

Botox Injection for Laryngeal Dysfunction in Alexander Disease

Amy Rutt, and Selmin Karatayli Ozgursoy, Jacksonville, Florida

INTRODUCTION

Alexander disease (AD) is a rare neurodegenerative disorder caused by mutations in the gene encoding the glial fibrillary acidic protein (GFAP).¹ AD was first described in an infant in 1949^{2,3} and characterized by the presence of Rosenthal fibers (RFs)—eosinophilic inclusions localized in astrocytic cytoplasm—found in perivascular, periventricular, and subpial spaces of the cerebral hemispheres, the cerebellum, and the brainstem.⁴ Brainstem involvement may cause otorhinolaryngologic manifestations, including dysphonia, dysphagia, tremulous voice, nasal dysarthria, and palatal tremor (PT). There is no cure for this condition and support is aimed at medical management of symptoms. We present a case of a 51-year-old man with AD who initially presented to the laryngology clinic with dysphonia, dysphagia, and PT and benefited from periodic Botox injection. To our knowledge, this is the first report of Botox injection for dysphonia and dysphagia in a patient with AD.

CASE REPORT

The patient is a 51-year-old man who presented with dysphagia for solids and liquids and questionable aspiration. He had dysarthria, drooling, choking, and dyspnea for a few years. He also complained of breathiness in his speaking voice, vocal fatigue, voice breaks, trouble projecting his voice, vocal strain, frequent throat clearing, coughing, and difficulty speaking on the telephone.

He had a history of “syncope events” with onset in first-grade and episodic “vasovagal syncope” for many years. The patient also has had some difficulties with gait and balance.

The patient had dysarthria displaying a breathy voice and dyspnea; however, he was able to count to 20 in one breath. He had a PT and displayed an enhanced jaw jerk. His smooth pursuits were quite saccadic, and square wave jerks were evident with visual fixation.

Laryngeal examination was remarkable for laryngeal tremor, and there was evidence of PT as well.

The patient had a recent neurologic evaluation, which revealed very subtle, upper motor neuron distribution weakness in his upper extremities, which was symmetric. He did have pathologically brisk myotonic stretch reflexes in the upper extremities with bilateral Hoffmann signs. There was evidence of dysdiadochokinesia and dysmetria, which were relatively mild and symmetric. The evaluation was consistent

with progressive ataxia and PT with suspicion of an underlying genetic mutation. The overall pattern of abnormality was consistent with a neuromuscular disease, with associated upper airway and bronchial hyper reactivity. Brain magnetic resonance imaging (MRI) revealed upper cervical cord and medullary atrophy.

Whole-genome sequencing revealed a likely pathogenic variant in GFAP that is associated with AD. The patient’s phenotype was consistent with adult-onset Alexander disease (AOAD). Autosomal dominant inheritance with reduced penetrance and variable expressivity were discussed with the patient. Because first-degree relatives have a 50% risk of inheriting the GFAP variant, benefits and risks of presymptomatic testing for asymptomatic at-risk relatives were also reviewed. The patient was also informed that support was aimed at medical management of symptoms and that there was no cure for this condition.

Modified barium swallow study revealed mild oropharyngeal dysphagia characterized by penetration of thin liquids when taken in larger volumes, nonpenetration with small volumes, absence of postswallow oral or pharyngeal residue, premature spillage of thin liquids, and delayed esophageal clearance.

As part of symptomatic treatment, physical and respiratory therapy for coordinated efforts of speech was administered. There was question of whether Botox injections into the oropharynx may be useful. The patient was not bothered by the PT. His main concern was the “vocal cords moving so quickly and cutting of his breath.”

After taking informed consent, the patient was administered 2 units of Botulinum toxin type A (BOTOX, Allergan, Irvine, CA) to the bilateral thyroarytenoid muscles. A laryngeal electromyographic therapeutic needle was used and injection was performed under electromyographic guidance. The needle was passed through the cricothyroid membrane and into the medial belly of the thyroarytenoid muscle. At the patient’s first procedure, 2 units of Botox was injected bilaterally. He had five subsequent injections, each increasing in dosage from 3 to 8 units into the bilateral thyroarytenoid muscles 3–6 months apart each, after the effects of the previous injection wore off. Palatal Botox was not performed. On follow-up, the patient reported less breaks in his voice. He was able to eat without aspiration and enjoy an improved voice. The patient reported that swallow and speech difficulties were worse when the Botox wore off.

DISCUSSION

Currently, there are three forms of AD based on age at onset: infantile, juvenile, and adult. AOAD is the most variable and the least common form.³ AOAD can be similar to the juvenile form with later onset and slower progression.^{3,5}

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From the Department of Otolaryngology, Mayo Clinic, Jacksonville, Florida.

Address correspondence and reprint requests to Selmin Karatayli Ozgursoy, Department of Otolaryngology, Mayo Clinic, Jacksonville, FL, 4500 San Pablo Road S, Jacksonville FL, 32224. E-mail: selminkrt@hotmail.com

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Based on a retrospective study of 13 individuals with late-onset AD, brainstem or spinal cord involvement may be common, resulting in symptoms such as nystagmus, dysphagia, dysarthria, spasticity or hyperreflexia, positive Babinski sign, gait abnormality, and weakness, although individual-to-individual and intrafamilial variabilities are seen.⁶

PT is a rhythmic involuntary movement associated with brainstem lesions, including neurodegenerative disorders. PT (previously known as palatal myoclonus) is a rare clinical finding and has been reported to be strongly suggestive of AOAD in a series of 11 AOAD cases.⁷ In the same series, the most frequent clinical features in AOAD were reported to be dysarthria, dysphagia, dysphonia, and PT because the pathologic site mainly involved is the brainstem-spinal cord junction. The most common MRI findings were atrophy of the medulla oblongata extending caudally to the cervical spinal cord.⁷ Our patient had similar presenting symptoms and MRI findings.

Survival of patients with AOAD ranges from a few years to a number of decades after the onset of symptoms. Some individuals have been diagnosed incidentally during autopsy for other conditions. Reports of molecularly confirmed familial cases support the existence of asymptomatic adults with AD.^{1,8–10}

The pathologic features in all forms are characterized by widespread RF formation, diffuse demyelination, and preserved neurons. RFs are cytoplasmic inclusions in astrocytes containing GFAP and small heat-shock proteins (HSP27), and b-crystallin.³ Heterogenous factors might play a role in RF formation because incidental RFs were also reported in neurologically free adults, with the backgrounds of severe complicated medical illnesses, malignancies, alcohol intoxication, barbiturate abuse, and solvent abuse.³

Laryngeal tremor, which one might assume would be one of the most common otolaryngologic symptoms of patients with AOAD due to brainstem-spinal cord junction involvement, might well be treated with Botox as reported here. Essential tremor of the voice (ETV) was reportedly treated with Botox successfully.¹¹ The subjective assessment of treatment success by the patients was attributed to correlation of patient perception of vocal effort with the aerodynamic estimate of laryngeal airway resistance. Patients may benefit from Botox because it effectively reduces the airway resistance by limiting vocal fold adduction, and Botox may have the subjective effect of reducing vocal effort during phonation. The objective response rate, however, was lower than those usually observed in patients with adductor spasmodic dysphonia (ADSD). This finding was attributed to the significant differences in pathophysiology between these

two diseases, as in ADSD the dysfunction is usually limited to the thyroarytenoid muscle; however, in ETV, the muscles involved are throughout the upper aerodigestive tract. These muscles include the levator veli palatini, hypoglossus, sternothyroid, thyrohyoid, rectus abdominis, and diaphragm. Because laryngeal tremor in patients with AOAD is similar to the tremor in ETV rather than in ADSD, subjective improvement in voice assessed by the patient after each Botox injection can be attributed to decreased resistance in the airway and reduced vocal effort during phonation.

Dysphonia and dysphagia of the reported case was treated with periodic Botox injection, which helped improve the patient's voice, as well as his swallowing. To our knowledge, this is the first report of the use of Botox for dysphonia and dysphagia in a patient with AD. Because there is no cure for patients with AD, all possible symptomatic treatment modalities should be provided to these patients.

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