levels within the normal range. The subjective and objective ratings of voice quality also improved systematically during treatment, establishing a normal to near normal voice. These findings suggest that the increased pretreatment scores of psychological and somatic complaints were secondary to the voice disorder.

In just two studies the effect of treatment of spasmodic dysphonia on standardized psychometric tests was assessed.[8,9] In the first study, Murry et al[8] demonstrated that 32 subjects displayed significantly elevated depression and anxiety in the absence of significantly elevated somatic complaints. The effects of Botox® generally reduced measures of depression and anxiety at one week after injection and were maintained during the ensuing two months. The authors concluded that the elevated depression and anxiety could be the result of acquiring spasmodic dysphonia. These results are in line with ours, but in their study there was a problem in terms of subject compliance. Starting with 32 patients, after one week, assessing short-term influence of Botox® treatment, already 10 patients were lost to follow-up. Long-term influence (defined as two months after treatment) could only be determined for 13 of the original 32 subjects, thus reducing validity.

The second study in which patients with spasmodic dysphonia were examined by means of psychometric tests was conducted by Cannito et al.[9] They examined the communication attitudes of 20 patients with adductor spasmodic dysphonia before and after botulinum toxin injection. Although significant attitudinal improvement was observed, the patient group remained significantly different in their attitudes toward communication compared to the normal controls. The amount of change in communication attitudes was significantly related to the amount of change in standardized psychological measures of depression and anxiety. However, in this study the same problem was encountered as in Murry's et al. Initially, 20 patients were included and could be analyzed after one week following Botox® treatment. However, only 14 of the 20 patients returned for the 2-month post-injection follow-up examination. Moreover, prior to the Botox® injection, 6 of 20 patients' test scores (Erickson Scale of Communication Attitudes) already fell within the normal range.

We have to emphasize that based on the results of our study no inferences can be made about causality and the role of psychological risk factors to the development of spasmodic dysphonia. However, results of recent research in the area of health psychology demonstrates that personality characteristics are stable constructs, which are unrelated to somatic disorders.[24] On the other hand, the response to a somatic treatment does not necessarily rule out a psychogenic contribution to either symptoms or symptom severity. A longitudinal study would be more appropriate to elucidate a possible causal relation between specific personal attributes and the occurrence of adductor spasmodic dysphonia.

Conclusion

In this study standardized psychometric tests were used to quantify the psychological aspects of patients with adductor spasmodic dysphonia. No differences in personality characteristics between ADSD patients and a representative normgroup were found. However, patients showed significant more psychological and somatic complaints. After establishment of a (near) normal voice with botulinum toxin injections, these features were reduced to normal levels. This suggests that the psychological and somatic complaints are secondary to the voice disorder. These findings, and the normal personality characteristics, do not support a psychogenic cause of adductor spasmodic dysphonia.

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Transcranial magnetic stimulation in adductor spasmodic dysphonia

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Transcranial magnetic stimulation in adductor spasmodic dysphonia.
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Introduction

Spasmodic dysphonia is an uncommon but often severely disabling chronic voice disorder of unknown etiology. Two main types of spasmodic dysphonia are recognized. The adductor type of spasmodic dysphonia (ADSD) is characterized by difficulty with voice initiation, a strain-strangled, effortful phonation with voice breaks, and glottal fry. The less common abductor type (ABSD) is characterized by intermittent hyperabduction of the vocal cords leading to a weak, breathy but still effortful voice particularly on voice onset.

Until recently, it was believed that spasmodic dysphonia was psychogenic in origin. Now it is supposed that it is a focal dystonia,[1] which is partly based on characteristic EMG patterns.[2] This view is supported by the association of spasmodic dysphonia with other focal and generalized dystonias or involuntary movements, such as myoclonus and tremor.[3] Dystonia is characterized by sustained involuntary muscle contractions leading to abnormal postures or movements generally occurring during voluntary activity. Therefore, spasmodic dysphonia can be considered as an action-induced laryngeal movement disorder.[4] Patients with generalized dystonia, spasmodic torticollis, blepharospasm or writer's cramp exhibit reduction of reciprocal inhibition even in asymptomatic arms. These findings, along with observations of abnormal blink- and H-reflex recovery curves or modifications of

exteroceptive reflexes suggest a generalized disorder characterized by lack of inhibition or hyperreactivity of motor brain structures,[5] despite the focal nature of the signs.

Transcranial magnetic stimulation (TMS) allows the evaluation of excitability of corticospinal pathways by evaluation of both excitatory effects i.e., motor evoked potentials (MEP) as well as inhibition of ongoing motor activity. In unilateral focal dystonia of arm muscles, TMS has shown evidence of increased excitability. Facilitation by voluntary activation was increased.[5,6] The silent period (SP) was described as either normal[6] or prolonged,[5] which latter finding may be interpreted as decreased excitability. A double-stimulus paradigm resulted in decreased suppression.[7] Thresholds did not differ between patients and control subjects.[5-7] Of note is that asymmetries were absent,[6,7] suggesting that the abnormalities need not be specific to the motor area governing the abnormal movements. If generalized hyperexcitability is a feature of focal dystonias, then studies of muscles other than laryngeal ones, themselves not being accessible to TMS, may show abnormalities.

The aim of this study was to assess whether TMS of hand muscles revealed abnormal motor excitability in adductor spasmodic dysphonia.

Methods

Subjects

Twenty-one patients (14 female and 7 male) with ADSD and 16 healthy volunteers (10 female and 6 male) matched for age, sex and handedness participated in the study. The mean age of all patients was 50.8 ± 14.6 (22 to 72) years. For women the average duration of symptoms was 9.0 ± 5.9 (1 to 18) years and for men 8.0 ± 12.8 (1 to 36) years, respectively. Informed consent was obtained from all subjects and the study was approved by the local ethics committee. The diagnosis of ADSD was made independently by a speech-language pathologist and an otolaryngologist. The patients had no history of psychiatric or neurologic disorders, particularly, no other dystonias or familial tremors. All patients had had ADSD for more than one year. The diagnosis was corroborated in all patients by improvement of voice quality after treatment with local injections of botulinum toxin.[8]

MEP procedures

Cortical excitability to magnetic stimuli was assessed with two different paradigms. The first concerned documentation of the stimulus-response relationship,[9,10] and the second concerned the silent period.

Subjects were seated in a comfortable armchair with their hands in a frame to ensure unchanging limb positions. For determination of the maximum voluntary force the subjects had to abduct their little finger against the resistance of a sensitive weighing scale. The limit of the arc of movement of the little finger was determined, after which the angle was fixed at one half the maximum excursion to ensure isometric contraction. Subjects were first asked to exert maximum voluntary force (MVC), measured in kg. Subjects were then instructed to apply force at 10% of MVC. Force levels were controlled before each stimulus using visual feedback.

To document the stimulus-response relationship, 3 stimuli were given at a range of stimulus intensities up to maximum stimulator output (100%) using a Novametrix Magstim 200. Stimulus intensities ranged from 10% to 100% in 10% steps. A 9 cm high-power coil was used, held over the vertex. Both body sides were investigated; for each side, the coil was held in a way to induce maximal responses in that side (i.e., "A-up" for the right side and "B-up" for the left side). MEPs were measured with a Nicolet Viking III EMG machine (bandpass 30Hz-10kHz), from the hypothenar eminence. At each intensity, the latency and peak-to-peak amplitude of the MEP was measured. The mean of the three measurements was used for further analysis. MEPs were considered present when the amplitude exceeded 50 microVolts. The threshold intensity was defined as that intensity at which MEPs were present in 2 out of 3 trials, remaining present at all higher intensities.[9]

The silent period (SP) was measured at 50%, 75%, and 100% intensity. Subjects were instructed to apply 50% of MVC. Three stimuli were given at each intensity for each hand. To keep contraction periods short, subjects were taught to contract for several seconds after receiving a warning signal, i.e., they were taught to keep contracting until well after the stimulus. A 500 ms analysis period was used. The onset of SP was defined as the end of the MEP, its end as the return of EMG activity. The mean duration of the SP of the three trials was noted for further analysis.

To measure the central motor conduction time (CMCT), the MEP latency at 80% intensity over the spinous process of the 7th cervical vertebra was subtracted from the mean cortical latency at each intensity.

Electrical supramaximal stimulation of the ulnar nerve at the wrist was performed to measure the compound muscle action potential (CMAP) amplitude, allowing correction for different muscle masses through calculation of the 'amplitude ratio': MEP amplitude as a ratio of CMAP amplitude.[9]

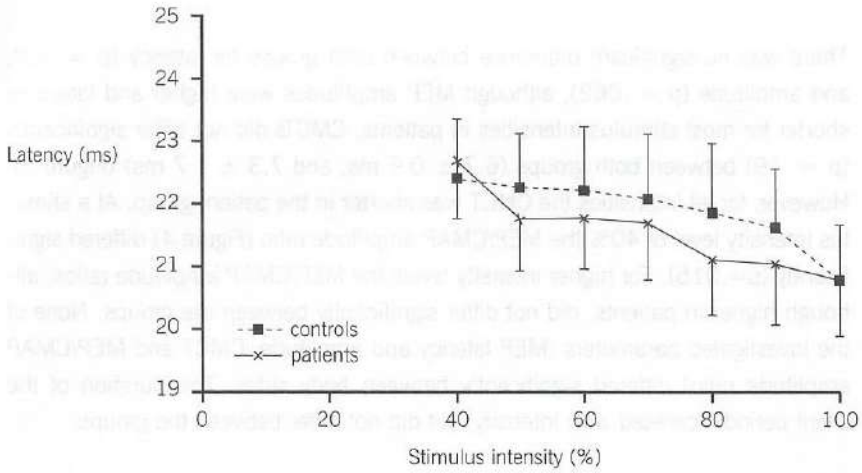
The following parameters were noted: the threshold, and ranges of amplitudes, amplitude ratios, latencies, and CMCTs. This approach allows quantification of not just the most easily excitable motor units (the conventional threshold), but also of those of less excitable motor units. Thresholds of the most excitable units do not necessarily relate to those of less excitable ones.[9]

Statistical analysis

Thresholds were compared between groups using the Mann-Whitney test. Amplitudes, amplitude ratios, latencies, CMCTs, and SPs over the range of intensities used were investigated for differences between the groups using repeated measures analysis of variance (RM-ANOVA). P values $< .05$ were considered significant.

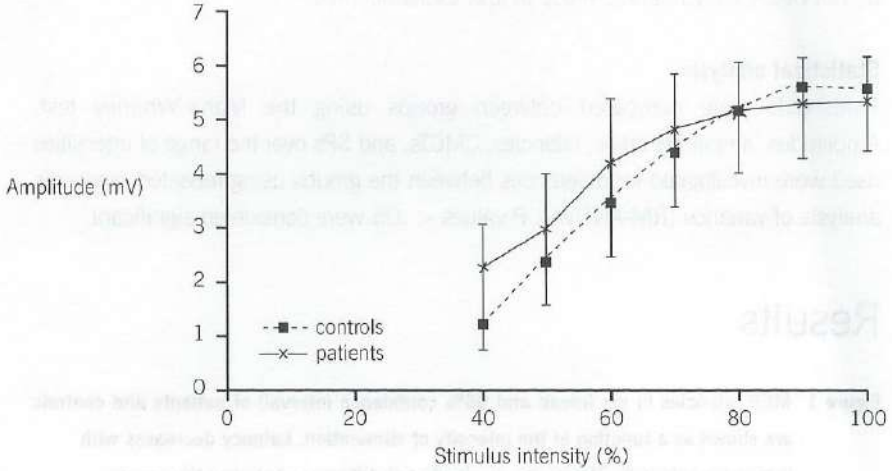
Results

Figure 1. MEP latencies in ms (mean and 95% confidence interval) of patients and controls are shown as a function of the intensity of stimulation. Latency decreases with increasing intensity. There was no significant difference between the groups.



Thresholds did not differ significantly ($p = .83$) between the ADSD ($40.4 \pm 6.7\%$) and control group ($40.8 \pm 4.9\%$). MEP latency decreased with stimulus intensity, as expected (Figure 1), and MEP amplitude increased (Figure 2) significantly ($p < .001$ for both).

Figure 2. MEP amplitudes in mV (mean and 95% confidence interval) of patients and controls are shown as a function of the intensity of stimulation. Amplitude increases with increasing intensity. There was no significant difference between the groups.



There was no significant difference between both groups for latency ($p = .49$), and amplitude ($p = .062$), although MEP amplitudes were higher and latencies shorter for most stimulus intensities in patients. CMCTs did not differ significantly ($p = .19$) between both groups (6.7 ± 0.9 ms, and 7.3 ± 1.7 ms) (Figure 3). However, for all intensities the CMCT was shorter in the patient group. At a stimulus intensity level of 40% the MEP/CMAP amplitude ratio (Figure 4) differed significantly ($p=.015$). For higher intensity levels the MEP/CMAP amplitude ratios, although higher in patients, did not differ significantly between the groups. None of the investigated parameters (MEP latency and amplitude, CMCT and MEP/CMAP amplitude ratio) differed significantly between body sides. The duration of the silent period increased with intensity, but did not differ between the groups.

Figure 3. CMCTs in ms (mean and 95% confidence interval) of patients and controls are shown as a function of the intensity of stimulation. CMCT decreases with increasing intensity. There was no significant difference between the groups.

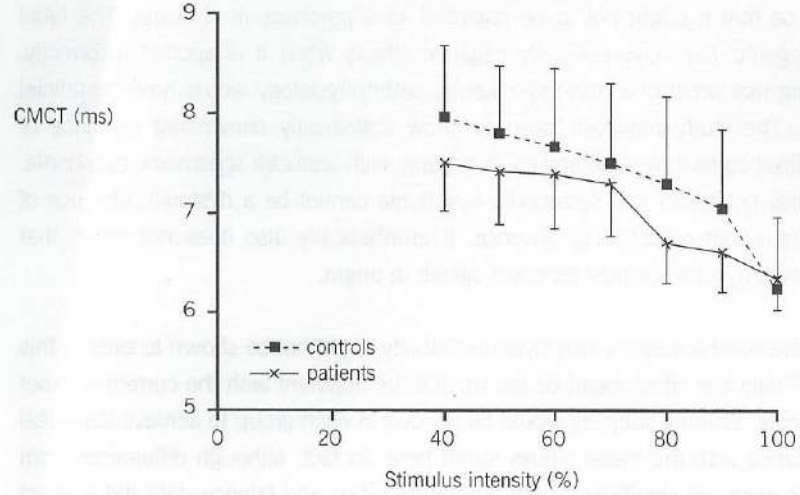
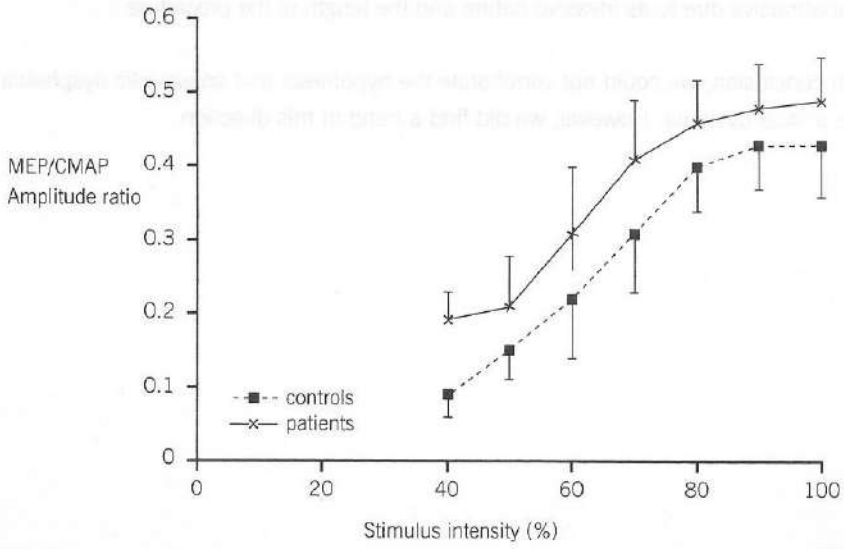


Figure 4. MEP/CMAP amplitude ratios (mean and 95% confidence interval) of patients and controls are shown as a function of the intensity of stimulation. The MEP/CMAP amplitude ratio increases with increasing intensity. The MEP/CMAP amplitude ratio differed significantly between the groups at a stimulus intensity level of 40%, only.



Discussion

This investigation attempted to substantiate the hypothesis that spasmodic dysphonia should be regarded as a focal dystonia. The logical consequence of such findings would be that it ought not to be regarded as a psychogenic disorder. The label "psychogenic" can have seriously negative effects when it is applied incorrectly, meaning that proof of a non-psychogenic pathophysiology would have beneficial effects. The study however failed to show statistically convincing evidence of generalized cortical hyperexcitability in patients with adductor spasmodic dysphonia. This does not mean that spasmodic dysphonia cannot be a dystonia: absence of evidence is not evidence of absence. It emphatically also does not mean that spasmodic dysphonia must be psychogenic in origin.

There are several reasons why hyperexcitability could not be shown to exist in this study. Firstly, the effect might be too small to be apparent with the current number of subjects. Seventy subjects would be needed in each group to achieve statistical significance with the mean values found here. In fact, although differences from controls were not significant, both amplitude ratios and latency data did suggest hyperexcitability. Secondly, the study was based on the premise that cortical hyperexcitability is a generalized phenomenon even in focal dystonia. Previous studies showing bilateral hyperexcitability in unilateral conditions concerned forms of dystonia affecting the upper limb; it is not known whether such a generalization also holds for completely different muscle groups, such as laryngeal muscles. Ideally, the study should have focused on laryngeal muscles rather than hand muscles. The only way to do so would be to use needle electrodes, which was unattractive due to its invasive nature and the length of the procedure.

In conclusion, we could not corroborate the hypothesis that spasmodic dysphonia is a focal dystonia. However, we did find a trend in this direction.

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Summary and conclusions

7

Chapter 1, the General Introduction, is divided into three sections. In the first section, the importance of intact verbal communication for normal human interaction is described. This thesis focuses on a rare voice disorder that primarily affects verbal expression and with that communication: adductor spasmodic dysphonia (ADSD).

The second section is concerned with an extensive literature review, in which history, symptomatology, epidemiology, diagnostic assessment, and the treatment options are described. ADSD has for many years been labeled as a psychogenic voice disorder. Nowadays, it is however generally accepted that ADSD has a neurologic cause: it may be considered as a focal laryngeal dystonia, accompanied with much psychological and physical distress. Localized injections of botulinum toxin (Botox®) have become the treatment of choice for controlling symptoms in patients with adductor spasmodic dysphonia.

The third part of the introduction outlines the aims of the thesis:

> defining diagnostic perceptual characteristics of ADSD
> assessing the optimal voice quality and performance through botulinum toxin injections
> determining the effect of botulinum toxin injections on the quality of life
> assessing the pathophysiology of ADSD

A team consisting of an otolaryngologist, neurologist, and speech-language pathologist is necessary for adequate evaluation of patients with spasmodic dysphonia.

Diagnosis is based on history, physical examination, perceptual evaluation of speech, and laryngological and general neurologic examination. The analysis of perceptual symptoms is one of the mainstays in the diagnostic work-up of spasmodic dysphonia. The most widely used perceptual rating system is the GRBAS scale. But it does not account for all audible features of ADSD. We therefore extended the GRBAS system with six additional parameters. The aim of the study described in **Chapter 2** was to assess the perceptual characteristics of ADSD with the extended GRBAS system and evaluate its reproducibility.

Speech samples of seventy-seven patients were scored independently by three experienced observers, quantifying the voice sound profile. Prevalent characteristics were strain, staccato, asthenia, vocal fry, and tremor. Cluster analysis distinguished four different voice types. Intraobserver and interobserver agreement determined in eight less-experienced observers appeared to be fair to good. The extended GRBAS system can therefore be used for accurate and reproducible perceptual characterization of adductor spasmodic dysphonia. Moreover, this system identified four voice clusters of ADSD with significant differences in voice and demographic characteristics. The relevance of this finding is not clear and requires further investigation.

Chapter 3. Thyroarytenoid injection of botulinum toxin (Botox®) is the therapy of choice in spasmodic dysphonia. However, there is no convincing evidence whether unilateral or bilateral injections are to be preferred. For this reason, a prospective study was designed in which voice quality, duration of effect and side effects served as parameters for this question.

Twenty-seven patients with adductor spasmodic dysphonia were treated with percutaneous Botox® injections. The first treatment consisted of injection of 5 units Botox® in the left thyroarytenoid muscle. The second treatment, 2.5 units in both sides, took place when the effect of the first procedure had completely worn off. All patients underwent both procedures. By means of self-rating scales effects and side effects were assessed during at least three months.

There was no difference in duration of voice improvement nor in the occurrence of breathy dysphonia between the two treatment approaches. After a bilateral injection significantly more patients mentioned swallowing problems. However, most patients preferred the bilateral injection despite more and longer-lasting side effects because of a better voice quality.

In **Chapter 4** the efficacy of botulinum toxin injections in adductor spasmodic dysphonia patients was assessed by three different modalities: perceptual and acoustic analyses, and subjective self-assessment. This was done by comparing

ADSD patients' pretreatment and posttreatment values and comparing these values with those of normal control speakers. In contrast to most other studies, the posttreatment status was defined as the optimal voice quality as judged by the patient. The aim of the present study was therefore to assess to what extent Botox® injections actually improve voice quality and function.
The ADSD subjects rated a significantly improved voice quality and function after Botox® treatment. However, the results were never within normal limits. Perceptually, the characteristic and severely impaired ADSD voice improved, but another "type" of pathological voice was detected after Botox® treatment. Acoustic analyses demonstrated a significant improvement, as well. Nevertheless, the "optimally" treated ADSD voice still remained significantly deviant as compared to normal voice production.
Currently, Botox® injection is the therapy of first choice for adductor spasmodic dysphonia. Although significant improvement could be measured perceptually, acoustically, and subjectively, the optimal voice that was achieved never fully matched normal voice quality or function.

In **Chapter 5** a study is described in which standardized psychometric tests were used to assess the personality characteristics and psychological and somatic well-being in forty-six patients with ADSD. Moreover, the effect of Botox® treatment on their well-being was evaluated.
No significant differences could be detected between patients and a representative normgroup concerning seven personality characteristics. Nevertheless, before treatment there were significantly more psychological and somatic complaints. After establishing a normal to near normal voice with botulinum toxin injections, these complaints were reduced to normal levels, suggesting that these phenomena were secondary to the voice disorder. These findings, and the normal personality characteristics, do not support a psychogenic cause of adductor spasmodic dysphonia.

Chapter 6. Adductor spasmodic dysphonia, historically seen as a psychogenic voice disorder, may be considered as a focal dystonia. If so, transcranial magnetic stimulation (TMS) might show evidence of cortical hyperexcitability. Unfortunately, laryngeal muscles are not accessible to TMS. However, bilateral abnormalities have been reported in other focal dystonias, suggesting a generalized hyperexcitability.
TMS was carried out on abductor digiti minimi muscles in 21 patients with adductor spasmodic dysphonia and in 16 controls, matched for age, sex and handedness. Excitability was quantified with latencies, amplitudes, central motor

conduction times, and amplitude ratios over the full range of intensities, i.e., with stimulus-response curves, and with the silent period.
There were no significant differences between both groups. However, latencies were shorter and amplitude ratios higher in the ADSD group. Although suggestive of hyperexcitability in ADSD, this study carries no hard evidence that ADSD should be seen as a dystonia. A possible explanation is that abnormalities of laryngeal control need not extend to hand muscles.
In conclusion, the hypothesis that spasmodic dysphonia is a focal dystonia could not be corroborated, but we did find a trend in this direction.

Samenvatting en conclusies

7

Hoofdstuk 1, de algemene inleiding, bestaat uit drie onderdelen. In het eerste gedeelte wordt het belang van een intacte verbale communicatie beschreven voor normale intermenselijke relaties. Dit proefschrift richt zich op een zeldzame stemstoornis, waarbij primair het spreken gestoord is en daarmee de intermenselijke communicatie: adductor dysphonia spastica (ADSD).
In het tweede deel wordt een uitgebreid literatuuroverzicht gegeven, waarin de geschiedenis, symptomatologie, epidemiologie, diagnostiek en therapeutische mogelijkheden beschreven worden. Gedurende tientallen jaren is ADSD beschouwd als een psychogene stemstoornis. Tegenwoordig wordt echter algemeen aangenomen dat het een neurologische aandoening is, waarvan de oorzaak nog onbekend is. Zeer waarschijnlijk betreft het hier een laryngeale dystonie, die gepaard gaat met veel psychische en lichamelijke klachten. De behandeling van ADSD is symptomatisch: injecties met botuline toxine.
In het derde gedeelte van de inleiding worden de doelstellingen van dit proefschrift beschreven:

> het ten behoeve van de diagnostiek definiëren van perceptieve karakteristieken van ADSD
> het bepalen van de optimale stemkwaliteit en stemfunctie na behandeling met botuline toxine injecties
> onderzoek naar het effect van botuline toxine injecties op de kwaliteit van leven
> onderzoek naar de pathofysiologie van ADSD

Voor de diagnostiek van patiënten met dysphonia spastica is multidisciplinair onderzoek vereist. De KNO-arts, neuroloog en logopedist spelen hierbij een centrale rol. De diagnose dysphonia spastica wordt gesteld op de typische anamnese, lichamelijk onderzoek, perceptieve analyse van de stemkwaliteit, laryngologisch en algemeen neurologisch onderzoek. Een belangrijke rol is hierbij weggelegd voor de perceptieve analyse van de stem. Voor de perceptieve beoordeling van de stemkwaliteit wordt het GRBAS-scoringssysteem het meest gebruikt. Hiermee kunnen echter niet alle perceptieve kenmerken van ADSD worden beschreven. Daarom hebben wij het GRBAS-systeem uitgebreid met zes parameters ("Extended" GRBAS-systeem). In **Hoofdstuk 2** worden de perceptieve kenmerken van ADSD onderzocht met behulp van dit "Extended" GRBAS-systeem en wordt de reproduceerbaarheid hiervan geëvalueerd.
Om het profiel van de stemkwaliteit te kwantificeren werden zevenenzeventig patiënten met ADSD onafhankelijk gescoord door drie ervaren luisteraars. De meest voorkomende kenmerken waren: "strain", "staccato", "asthenia", "vocal fry" en "tremor". Door middel van cluster analyse konden vier verschillende perceptieve "types" van ADSD onderscheiden worden. De overeenstemming (intra- en interbeoordelaar) onder acht minder ervaren luisteraars bleek redelijk tot goed.
Uit dit onderzoek is gebleken dat het "Extended" GRBAS-systeem gebruikt kan worden voor een accurate en reproduceerbare perceptieve beoordeling van patiënten met ADSD. Bovendien konden hiermee vier clusters van ADSD geïdentificeerd worden met significante verschillen in stemkwaliteit en demografische kenmerken. Nader onderzoek zal moeten uitwijzen wat de betekenis hiervan is.

Hoodstuk 3. De eerste keuze van behandeling van dysphonia spastica is een injectie met botuline toxine (Botox®) in de m. thyroarytenoideus. Tot nu toe was er geen overtuigend bewijs of een één- dan wel een tweezijdige injectie de voorkeur moest hebben. Daarom werd een prospectief onderzoek verricht waarbij de stemkwaliteit, de werkingsduur en bijwerkingen werden onderzocht.
Zevenentwintig patiënten met ADSD werden met percutane botuline toxine injecties behandeld. Bij de eerste behandeling werden 5 eenheden Botox® geïnjecteerd in de linker m. thyroarytenoideus. De tweede behandeling vond plaats wanneer het effect van de eerste volledig was verdwenen. Hierbij werden in beide kanten 2,5 eenheden Botox® geïnjecteerd. Alle patiënten ondergingen beide behandelingen. Gedurende tenminste 3 maanden werden de duur van het effect en de eventuele bijwerkingen door de patiënten bijgehouden op scoringslijsten.
Het bleek dat er geen verschillen waren tussen beide procedures wat betreft de duur van de stemverbetering en het voorkomen van een hese en zwakke stem. Na een tweezijdige inspuiting werden er door meer patiënten slikproblemen vermeld;

desondanks prefereerden de meesten een tweezijdige injectie, gezien de subjectief betere stemkwaliteit.

In **Hoofdstuk 4** wordt de werkzaamheid van botuline toxine injecties in patiënten met adductor dysphonia spastica onderzocht aan de hand van drie verschillende modaliteiten: perceptieve en akoestische analyse en subjectieve beoordeling door de patiënt. Hierbij werden de waarden voor en na de behandeling met elkaar vergeleken en de laatste werd vergeleken met de waarden van gezonde vrijwilligers zonder stemklachten. In tegenstelling tot de meeste andere onderzoeken werd de toestand na behandeling gedefiniëerd als het beste stemresultaat dat tot dan toe bereikt werd. Het doel van het onderzoek was om na te gaan in hoeverre botuline toxine injecties daadwerkelijk de stemkwaliteit en functie verbeterden.
Na behandeling met Botox® injecties beoordeelden alle patiënten hun stem als significant verbeterd. De resultaten vielen echter nooit binnen de normaalwaarden. Ook perceptief was er een significante verbetering van de stemkwaliteit. Hoewel minder ernstig, bleef de stem afwijkend van karakter na de Botox® injecties. Akoestische analyses lieten een zelfde verbetering zien. Desalniettemin bleef de "optimaal" behandelde ADSD-stem significant verschillend ten opzichte van de normale stemgeving.
Tot nu toe zijn botuline toxine injecties de behandeling van eerste keuze voor dysphonia spastica. Hoewel er een significante verbetering is bij zowel perceptieve en akoestische analyse als bij subjectieve beoordeling van de stem, wordt een "optimaal" behandelde ADSD-stem toch niet helemaal normaal wat betreft stemkwaliteit en functie.

Adductor dysphonia spastica is een controversiële en raadselachtige stemstoornis. Algemeen wordt aangenomen dat het een neurologische aandoenig is, waarvan de oorzaak onbekend is en dat het met veel psychische en lichamelijke klachten gepaard gaat. In **Hoofdstuk 5** wordt een onderzoek beschreven waarin met behulp van psychometrische tests enkele persoonlijkheidskenmerken en het psychisch en lichamelijk welbevinden van 46 patiënten met ADSD onderzocht wordt. Tevens wordt het effect van de botuline toxine behandeling op hun algemeen welbevinden geëvalueerd.
Met betrekking tot zeven persoonlijkheidskenmerken werden geen significante verschillen gevonden tussen de patiëntengroep en een representatieve normgroep. Voor de behandeling werden er echter significant meer psychische en lichamelijke klachten gemeten. Nadat de stem met botuline toxine injecties optimaal behandeld was, namen de klachten af tot waarden binnen de normaal waarden. Dit suggereert dat deze klachten secundair waren aan de stemstoornis.

Deze bevindingen en de normale persoonlijkheidskenmerken maken de hypothese dat adductor dysphonia spastica een psychogene origine heeft, minder waarschijnlijk.

Hoofdstuk 6. Adductor dysphonia spastica is gedurende lange tijd gezien als een psychogene stemstoornis. Tegenwoordig wordt het beschouwd als een focale dystonie. Met die aanname zouden er bij transcraniële magnetische stimulatie (TMS) aanwijzingen kunnen zijn voor corticale hyperexcitabiliteit. Helaas is de larynxmusculatuur niet toegankelijk voor TMS. Bij andere focale dystonieën, zijn er echter bilateraal afwijkingen gevonden, hetgeen een gegeneraliseerde hyperexcitabiliteit suggereert.
Op basis hiervan is bij 21 patiënten met ADSD en 16 controles, met overeenkomstige leeftijd, geslacht en dominante hemisfeer TMS verricht, waarbij de activiteit gemeten werd aan de m. abductor digiti minimi. De excitabiliteit werd gekwantificeerd met de latentietijd, amplitude, centrale geleidingstijd en amplitude ratio gemeten voor alle intensiteiten aan de hand van stimulus-responscurven en met de "silent-period".
Tussen beide groepen werden geen siginificante verschillen gemeten. De latentie tijden waren echter korter en de amplitude ratio's hoger in de patiënten groep. Hoewel suggestief, kon in dit onderzoek niet aangetoond worden dat ADSD als een focale dystonie gezien zou moeten worden. Een mogelijke verklaring hiervoor is dat de stoornis, die het aansturingsmechanisme van de larynx compromitteert, die van de handmusculatuur ongemoeid laat. Hoewel er geen bewijs werd verkregen dat dysphonia spastica een focale dystonie is, kon deze hypothese met dit onderzoek ook niet ontkracht worden.

Final comments

8

Verbal expression, on which normal communication relies, is fundamental for human relationships. Impaired communication often results in withdrawal from social life and isolation. One of the main characteristic features of ADSD is impaired verbal expression and as a result, communication. In addition, many spasmodic dysphonia patients are regarded as having a psychogenic disorder, enhancing their feelings of frustration, depression and anxiety. Due to the botulinum toxin treatment, their voice quality and function was improved and communication restored. The burden of the impaired voice was lifted and the psychogenic stigma resolved. As a result of this symptomatic treatment, patients again perceived themselves as normal functioning, fully integrated members of society.

Reflecting on this bizarre and enigmatic disorder, several striking features can be recognized. First, the differences in clinical presentation. One of the mainstays in the diagnostic process of spasmodic dysphonia is the analysis of perceptual symptoms. Although a strained-strangled, staccato voice is a defining feature of ADSD, four different voice clusters could be identified, all representing adductor spasmodic dysphonia. In addition, from observation it has become clear that the voice also varies during different tasks and in different situations. Patients may whisper or speak in falsetto in an attempt to escape from the strained-strangled, staccato voice, thus masking their dystonia and hampering diagnosis. Therefore, as was already suggested by Drost (1996), spasmodic dysphonia is the chameleon among the voice disorders. This heterogeneity leads to difficulties in identifying

the disorder and tends to invite the ever-convenient label: "psychogenic voice disorder".

A second intriguing observation is the psychological relief that occurred when patients were informed about their diagnosis. For the first time their affliction had been recognized and had been given a name. After so many years they finally knew the origin of their suffering: a chronic, organic disease instead of a psychogenic, stigmatizing disorder. The diagnosis gave substantial psychological relief to many patients before any treatment was given.

A third striking feature is the high success rate of botulinum toxin therapy in relation to the gravity of the disorder. For many years ADSD had been an incurable and devastating voice disorder. With the introduction of botulinum toxin injections in almost all ADSD patients voice improvement could be established. Although a long-lasting, normal voice can never be achieved, most patients can again function as normal individuals. Moreover, although the voice deteriorates in course of time (due to the mode of action of botulinum toxin) the patients' well-being generally will not. It is probable that the prospect of improvement after another injection of botulinum toxin provides them with enough confidence to remain well-balanced, both psychologically and physically.

A fourth remarkable phenomenon of ADSD and botulinum toxin treatment is that unilateral and bilateral thyroarytenoid injections both result in the same efficacy. After a unilateral injection the spasms will disappear in the opposite side as well. This cannot be explained by local diffusion of the botulinum toxin into the not injected muscle. This strongly suggests that the beneficial response of the botulinum toxin in the treatment of ADSD, is attributed to modulation of the afferent input to the central nervous system.

The current treatment of choice for spasmodic dysphonia is botulinum toxin injection. On the other hand, the preliminary results of the midline lateralization thyroplasty as proposed by Isshiki (2000) are promising. In this procedure the excessive tight closure of the glottis on phonation is diminished. In the past several (comparable) surgical techniques to reduce the vocal cord overpressure have been employed, without permanent success. Long-term follow-up of Isshiki's midline lateralization thyroplasty is needed to answer the question: "Could surgery ultimately be more successful than botulinum toxin injections?"

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Curriculum Vitae

Ton Langeveld was born in Leiden on September 29th, 1962. He attended the Fioretti College in Lisse (Gymnasium ß). Subsequently, from 1981 he studied medicine at the University of Leiden. After obtaining his medical degree in 1989, he worked as resident at the departments of General Surgery at the Bergwegziekenhuis, Rotterdam and the University Hospital Maastricht. From 1991 to 1996 he specialized in Otorhinolaryngology at the University Hospital Leiden. During this time he started the research which is described in this thesis. In 1996 and 1997 he worked as a clinical fellow in head and neck oncology in the Daniël den Hoed Kliniek, Rotterdam. Since then, he has been employed as staff-member at the department of Otorhinolaryngology of the Leiden University Medical Center.

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Stellingen

behorende bij het proefschrift

Adductor Spasmodic Dysphonia

1 Alle geavanceerde technologieën ten spijt vormt de perceptieve analyse van de stem nog steeds de hoeksteen van de diagnostiek bij dysphonia spastica. *(dit proefschrift)*

2 Het effect van een unilaterale botuline toxine injectie op de contralaterale larynxhelft ondersteunt de hypothese dat bij dysphonia spastica de centrale verwerking van het afferente systeem gestoord is. *(dit proefschrift)*

3 Not all bizarre and variable voice disorders should be ascribed to the psyche. *(dit proefschrift)*

4 De optimaal behandelde stem van een patiënt met dysphonia spastica is niet normaal. *(dit proefschrift)*

5 C'est (le) *Ton* qui fait la musique. *(dit proefschrift)*

6 Fluisteren is niet slecht voor de stem.

7 Stemrust na een stemverbeterende ingreep dient vooral de gemoedsrust van de dokter.

8 Op basis van de huidige gegevens is er onvoldoende aanleiding om de techniek van het 'sluderen op de kap' te verlaten.

9 Kanker is de keerzijde van de evolutie.

10 Although patients are the first and obvious victims of medical mistakes, doctors are wounded by the same errors: they are the second victims. *(Albert W Wu, BMJ 2000;320:726-7)*

11 Het waarborgen van de privacy van de patiënt is een groot goed. Echter, de interpretatie hiervan door regelgevers is een depreciatie van het basale vertrouwen tussen arts en patiënt, een nodeloze hinderpaal voor efficiënte gezondheidszorg en de genadeklap voor diverse vormen van patiëntgebonden wetenschappelijk onderzoek.

12 'Collateral damage' is, mits op tijd gesignaleerd en juist geïnterpreteerd, een onmisbare katalysator van vooruitgang van de geneeskunde. *(RJ Baatenburg de Jong, Je stem of je leven, oratie 1999)*

13 Tijdens het motorrijden zijn geestelijke vrijheid en lichamelijke kwetsbaarheid in een wankel evenwicht.

Leiden, 21 maart 2001 **Ton Langeveld**

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