Negative Dystonia of the Palate: A Novel Entity and Diagnostic Consideration in Hypernasal Speech

Catherine F. Sinclair, MD; Kristina Simonyan, MD, PhD; Mitchell F. Brin, MD; Andrew Blitzer, MD, DDS

Objective: To present the first documented series of patients with negative dystonia (ND) of the palate, including clinical symptoms, functional MRI findings, and management options.

Study Design: Case series ascertained from clinical research centers that evaluated patients with both hyperkinetic and hypokinetic movement disorders.

Methods: Between July 1983 and March 2013, data was collected on patient demographics, disease characteristics, functional MRI findings, long-term management options, and outcomes. We sought patients whose clinical examination demonstrated absent palatal movement on speaking, despite normal palatal activity on other activities.

Results: Five patients (2 males, 3 females) met clinical criteria. All patients presented with hypernasal speech without associated dysphagia. Clinical examination revealed absent palatal movement on speaking despite intact gag reflexes, normal palate elevation on swallowing, and normal cranial nerve examinations. Other cranial and/or limb dystonias were present in four patients (80.0%). Three patients (60.0%) had previously failed oral pharmacologic therapy. Two patients underwent functional magnetic resonance imaging (fMRI) studies, which demonstrated an overall decrease of cortical and subcortical activation during production of symptomatic syllables and asymptomatic coughing. Management included speech therapy (all patients) and palatal lift (2 patients) with limited improvement. Calcium hydroxyapatite injection (1 patient) into the soft palate and Passavants' ridge was beneficial.

Conclusions: This is the first report of ND of the palate. Characteristic findings were task-specific absent palatal movement with speech, despite normal movement on swallowing, coughing, and an intact gag reflex, as well as disorder-specific decreased brain activation on functional MRI. A diagnosis of ND of the palate should be considered for patients who present with hypernasal speech.

Key Words: Dystonia, movement disorders, soft palate, velopharyngeal insufficiency, speech.

Level of Evidence: 4.

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INTRODUCTION

Dystonia is characterized by sustained muscle contractions frequently causing twisting and repetitive movements or abnormal postures that may be sustained or intermittent. Dystonia can involve any voluntary muscle. Coexisting agonist and antagonist muscle activity contribute to the increased tone component. Although genetic testing is available for limited forms of dystonia,[1] the diagnosis of dystonia is clinical, with the core being abnormal postures (with or without tremor) and the recognition of specific features such as *geste antagoniste*, overflow, and mirror movements.[2] Recently, the concept of negative dystonia (ND) has been introduced to describe a predominance of pseudoparetic type symptoms due to deficient muscle activation, with or without the traditional sustained muscular contractions.[3] Conditions hypothesized to represent ND included apraxia of lid opening (ALO),[3,4] the paretic form of writer's cramp,[3] and abductor spasms associated with abductor spasmodic dysphonia (SD).[5] Integral to the classification of ND is the absence of muscle paralysis of central or peripheral origin or of local myopathic diseases. In the current study, we present a series of patients with ND of the palate. Diagnostic considerations and results, including functional magnetic resonance imaging (fMRI), are discussed, and potential management strategies are outlined.

MATERIALS AND METHODS

Retrospective review of case series of five patients assessed at clinical research centers between July 1983 and March 2013. The institutional review board of Icahn School of Medicine at Mount Sinai approved the study.

Outcome Measures

Prospective data were collected on patient demographics, symptom and disease characteristics, and clinical examination

TABLE I.
Negative Palatal Dystonia: Patient Characteristics.

	N (%)	Patient
Gender		
Male	2 (40.0)	1,4
Female	3 (60.0)	2,3,5
Dystonia of other body parts	4 (80.0)	2,3,4,5
Trial of oral medications prior to presentation	4 (80.0)	2,3,4,5
Symptomatic improvement with oral medications		
Overall	2 (40.0)	4,5
Clonazepam	1 (20.0)	4
Lamotrigine	1 (20.0)	5
Genetic testing		
Negative	1 (20.0)	1,2,3,4
Not tested	4 (80.0)	5

findings. All patients underwent a comprehensive neurological examination, relevant diagnostic testing as well as MRI. Flexible fiberoptic nasolaryngoscopy was performed on all patients following topical anesthesia of the nasal cavity to observe palatal movements on speaking and swallowing and to enable identification of co-incident neurological abnormalities of the upper aerodigestive tract. Functional MRI studies were performed on 2 patients to examine the pattern of brain activity compared to healthy subjects and to patients with SD.

Functional MRI

Brain imaging data were collected on a 3.0 Tesla Philips MRI scanner equipped with an 8-channel head coil. A high-resolution T_1-weighted anatomical image was collected using three-dimensional magnetization-prepared rapid acquisition gradient echo sequence to rule out brain structural abnormalities and to provide an anatomical reference for the functional scans. Whole-brain functional images were acquired with a gradient echo planar imaging pulse sequence using an event-related sparse sampling design and blood oxygenation level-dependent contrast. During the fMRI scan, patients were asked to either produce repetitive syllables (/i-i/) or voluntary coughs to assess the brain activity during production of both symptomatic and asymptomatic tasks, respectively. Imaging data were compared to 12 existing age- and gender-matched patients with SD (6 with adductor SD and 6 with abductor SD) and 12 healthy controls, as reported in a previous study.[6]

Processing of fMRI was performed using AFNI software (Cox and Hyde, 1997) as described earlier.[6] Data from two ND patients were examined on the individual basis at $P \leq 0.05$ corrected for family-wise error and then compared to the group results from patients with SD and healthy controls at a corrected $P \leq 0.05$.

RESULTS

Patient History and Clinical Examination Findings

Average age of neurologic symptom onset was 44.5 ± 16.5 years. All patients had normal birth and developmental histories without a family history of neurological disease. No patient had neuroleptic medication exposure prior to symptom onset. Additional patient group demographics are sumarized in Table I. All presented with hypernasal speech without associated dysphagia or nasal regurgitation on swallowing. Examination findings common to all patients and unique to individual patients are summarized in Table II. The

TABLE II.
Examination Findings.

| Area Examined	Examination Findings Common to All Patients	Patient	Finding
		Unique Examination Findings	
Oral cavity	Absence of palatal elevation with speech despite normal gag reflex	2	Lingual dystonia
		3	Lingual dystonia (posterior tongue)
		5	Lingual dystonia
Superior palate	Absent palatal movement with speech		
	Normal palatal movement and velopharyngeal closure with swallowing (and singing for patient 2)		
Pharynx	Decreased lateral pharyngeal constriction with speech		
	Normal lateral pharyngeal constriction with swallowing		
Larynx	Normal mucosal appearance	1	Vertical laryngeal tremor
	Normal function of larynx	3	Supraglottic contraction on connected speech
Cranial nerves	I–XII normal (excluding lingual dystonic movements)	5	Decreased up-gaze
Other		1	Left-hand intention tremor
		4	Right-hand dystonic writer's cramp (ulnar deviation and hyperflexion of index finger on right handwriting with wrist hyperextension)
		5	Spastic scissor gait
			Cranial dystonia involving facial and buccal regions
			Illegible fast handwriting, which normalized on slow printed writing
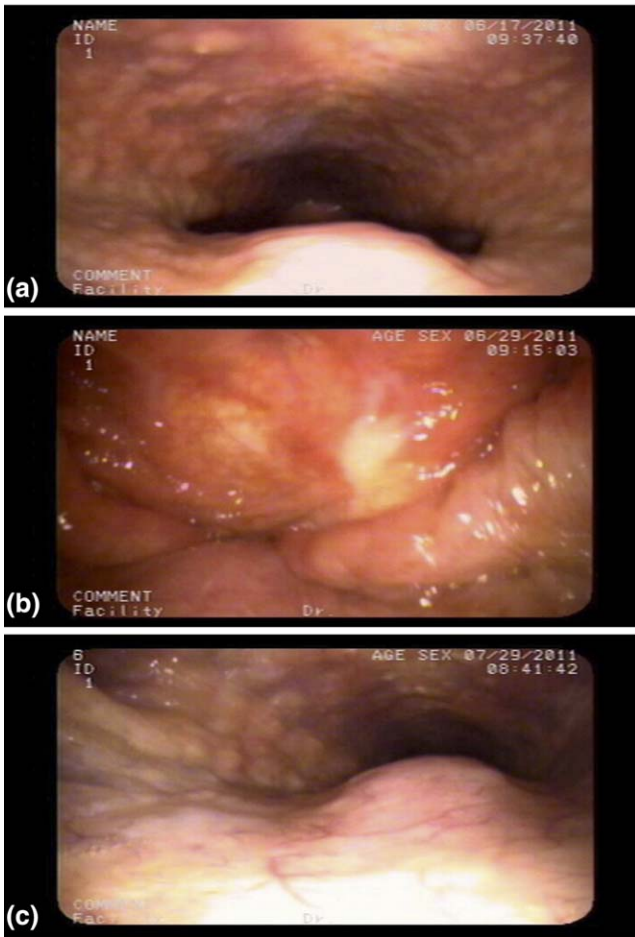
Fig. 1. (a) View of superior palate showing absence of palatal movement on speaking; (b) View of superior palate showing normal palatal closure on swallowing; (c) View of superior palate during speaking, 8-months postinjection augmentation, showing increased lateral pharyngeal wall constriction. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com]

most striking otolaryngological finding was the absence of palatal movement on speech tasks, despite normal palatal movement during swallowing, coughing, and other nonspeech maneuvers. This was best visualized during examination of the palate from above via flexible transnasal nasendoscopy (Figs. 1a,b). Maneuvers assessing lip and anterior tongue function ('pa-pa,' 'ta-ta') were acoustically normal for all patients; however, those requiring velopharyngeal closure ('prikata-prikata,' 'coca-cola') were markedly hypernasal. Individual significant findings for each patient are presented below and summarized in Tables I and II. Unless specifically mentioned, other components of neurological and otolaryngological examinations were normal. Brain radiological evaluation revealed normal anatomy without gross abnormalities. Genetic testing performed on the blood samples from two patients found no GAG and THAP mutations associated with DYT1 and DYT6 genes, respectively.

Patient 1

68-year-old male presented with hypernasal speech of 15 years duration. Past surgical history included a parotidectomy for benign disease. Medications included lisinopril for hypertension. He had been referred for a palatal lift appliance early in the disease course; however, there was no symptomatic improvement and it was discontinued. He was treated with an intraoral injection of calcium hydroxyapatite (Radiesse, Merz Aesthetics, San Mateo, CA) into Passavants ridge posteriorly, both lateral pharyngeal walls, and the soft palate. Although he continued to exhibit hypernasal speech after treatment, his nasopharyngeal to oropharyngeal aperture was smaller, which minimized speech-related velopharyngeal insufficiency (VPI) symptoms and positively affected speech quality. Also, some movement of the lateral pharyngeal walls and palate returned, as seen on fiberoptic examination 2 months postinjection (Fig. 1c). The patient was referred for speech therapy and had good symptomatic improvement with this regime. One year after initial injection, symptoms of hypernasality worsened, and he underwent further soft palate and posterior pharyngeal wall injections of Radiesse with good results. Injections were repeated again 6 months later. At last review, 26 months after initial injection and 8 months since the last injection, nasoendoscopic examination revealed voluntary contraction of lateral pharyngeal wall musculature with speech-related tasks, which was increased compared to prior examinations and ongoing palatal immobility. There was minimal evidence of residual augmentation material.

Patient 2

60-year-old female presented with 5 years of dysarthria and hypernasality on speaking. She was able to sing clearly without hypernasality. Past medical history was significant for hypothyroidism treated with levothyroxine. Her lingual dystonia (Table II) was present with speech, but not with other tasks, without tongue fasciculations or weakness. Speech therapy provided no benefit.

Patient 3

23-year-old female presented with marked hypernasal speech, breathy voice symptoms of abductor SD, and a normal gag reflex. She had additional cranial (upper and lower face), nuchal/axial, and appendicular dystonia involving upper more than lower extremities. In addition, she had increased appendicular tone and gait and balance difficulties. Speech was further associated with overflow dystonic contractions of the orbicularis oris and jaw muscles; swallowing was impaired. The patient's condition gradually progressed, and an extensive evaluation for symptomatic dystonia did not reveal a specific diagnosis. Speech therapy, clonazepam, onabotulinumtoxinA treatment to the posterior cricoarytenoid muscles, baclofen, levodopa/carbidopa, dopamine agonists, sertraline, and other centrally active agents provided either equivocal or no benefit.

Patient 4

60-year-old male presented with 10 years of hypernasal speech, with onset following an upper respiratory

tract infection. Speech progressively worsened after infection resolution. Past surgical history included removal of a vocal fold polyp the year following symptom onset. Extensive speech therapy, carbamazepine, clonazepam, and a palatal lift appliance did not provide symptomatic benefit. One month after discontinuing use of the lift, the patient spontaneously regained normal speech. Six years later, he again developed gradual onset of hypernasality during speech, vocal strain, vocal fatigue, and nasal air emissions. Recommencing clonazepam provided partial relief. He was commenced on gabapentin.

Patient 5

48-year-old right-handed female presented at age of 20 years with hypernasal speech with a normal gag reflex. She also exhibited cranial dystonia involving facial, buccal, and lingual musculature, with associated dysarthria. Initially misdiagnosed as psychogenic, she was treated with psychotherapy for 5 years. Because of other examination findings suggesting symptomatic dystonia, an extensive evaluation was performed. A specific diagnosis could not be made. The patient was trialed on multiple oral medications, including haloperidol, clonazepam, venlafaxine, levodopa/carbidopa and trihexyphenidyl, and other centrally active agents, without symptomatic benefit. Speech temporarily improved with each of three pregnancies. She underwent a palatal flap procedure with minimal effect on hypernasality and was subsequently commenced on lamotrigine with a notable improvement in her hypernasal speech.

Functional MRI Results

In patients 1 and 2, functional brain activity during production of symptomatic repetitive syllables (/i-i/) and asymptomatic coughing was compared to respective fMRI from healthy subjects and patients with SD (Fig. 2). Compared to healthy controls, both ND patients showed decreased activity in the bilateral orofacial sensorimotor cortex, basal ganglia, thalamus, and cerebellum during production of both tasks. Compared to SD patients, the ND patients showed brain functional abnormalities in the opposite direction. That is, whereas the SD patients had increased sensorimotor activity during both symptomatic and asymptomatic tasks,[6] the ND patients showed decreased activation in these brain regions.

DISCUSSION

Dystonia is a heterogenous group of movement disorders for which sustained, involuntary muscle contractions produce twisting and repetitive movements and postures, typically directional in nature and often task-specific.[1,7] The classic physiological hallmark of dystonia is simultaneous agonist–antagonist muscle contractions, which reflect dysfunction in central nervous system (CNS) regions controlling sensory–motor integration with a lack of inhibitory motor control.[3,8–11] Dystonia is the third most common movement disorder after Parkinson's disease and essential tremor,[9] and is generally classified based on the somatic distribution of symptoms

(focal, segmental, or generalized), age of disease onset (early or late), and etiology (primary or secondary). Patients with primary or idiopathic etiology have no evidence of any identifiable cause for the dystonic symptoms. Primary dystonia is typically action-induced. Symptoms are enhanced with use of the affected body part, which may appear normal at rest. Many cases of dystonia have a genetic basis, although diagnostic genetic testing is available for very few subtypes.[1]

Idiopathic dystonia is deemed to be associated with altered synaptic circuitry of the motor system.[12] The excessive, undesired movements in dystonia are at least partly determined by a loss of motor-control inhibitory mechanisms, both at cortical and subcortical levels, that are essential for sharpening motor commands. As a network disorder with involvement of the basal ganglia and thalamus, there is a growing literature supporting the role of the cerebellum and brainstem nuclei in the pathophysiology of dystonic symptoms.[11,13,14] Alterations in synaptic plasticity are also likely important, as are the alterations in sensory feedback and inappropriate associations between sensory input and motor cortical output that are formed by maladaptive plasticity.[15] These aberrations possibly lead to cocontractions of muscles usually not involved in the desired movement when the motor system is voluntarily activated.[16,17] Sensory tricks (*geste antagoniste*), whereby afferent proprioceptive sensory input temporarily relieves dystonic symptoms, represent a specific clinical feature of many dystonias.[18] Reducing sensory input from dystonic limbs without altering muscle strength via injections of dilute local anesthetic can improve symptoms in writer's cramp.[8,19–21] Similarly, the efficacy of botulinum toxin injections for chronic motor syndromes may in part be attributed to an effect on sensory feedback, in addition to its obvious effects at the neuromuscular junction.[9,22]

Pseudoparetic symptoms associated with cervical dystonia have been previously described but potentially misclassified.[9,23] In 1992, we first described cranial dystonia patients with abnormal diaphragmatic function manifested by discoordination of the hemidiaphragm or portions of the diaphragm. Some appeared to have hemidiaphragm paralysis—or alternatively, spasmodic diaphragm contraction—during normal respiration.[24,25] Diaphragm movement normalized when the patients were instructed to sniff or pant. These patients manifested task-specific akinesia in the setting of dystonia (i.e., ND).

The term *negative dystonia* was first coined in 1995 when Kaji et al. characterized the focal hand dystonia, writer's cramp, as a disorder of the motor subroutine associated with failure of muscle activation.[21] Jeon (1996) and Mezaki (1997) independently described ALO as a possible form of ND whereby the closed lids are unable to be opened at will but can be activated by sensory tricks, with the patient being able to keep the eyes open for some time once they are activated.[26,27]

In 2007, Mezaki reviewed the literature and added other cases, proposing a redefinition of dystonia as "a symptom characterized by the central non-paretic loss of voluntary control of muscle activities, which may result
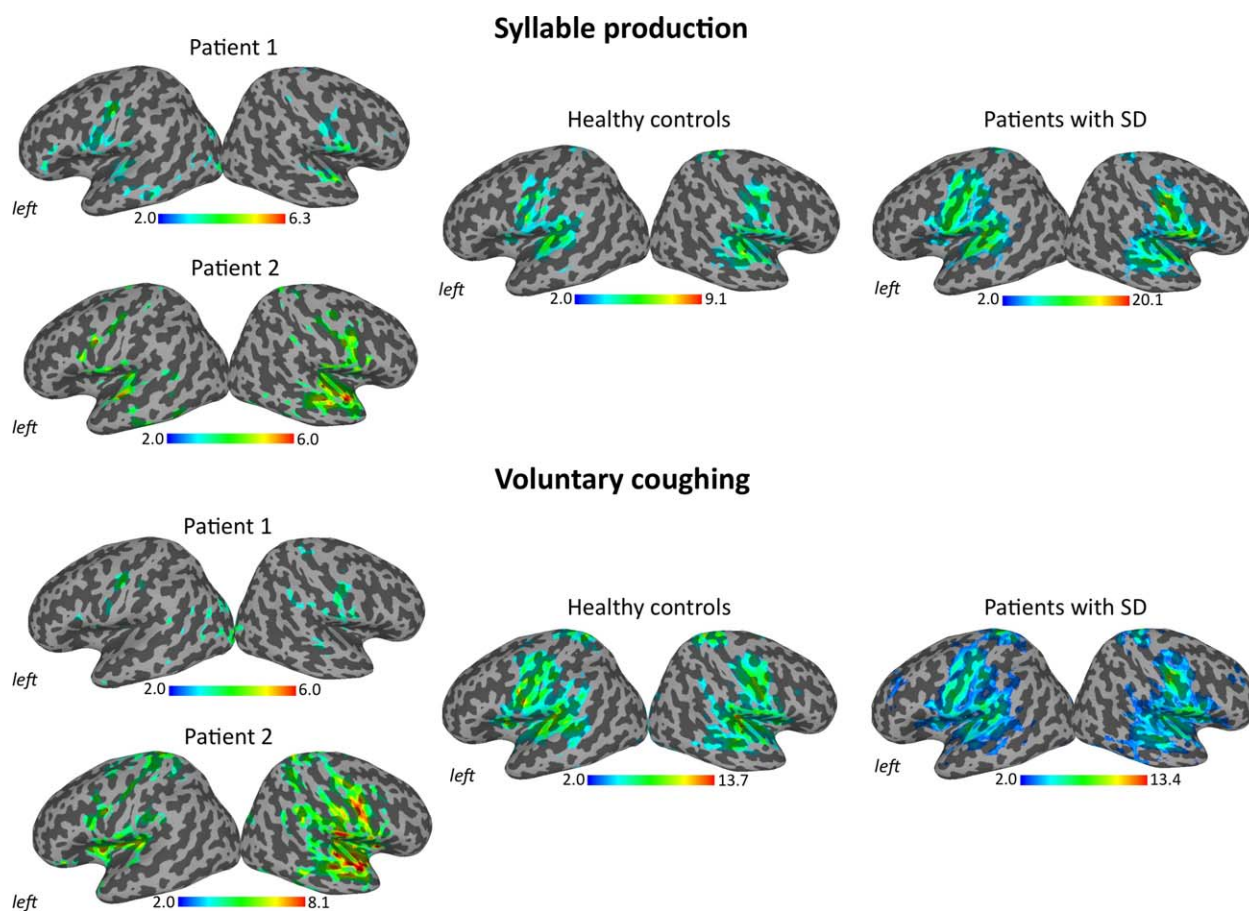
Fig. 2. Functional brain images of two patients with negative dystonia compared with 12 age- and gender-matched controls and 12 patients with spasmodic dysphonia. Functional brain activity during syllable production and voluntary coughing is presented on the inflated brain surfaces normalized to the standard Talairach-Tournoux brain. The color bar indicates the *t* statistics.

in either excessive or deficient contractions of muscles, frequently causing twisting and repetitive movements, limitation of movements, or abnormal postures."[3] He noted that some patients with cervical dystonia do not resume normal range of motion even after neutralization of dystonic muscular contraction with botulinum toxin, particularly to the side contralateral to that of involuntary rotation, and that activation of the sternocleidomastoid muscle responsible for rotating the head to the side contralateral to the torticollis is reduced, as measured by surface electromyography. Mezaki suggested this as an example of pseudoparetic ipsilateral sternocleidomastoid muscle.[4] We have also seen a patient with an isolated dropped head who paradoxically improved with small injections of botulinum toxin to affected muscles (M.B. personal observation).

The most striking symptom of negative palatal dystonia is marked hypernasality on connected speech secondary to VPI. This task-specific hypernasality may normalize with alternative vocalization tasks such as singing. Palatal movement on swallowing is also unaffected; thus, nasal regurgitation with oral intake did not occur in our patients with negative palatal dystonia. We present the first case series of patients with negative pal-

atal dystonia based on the: a) task-specific nature of symptoms with speech but not swallowing or gag reflex; b) absence of other causes of muscle paralysis of central or peripheral origin or local myopathic disease. Our case series also had patients who displayed a) absence of structural brain abnormalities (n = 4, patients 1–4); b) coexistence of dystonia of other body parts (n = 4, patients 2–5); and c) improvement in symptoms following injection augmentation of the pharynx and palate (patient 1), which may represent the classic sensory trick. Patient 1 exhibited sustained improvement in coordinated lateral pharyngeal musculature contraction, and thus a lessening of his hypernasal speech following injection augmentation of posterolateral pharyngeal walls and soft palate. Given the long duration (> 20 years) of absent pharyngeal/palatal muscle contractions prior to injection, with coordinated muscle contractions returning after injection augmentation, we hypothesize that the injection acted as a sensory trick whereby altered afferent sensory feedback augmented muscle contractions.

Advances in fMRI have demonstrated that dystonia affects not only the basal ganglia, but also various regions of the cerebral cortex and cerebellum, most probably presenting as a brain network disorder.[13,14,28]

Abnormal brain activation in sensorimotor cortical regions, including the primary motor and sensory cortices, premotor cortex, supplementary motor area, and cingulate cortex—as well the putamen, thalamus, and cerebellum—have been reported in studies examining symptomatic and asymptomatic task production in patients with different forms of primary focal dystonia. Although these studies agree on the anatomical location of brain functional abnormalities in primary dystonias, they differ in their range of reported alterations, including both increases and decreases of brain activation. The discrepancies may depend on the study paradigm, details of experimental tasks, and selected populations of patients. In oromandibular dystonia, brain activity has been found to be decreased in the primary motor and premotor cortices and increased in the primary somatosensory cortex and supplementary motor area during whistling.[29] In SD, two studies have reported increased sensorimotor brain activity during the production of spontaneous speech and symptomatic repetitive syllables, respectively,[6,30] whereas another study found decreased activity during the production of continuous vowels.[31] In ND, we found that both patients showed decreased brain activity compared to controls and SD patients. In addition, patient 1 showed further decreased brain activity during the production of both tasks compared to patient 2, which may be due to the cooccurrence of lingual dystonia with ND in patient 2. Although our fMRI study in ND patients was underpowered and exploratory, we have presented the first evidence that may suggest the tendency to decreased brain activity as a representative feature of this disorder. Future studies are needed to verify and extend these findings.

Management of VPI can be divided into conservative and surgical approaches. Speech therapy in severe VPI is not considered a useful management strategy until the primary deficit is repaired surgically[32] and, as a sole modality, was not helpful in our cases. In this case series, speech therapy only improved hypernasality in patient 1 following injection augmentation of the pharynx and palate. Oral medications are often poorly effective at improving symptomatology in focal dystonias of the head and neck, including SD and oromandibular dystonia,[33] which proved true in our patients who all responded poorly to systemic therapies. In contrast to positive dystonic symptoms where reduction in muscular function is desirable, the use of botulinum toxin in ND may be expected to worsen symptoms and management. In addition, other theoretically attractive conservative augmentation options, such as obturators and palatal lifts, are often poorly tolerated by patients and rarely facilitate long-term symptom relief.

Reported procedural management options for general VPI include pharyngoplasty for patients with deficient palatal and lateral pharyngeal wall movement and pharyngeal flap repair for patients with good lateral pharyngeal wall motion but persistent central gap. Injection augmentation can be used in both situations but is reported to be most efficient for persistent central velopharyngeal gaps.[34,35] It is unknown whether pharyngoplasty would improve hypernasality in ND as it does in circumferential VPI of other causes. However, one should approach such irreversible management options with caution; dystonia is fundamentally a CNS disease and local management measures may have variable final outcomes. The temporary nature of injection augmentation with duration of effect depending on material injected is thus an acceptable initial management option, especially given the partial return of lateral pharyngeal wall function in patient 1 following injection.

CONCLUSION

We report the first case series of patients with ND of the palate. Diagnostic examination findings include hypernasality secondary to task-specific absence of palatal movement with speech, despite normal palatal movement on other maneuvers such as swallowing and an intact gag reflex. Other causes of velopharyngeal incompetence, including neurological disease, must be excluded before a diagnosis of ND can be considered.

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