

Vocal Cord Dysfunction in Amyotrophic Lateral Sclerosis Four Cases and a Review of the Literature

Four Cases and a Review of the Literature

Abstract

We describe 4 patients with amyotrophic lateral sclerosis (ALS) and glottic narrowing due to vocal cord dysfunction, and review the literature found using the following search terms: amyotrophic lateral sclerosis, motor neuron disease, stridor, laryngospasm, vocal cord abductor paresis, and hoarseness. Neurological literature rarely reports vocal cord dysfunction in ALS, in contrast to otolaryngology literature (4%-30% of patients with ALS). Both infranuclear and supranuclear mechanisms may play a role. Vocal cord dysfunction can occur at any stage of disease and may account for sudden death in ALS. Treatment of severe cases includes acute airway management and tracheotomy.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by features indicative of both upper and lower motor neuron degeneration. Initial manifestations usually include weakness in the bulbar region or weakness of the limbs. Progressive weakness leads to increasing disability and respiratory insufficiency, resulting in death. The median survival time is 2.5 to 3 years from onset of symptoms; the 5-year survival rate is approximately 25% to 30%.^{1,2}

Dyspnea is a frequent and well-known symptom in patients with ALS and occurs when respiratory muscles become weak. However, acute dyspnea may also be the result of glottic narrowing due to paresis of the vocal cord abductors. Vocal cord dysfunction has received little attention in ALS literature.

Symptoms of vocal cord dysfunction range from hoarseness, hypophonia, and short phonation time to nocturnal nonproductive cough and attacks of inspiratory stridor and dyspnea.³⁻⁶ Inspiratory stridor is defined as a harsh, strained sound with a higher pitch than snoring.⁷ When stridor is caused by vocal cord abduction paresis (VCAP), it is potentially life threatening, as a predominance of vocal cord adduction results in glottic narrowing or even occlusion. Assessment by an otolaryngologist is then of the highest priority. Stridor is a well-known symptom in multiple system atrophy and may also incidentally occur in other neurodegenerative diseases.⁸⁻¹⁰ Laryngospasm, a sudden and uncontrollable closure of the larynx, is another symptom of vocal cord dysfunction.¹¹ Laryngeal electromyography may be helpful in the diagnosis of vocal cord dysfunction.¹²

We describe 4 patients with ALS and acute dyspnea due to vocal cord dysfunction resulting in glottic narrowing. Three developed the symptoms in the course of their disease; in the fourth patient, they were present at the time of diagnosis. We also review the literature on this subject. Search terms included: amyotrophic lateral sclerosis, motor neuron disease, stridor, laryngospasm, vocal cord abductor paresis, hoarseness, and multiple system atrophy. Relevant references in publications were hand searched.

Report of cases

Patient 1

A 56-year-old woman presented with weakness, atrophy, and hyperreflexia of her right arm and was diagnosed with familial superoxide dismutase 1–negative ALS. Three of her brothers

and 2 paternal cousins had died of ALS. Disease progression comprised atrophic tetraplegia and dysarthria, with hyperreflexia in the limbs but only lower motor neuron signs in the bulbar region. Four years after diagnosis she experienced 6 attacks (4 of them nocturnal) of acute dyspnea, during which she felt an involuntary airway closure. Laryngoscopy showed paresis of vocal cord abduction, and a tracheotomy was performed. Vital capacity (VC) was still 100% of that predicted, and findings of arterial blood gas analysis were normal. She died 1 year later of respiratory failure after an episode of rapidly declining VC because she refused to be mechanically ventilated. None of her affected family members had had a history of vocal cord problems, but they had never been examined by an otolaryngologist.

Patient 2

A 63-year-old man visited an otolaryngologist because of dysarthria and dysphagia for 1 year. Laryngoscopy revealed no abnormalities of the vocal cords. He was then referred to a neurologist. Upper motor neuron signs (pseudobulbar affect) were prominent in the bulbar region but he also had some atrophy of the tongue. Neurological examination and results of needle electromyography (EMG) of the limbs appeared normal, as did brain magnetic resonance imaging. His VC was 95% of predicted. A diagnosis of sporadic possible ALS with bulbar onset according to the revised El Escorial¹³ criteria was made. Some months later he had widespread fasciculations in his arms and legs with still normal strength, brisk reflexes, and an equivocal plantar response.

Nearly 1 year later he had an attack of acute dyspnea and stridor at night. Laryngoscopy revealed vocal cord abduction paresis; subsequently, tracheotomy was performed. One year after tracheotomy he experienced respiratory failure. He chose not to be mechanically ventilated and died shortly thereafter, 4 years after onset of symptoms.

Patient 3

A 58-year-old woman visited a neurologist because of slurred speech and dysphagia. She had signs of upper and lower motor neuron involvement in the bulbar region. Neither neurological examination nor needle EMG showed abnormalities in the limbs. A brain magnetic resonance image appeared normal. A diagnosis of sporadic possible ALS with bulbar onset was made. Her VC was 130% of predicted. At a later stage of the disease, she developed weakness of the hands.

One year after onset of symptoms, she incidentally felt sudden spasms of her throat following aspiration, leading to cyanosis. These spasms were very concerning to her. Performance of percutaneous endoscopic gastrostomy was complicated by laryngospasm. She was referred to an otolaryngologist who confirmed paresis of the vocal cord abductors with both vocal cords almost in midline position. She was advised to have tracheotomy, which she initially declined, but eventually a tracheotomy was performed. Results of capillary blood gas analysis were still normal. Shortly thereafter, she had respiratory failure and received mechanical ventilation. A few months later, she expressed the wish to die. After a careful evaluation of her condition, her request for euthanasia was granted.

Patient 4

A 69-year-old man was referred to our neurology department with progressive dysarthria, dysphagia, and pseudobulbar affect present for 1.5 years. He also experienced daily attacks of acute dyspnea with a sensation as if his throat were compressed, usually provoked by

aspiration or by a supine position. He had signs of upper and lower motor neuron involvement in the bulbar region. Results of neurological examination of the limbs were normal but needle EMG showed spontaneous activity and reinnervation in the trunk and leg region. A diagnosis of sporadic probable laboratory-supported ALS was made. His VC was 95% of predicted. Laryngoscopy triggered a laryngospasm with uncontrolled adduction of the vocal cords lasting for 1 minute. Needle EMG of the (adducting) vocal muscle revealed tonic activation in rest (Figure 1A). Motor units appeared normal. Needle EMG of the (abducting) posterior cricoarytenoid muscle showed no signs of denervation but polyphasic motor unit action potentials of long duration were compatible with reinnervation and a markedly reduced interference pattern during inspiration (Figure 1B). Results of blood gas analysis were normal. A tracheotomy was performed shortly thereafter. A follow-up laryngoscopy after tracheotomy revealed an almost midline position of the vocal cords at inspiration (Figure 2A). He is now anarthric, uses percutaneous endoscopic gastrostomy feeding, and is still ambulant but has weakness in his right arm.

Review of the literature

Epidemiology

Vocal cord abductor paresis and laryngospasm in ALS are rarely described in the neurological literature. There are 3 superoxide dismutase 1–positive Japanese cases of ALS presenting with hoarseness due to bilateral vocal cord paresis as an initial manifestation of the disease.^{3,6} A large survey of clinicians' practice in the symptomatic treatment of ALS in the United States recognized that laryngospasm is seldom mentioned in ALS literature but is present in 19% of patients when queried.¹⁴ A study of expiratory muscle function in patients with ALS found abnormal function of the vocal cords in 2 of 11 patients with respiratory symptoms.¹⁵ In this study, patients without respiratory symptoms did not have laryngoscopy. A study using a symptom questionnaire but no fiberoptic analysis of the vocal cords reported laryngospasm in 2% of 147 patients with ALS.¹⁶ This study stressed the role of pyrosis in some cases. It is known that laryngospasm may be triggered by aspiration of refluxed gastric contents, and an intense antireflux treatment can abolish the attacks of dyspnea.^{14,17,18}

In contrast, otolaryngology literature addresses VCAP and laryngospasm in ALS more often. Hoarseness was noted as the initial manifestation in 3.9% of 441 patients with ALS being seen by an otolaryngologist.¹⁹ A large cohort study that included more than 100 patients with bulbar-onset ALS who visited a specialized otolaryngology clinic found bilateral VCAP in as many as 30%.⁵ Vocal cord abductor paresis on laryngoscopy may not be correlated with audible stridor when respiratory muscles are too weak to generate sufficient negative pressure for the narrowed glottis to present a functional restriction.⁵ In more advanced cases, paradoxical inspiratory adduction of the vocal cords can be found in patients with ALS, especially during or just after coughing.⁴ Standardized analysis of acoustic parameters of the voice with appropriate software demonstrated early laryngeal deterioration in patients with a ALS with a perceptually normal voice that was not observed in healthy controls.²⁰

Several other neurological conditions can be accompanied by vocal cord dysfunction. Nocturnal stridor was found in 13% of patients with multiple system atrophy (MSA).²¹ Stridor can even be the presenting symptom in MSA.²² Stridor in patients with MSA is associated with (sudden) death, and MSA patients with stridor have a poorer survival rate than those without.^{7,10,22} No relation was found between dysphagia and vocal cord dysfunction in patients with MSA.²³ A fiberoptic study reported moderate to severe VCAP in 9 of 11 patients

with MSA with advanced disease.⁹Vocal cord dysfunction was also described in Parkinson disease.^{24,25}There are anecdotal cases of stridor in myotonic dystrophy, demyelinating hereditary motor and sensory neuropathy, and myasthenia gravis.²⁶⁻³⁰

Mechanisms of Glottic Narrowing

The size of the glottic aperture is determined by a balance of forces between the vocal cord abductor and adductor muscles. Either reduction of abductor muscle activity or increased activity of adductor muscles can narrow the glottic aperture. To maintain patency of the larynx, inspiratory coactivation of abductors and adductors is, to a certain extent, physiological in a reflex response to negative airway pressure.

Several underlying mechanisms of glottic narrowing and stridor in neurological disease have been described. Many of them focused on MSA, but none of them on ALS. In MSA, degeneration occurs not only in the central nervous system but also in pontine and spinal nuclei of lower motor neurons.^{31,32}Therefore, these studies may provide insight into mechanisms that could also apply to ALS. In patients with MSA, the reflex response of vocal cord abductors on inspiration may be depressed owing to weakness, and a net predominance of adduction results in laryngeal narrowing. Electromyography studies confirmed that excessive activation of vocal cord adductors during inspiration caused laryngeal narrowing and stridor in patients with MSA, rather than a pure VCAP.^{33,34}However, 2 postmortem studies demonstrated neurogenic atrophy in the (abducting) posterior cricoarytenoid muscle and a loss of neurons in the nucleus ambiguus in patients with MSA, suggestive of an infranuclear abductor paresis.^{9,35}A postmortem study comparing patients with Parkinson disease and vocal cord abductor paresis documented with fiberoptic laryngoscopy in patients with MSA did not demonstrate neurogenic atrophy in abductors or adductors in Parkinson disease.³⁶The authors postulate that there are so-called paralytic and nonparalytic types of vocal cord dysfunction. The nonparalytic type, being present in Parkinson disease, is supposed to be due to persistent overactivity of vocal cord adductors and of supranuclear origin. On the other hand, the paralytic type of MSA, with neurogenic atrophy and weakness of the posterior cricoarytenoid muscle, or a combination of the paralytic and nonparalytic type, is supposed to be present.³⁶

There are no autopsy studies that describe details of pathological examination of the vocal cords in patients with ALS. Given the nature of ALS, with its combination of upper and lower motor neuron signs, glottic narrowing in patients with ALS could well be of the infranuclear paralytic type, the supranuclear nonparalytic type, or a combination of the two.

Our cases also suggest that vocal cord dysfunction may occur as a result of supranuclear as well as infranuclear motor neuron degeneration. Patient 1 had only lower motor neuron bulbar symptoms, patient 2 showed mainly pseudobulbar symptoms, and patients 3 and 4 clearly had upper motor and lower motor neuron symptoms in the bulbar region. Nevertheless, all 4 patients developed acute dyspnea due to glottic narrowing. Needle myography findings in patient 4 provided evidence of a supranuclear nonparalytic component (overactivity of the adductors) as well as an infranuclear component (signs of reinnervation in the abductors).

Treatment

Treatment of severe airway compromise is based on general principles of acute airway management.³⁷If the patient cannot be ventilated, intubation should follow immediately.

Failure to intubate should prompt a cricothyroidotomy. If dyspnea subsides, a tracheotomy should be performed (semi)electively, if compatible with the patient's advance directives and after informed consent.

There are no studies on preventive treatment of vocal cord dysfunction with glottic narrowing in ALS. In patients with MSA, tracheotomy was recommended for the treatment of moderate to severe VCAP.³⁸ Assessment of severity in this study was based on laryngoscopy during sleep.

During the last decade there has been a growing interest in noninvasive treatment modalities for patients with MSA, as tracheotomy has shown implications for quality of life and deterioration of physical condition since this intervention was described.³⁹ During sleep, upper airway resistance increases, thus increasing negative airway pressure during inspiration, which may be the explanation for stridor occurring most frequently at night.³³ Reducing upper airway resistance through the application of continuous positive airway pressure or noninvasive positive-pressure ventilation was found to be successful in the treatment of some patients with MSA with nocturnal stridor.⁴⁰⁻⁴² Effects in mild to moderate cases of VCAP or laryngospasm in ALS are unknown.

It is important to realize that severe airway obstruction can also occur early in the course of ALS, as demonstrated by patient 4, in whom laryngeal symptoms were present before diagnosis was made. One must be aware of the fact that a (near)-normal VC predisposes patients to vocal cord dysfunction, as a narrowed glottis is more likely to become clinically symptomatic when respiratory muscles are still strong enough to generate negative airway pressure.^{4,5}

Glottic Narrowing and Sudden Death in ALS

Stridor in MSA is known to be a poor prognostic feature and is associated with short survival, presumably as a result of sudden death from glottic obstruction.⁷ A survey in the Netherlands focusing on euthanasia and physician-assisted suicide in 203 patients with ALS revealed that, of the patients who did not have any life-shortening intervention, 37% died suddenly and unexpectedly.⁴³ The authors do not elaborate on this finding. Another retrospective study on causes of death in ALS described unexplained sudden death in 12% of the patients.⁴⁴ There are no prospective studies on the occurrence of sudden death in patients with ALS. Given the fact that vocal cord dysfunction occurs in patients with ALS, some of these cases of sudden death may have been related to glottic obstruction.

Conclusion

Occurrence of vocal cord dysfunction in ALS is far from rare and may be of infranuclear as well as of supranuclear origin. Patients with reasonable or good VC in particular are at risk of potentially threatening glottic narrowing. Vocal cord dysfunction is not always related to major bulbar involvement. Hoarseness, hypophonia, short phonation time, nonproductive cough, stridor, sudden laryngeal spasms, choking, or paroxysmal dyspnea should raise suspicion and justify prompt referral to an otolaryngologist. In severe cases a tracheotomy, if compatible with the patient's advance directives, is usually needed but management in milder cases remains unclear. A prospective cohort study with clinical, laryngoscopic, and electromyographic evaluation of patients with ALS is required to provide insight into the epidemiology, pathophysiology, and prognosis of vocal cord dysfunction in ALS.

Correspondence: Maaïke van der Graaff, MD, Department of Neurology Room H2-234, Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, the Netherlands (m.m.vandergraaff@amc.uva.nl).

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