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ORIGINAL RESEARCH

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Characterization of a chronic cough in cerebellar ataxia, neuropathy, vestibular areflexia syndrome

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Abstract

Objectives: Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a common cause of late-onset ataxia that often presents with chronic cough. This study is the first to characterize the CANVAS cough both objectively and subjectively.

Methods: A cross-sectional study of 13 patients was conducted. Medical records and available esophagram, modified barium swallow study, esophageal manometry, and video laryngostroboscopy data were reviewed. Leicester cough questionnaire (LCQ) and Eating Assessment Tool-10 were administered to evaluate quality of life (QoL) impairments and dysphagia symptoms, respectively. CANVAS history questionnaire was developed to characterize the clinical course.

Results: 92% of patients endorsed chronic cough that preceded gait instability by a median of 16 years. Cough was dry (67%), disturbed sleep (75%), triggered by various factors, including talking, eating, and dry/spicy foods, did not respond to standard reflux therapy, and inconsistently responded to neuromodulators and superior laryngeal nerve injections. Despite perceived cough severity worsening or remaining constant in most patients, no correlation was found between cough duration and total LCQ scores. Patients reported significantly more negative social QoL impacts compared to physical QoL impacts. Ataxia duration and years of cough before ataxia symptoms were directly and inversely correlated with total LCQ scores, respectively. Imaging data revealed esophageal dysmotility (71%), vestibular penetration (57%), vestibular aspiration (14%), supraglottic compression (63%), vocal fold lesions/atrophy (50%), and arytenoid erythema (38%).

Conclusion: Chronic cough is a hallmark presenting symptom in CANVAS with predominantly psychosocial QoL effects and unrecognized laryngeal alterations. In cases of idiopathic, refractory chronic cough, genetic testing for CANVAS should be considered, especially in association with sensory, cerebellar, and/or vestibular involvement.

Level of evidence: VI.

This work was conducted at University of Chicago Medical Center.

KEYWORDS
CANVAS, chronic cough, neurodegenerative disease, quality of life

1 | INTRODUCTION

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset, neurodegenerative ataxic disorder characterized by slowly progressive somatosensory, bilateral vestibular, and cerebellar impairments.[1] Until recently, diagnosis of CANVAS was based on clinical and radiologic findings. The identification of biallelic intronic pentanucleotide AAGGG repeat expansions in replication factor C subunit 1 (RFC1) gene as a common genetic cause has allowed for multidisciplinary efforts to define the full phenotypic spectrum of this likely underdiagnosed entity.[2,3] Genetic analyses reveal an estimated CANVAS prevalence of ~1 in 20,000.[2] Common clinical features of CANVAS include lower limb paresthesia and dysesthesia, gait impairment, abnormal visually enhanced vestibulo-ocular reflex, downbeat nystagmus, oscillopsia, and dysautonomia.[1]

Interestingly, chronic cough has been reported by over 60% of patients with CANVAS and suggested as an integral clinical component.[4] This dry, spasmodic cough with normal ENT, and pulmonary examinations can precede the onset of significant neurologic symptoms by up to three decades.[4–6] The pathophysiologic mechanisms are unknown but are thought to be secondary to vagal neuronopathy or upper airway and esophagus hypersensitivity due to afferent fiber dysfunction.[7,8]

Despite recent efforts in neurology to understand CANVAS symptomatology, there have been almost no studies characterizing the cough as a hallmark presenting symptom in this neurodegenerative disease. This study aims to characterize the CANVAS cough both objectively and in terms of patient reported impacts on quality of life (QoL) to progress existing knowledge in the differential diagnosis of chronic cough.

2 | METHODS

2.1 | Patients and clinical characterization

The study population comprised 13 patients aged 20 years and older diagnosed with CANVAS at the University of Chicago Medical Center. Only patients with biallelic AAGGG repeat expansions in RFC1 and clinical features of CANVAS were included. Medical records were retrospectively reviewed, and the following information was collected for each patient as available: demographics; Eating Assessment Tool 10 (EAT-10) survey results; prior diagnostic, genetic, and imaging studies; prior treatments for CANVAS; and evidence of typical and atypical CANVAS features.

Diagnostic and imaging studies reviewed include esophagram, modified barium swallow study (MBSS), esophageal manometry, video laryngostroboscopy for objective measures of esophageal, laryngeal, and vocal cord function. Esophagram, MBSS, and manometry findings were evaluated for dysmotility, penetration, or aspiration. Video laryngostroboscopy findings were assessed using a modified version of the diagnostic tool published by Ricci-Maccarini, Bergamini, and Fustos.[9] The parameters studied included: supraglottic framework behavior (normal or mild, moderate, or severe compression); supraglottic framework anatomy (normal, edematous, or erythematous); vocal fold morphology (normal or presence of lesions); vocal fold motility (normal, hypo-mobile, or immobile); symmetry of glottic vibration (symmetric or asymmetric); glottic closure (complete, slightly incomplete, very incomplete, or inconstant); profile of vocal fold edge (straight, concave, convex, or irregular); and mucosal wave (normal, small, large, or absent). Each parameter was scored as either "normal" or "abnormal" based on examination findings, and the results obtained were combined into a single score according to the number of abnormal parameters. Overall video laryngostroboscopy findings were classified as normal (with 0 abnormal parameters), mild (with 1–2 abnormal parameters), moderate (with 3–4 abnormal parameters), or severe (with 5 or more abnormal parameters).

The study was approved by the University of Chicago Institutional Review Board, and written informed consent was obtained from each patient.

2.2 | Cough-related QoL, dysphagia, and CANVAS history characterization

The Leicester cough questionnaire (LCQ), a validated survey tool, was administered to every patient with cough to characterize patient perception of their cough. The LCQ is a 19-item QoL measure organized by the impact of chronic cough on three distinct domains: physical, psychological, and social.[10] Domain scores range from 1 to 7. The total score range is 3–21, with higher scores indicating a better patient-perceived QoL.

The EAT-10, a validated survey tool, was administered to patients at otolaryngology clinic visits. Not all patients presented to otolaryngology clinic by the time of data analysis. The EAT-10 is a 10-item dysphagia instrument that assesses for severity of dysphagia symptoms.[11] An EAT-10 score of 3 or higher is considered abnormal, with higher scores indicating worse dysphagia symptoms.

A 33-item CANVAS history questionnaire was developed and administered to characterize the clinical course of each patient. Variables assessed included age at onset of cough and ataxia symptoms; age at diagnosis; characteristics of and triggers for cough; treatments for cough; perceived symptoms of laryngeal, pharyngeal, and autonomic dysfunction; and smoking history.

2.3 | Statistical analysis

All statistical analyses were performed using STATA 16.0 (StataCorp, 2019). Standard descriptive statistics were obtained, and *T* tests and Spearman's rank-order correlations examined associations between CANVAS clinical history, LCQ scores, and video laryngostroboscopy scores. A *p*-value of ≤.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical findings

Clinical characteristics of all 13 patients are shown in Table 1. There were 3 men (23%) and 10 women (77%) with a median age of 59 years (range 47–74 years) at the time of survey administration. Two sibling groups were identified: patients 1, 7, and 9, and patients 10 and 11 are siblings with dissimilar timing and quality of symptoms within each family. All other cases were sporadic. Gait instability manifested between 30 and 68 years (median 52 years) with median age at the time of CANVAS diagnosis of 57 years (range 46–74 years). Other symptoms included dysphagia (62%), dysphonia (77%), and dysautonomia, including urinary dysfunction (46%), orthostasis (31%), and sweating changes (31%). There was no evidence of respiratory disease or allergies.

All but one patient (patient 6) endorsed chronic cough with median age at cough onset of 32 years (range 25–62 years). Cough antedated gait instability by a median of 16 years, except in patients 2, 12, and 13 where cough either postdated or coincided with ataxia symptoms. Characteristics of and treatments for cough are summarized in Tables 2 and 3, respectively. Cough was dry (67%), either worsened or stayed the same over the years (92%), worsened at night (50%), and disturbed sleep (75%). Various factors triggered cough, including spicy foods, chocolate, dry foods (e.g., crackers, bread, popcorn), carrots, speech, eating, smoke, intense emotions, temperature changes, and recumbency. Most patients were trialed empirically on reflux and post-nasal drip therapies. None of the patients received cough-inducing drugs (e.g., ACE inhibitors) or currently smoke. Associated symptoms included pain, dyspnea, rhinorrhea, urinary incontinence, and lacrimation. Alleviating factors included drinking water, cough suppressants, and adjusting amount of perceived tension in the larynx. Eight patients were empirically treated for neurogenic cough with neuromodulating medications (e.g., amitriptyline, gabapentin, and pregabalin), but only three endorsed some benefit. Five patients received superior laryngeal nerve injections, and most endorsed only decreased cough severity with no change in cough frequency.

3.2 | Subjective survey results

LCQ and EAT-10 data are shown in Table 4. EAT-10 scores were available for nine patients. Mean EAT-10 score was 11.7 (SD 7.3), and scores ranged from 5–25, indicating some degree of subjective dysphagia in all patients with survey results. Mean LCQ score was 11.6 (SD 3.7). Patients reported significantly more negative social QoL impacts compared to physical QoL impacts [3.1 (1.3) vs. 4.6 (1.5), $p = .02$]. While not statistically significant, social impacts were considerably more negative than psychological QoL impacts [3.1 (1.3) vs. 4.0 (1.2), $p = .09$]. No significant difference was found between psychological impacts and physical impacts [4.0 (1.2) vs 4.6 (1.5), $p = .29$]. Notably, a few specific cough-related factors contributed most to perceived negative QoL, such as (1) lack of control over cough, (2) stigmatization by strangers, (3) interference with conversations, and (4) frustration.

Despite perceived cough severity either worsening or remaining the same in most patients over time, no correlation was found between cough duration and total LCQ scores ($\rho = -.22$; $p = .48$) or age at onset of cough and total LCQ scores ($\rho = .13$; $p = .68$). Conversely, correlations were found between ataxia duration and total LCQ scores ($\rho = .63$, $p = .03$), ataxia duration and physical domain scores ($\rho = .75$, $p = .005$), and years of cough before ataxia symptoms and physical domain scores ($\rho = -.59$, $p = .04$), suggesting that coughing episodes tended to attenuate with ataxia symptoms. Association was found between years of cough before ataxia symptoms and total LCQ scores but did not reach statistical significance ($\rho = -.55$, $p = .06$). No correlations were found between years of cough before CANVAS diagnosis and total LCQ scores ($\rho = -.20$, $p = .54$) or age at onset of ataxia and total LCQ scores ($\rho = -.08$, $p = .81$).

3.3 | Objective imaging studies

Esophagram and MBSS revealed esophageal dysmotility in 5/7 (71%) patients, which was graded as mild in two patients, moderate in two patients, and severe in one patient. Manometry data were available for three of these patients, two of which had normal exams and one had distal esophageal spasms. MBSS revealed penetration in 4/7 (57%) patients, and aspiration in 1/7 (14%) patients. Video laryngostroboscopy results are summarized in Table 5 and revealed normal vocal fold motility, symmetric glottic vibration, complete glottic closure, and straight vocal fold edges in all eight patients with available data. Moderate to severe supraglottic compression was found in 5/8 (63%) patients; arytenoid or periarytenoid erythema and/or edema was found in 3/8 (38%) patients; atrophied or lesioned vocal folds were found in 4/8 (50%) patients; and reduced mucosal wave was found in 2/8 (25%) patients. Overall video laryngostroboscopy results were graded as normal in 1/8 (13%) patient, mild in 5/8 (63%) patients, and moderate in 2/8 (25%) patients. No severe results were found. Most patients with abnormal laryngoscopic findings endorsed dysphonia.

Statistically significant association was found between age at CANVAS diagnosis and laryngostroboscopy scores ($\rho = -.72$, $p = .05$). No statistically significant correlations were found between cough duration and laryngostroboscopy scores ($\rho = -.64$, $p = .09$), ataxia duration and laryngostroboscopy scores ($\rho = .36$, $p = .39$), years of cough before ataxia symptoms and laryngostroboscopy scores ($\rho = -.54$, $p = .17$), and total LCQ scores and laryngostroboscopy scores ($\rho = -.12$, $p = .77$).

TABLE 1 Summary of clinical data.

Patient	Sex	Age	Age of cough onset	Age of gait/balance problems onset	Age of CANVAS diagnosis	Cough duration	Years of cough before CANVAS diagnosis	Years of cough before ataxia symptoms	Ataxia duration	Dysphagia	Dysphonia	Autonomic dysfunction	Family history
1	M	63	31	62	63	32	32	31	1	+	+	Hypotension	Yes (sibling of 7 and 9)
2	M	74	62	59	74	12	12	−3	15	+	–	Hyperhidrosis	–
3	M	52	32	46	48	20	16	14	6	+	+	Hypotension UI	–
4	F	56	34	54	54	22	20	20	2	+	+	Hypotension Hyperhidrosis UI	–
5	F	63	30	58	62	33	32	28	5	–	+	–	–
6	F	47	–	30	47	–	–	–	17	+	+	Hyperhidrosis UI	–
7	F	50	25	43	48	25	23	18	7	–	–	–	Yes (sibling of 1 and 9)
8	F	70	40	68	69	30	29	28	2	+	+	Hypohidrosis	–
9	F	59	28	50	58	31	30	22	9	–	–	Hypotension Urgency	Yes (sibling of 1 and 7)
10	F	52	38	39	46	14	8	1	13	–	+	Urgency	Yes (sibling of 11)
11	F	53	29	40	49	24	20	11	13	+	+	UI	Yes (sibling of 10)
12	F	70	60	57	68	10	8	−3	13	+	+	–	–
13	F	58	30	30	55	28	25	0	28	–	+	–	–
Median (range)			59 (47–74)	32 (25–62)	52 (30–68)	57 (46–74)	25 (10–33)	22 (8–32)	16 (−3–31)	8 (1–28)			

Note: Clinical characteristics, including symptoms and disease timeline, of patients with CANVAS ($n = 13$).
Abbreviation: UI, urinary incontinence.

TABLE 2 Summary of cough characteristics.

Patients	Cough quality	Evolution of cough severity	Pain with cough/pain score (1–10)	Worsens at night	Disturbs sleep	No. of coughs per day	Associated symptoms	Aggravating foods	Other aggravating factors	Alleviating factors
1	Dry	Worsened	+/4	–	+	200	Rhinorrhea Lacrimation	Dry foods	Speech Eating	–
2	Dry	Stayed the same	+	–	–		–	–	Speech	–
3	Productive	Worsened	–	+	+	250	Dizziness Blurry vision	Many	Speech Temperature changes	Cough drops Chewing gum
4	Dry	Worsened	–	–	+	75	UI SOB Muscle spasms Emesis	Butter, greasy foods	Temperature changes Smoke Intense emotions Perfume	Cold water Cough syrup
5	Both	Stayed the same	+/8	–	–	100	UI	Milk chocolate Nuts	Speech Smoke	Deep breaths
7	Dry	Stayed the same	–	+	+	200	SOB Lacrimation Apnea	Spicy foods	Speech Eating	–
8	Dry	Worsened	+/5	+	+	50	UI	Spicy foods	Speech Eating Lying down	Water
9	Productive	Worsened	–	+	+	100	SOB	Spicy foods Chocolate	Eating Smoke	Water Relaxing throat muscles
10	Dry	Stayed the same	–	+	+	75	Rhinorrhea Emesis	Spicy foods Salt Garlic	Eating Cleaning products	–
11	Both	Improved	–	+	+	300	–	Carrots Vinegar Eggs	Speech Eating Intense emotions Lying down	Water Tightening throat muscles
12	Dry	Stayed the same	–	–	–		Rhinorrhea Lacrimation UI	–	–	Cough drops
13	Dry	Worsened	–	–	+	20		Dry foods Carrots	Smoke Intense emotions	–

Note: Cough characteristics, including cough quality, triggers, and associated symptoms, of patients with CANVAS endorsing chronic cough ($n = 12$).
Abbreviations: SOB, shortness of breath; UI, urinary incontinence.

TABLE 3 Summary of cough treatments.

Patient	Neuromodulators/effect	Superior laryngeal nerve injections/effect	Reflux therapy/effect	Postnasal drip therapy/effect
1	Gabapentin/no effect Pregabalin/some effect	+/Some effect	+/No effect	+/No effect
2	–	–	+ (H2 blocker)/no effect	–
3	–	+/Effective	+ (PPI)/no effect	+ (Intranasal steroid)/no effect
4	Amitriptyline/no effect Gabapentin/no effect	+/No effect	+/No effect	+ (Intranasal steroid)/no effect
5	–	–	+ (PPI)/no effect	–
7	Amitriptyline/effective	–	–	–
8	Gabapentin/some effect	+/No effect	+/No effect	+/No effect
9	Amitriptyline/no effect Gabapentin/no effect	–	–	+ (Oral antihistamines)/no effect
10	Amitriptyline/no effect	–	+/No effect	–
11	–	–	+/No effect	+ (Oral antihistamines)/no effect
12	Gabapentin/no effect	–	+ (PPI)/no effect	–
13	Gabapentin/no effect	+/No effect	+/No effect	–

Note: Efficacy of treatments for chronic cough, including neuromodulators, superior laryngeal nerve injections, laryngopharyngeal reflux therapy, and postnasal drip therapy, for patients with CANVAS endorsing chronic cough ($n = 12$).
Abbreviation: PPI, proton pump inhibitor.

TABLE 4 LCQ and EAT-10 results.

Patients	LCQ physical domain score	LCQ psychological domain score	LCQ social domain score	Total LCQ score	Total EAT-10 score
1	3.8	3	3.2	10.0	15
2	6.1	5.3	4.8	16.2	N/A
3	2.9	2.7	1.4	7.0	6
4	2.4	2.9	2.6	7.8	25
5	5.6	4.6	4.0	14.2	6
6	N/A	N/A	N/A	N/A	N/A
7	4.6	5.1	3.2	13.0	N/A
8	2.6	3.4	1.0	7.1	9
9	4.8	3.4	2.2	10.4	N/A
10	4.1	4.1	3.2	11.5	21
11	4.8	2.9	1.8	9.4	12
12	6.6	6.6	5.2	18.4	5
13	6.5	3.7	4.2	14.4	6
Mean (SD)	4.6 (1.5)	4.0 (1.2)	3.1 (1.3)	11.6 (3.7)	11.7 (7.3)

Note: Results of LCQ, a validated cough-related quality of life survey, and eating assessment tool-10, a validated dysphagia survey, for patients with CANVAS endorsing chronic cough ($n = 12$).
Abbreviations: EAT-10, eating assessment tool-10; LCQ, Leicester cough questionnaire; N/A, not available.

4 | DISCUSSION

CANVAS is a common cause of late-onset ataxia characterized by the clinical triad of progressive axonal sensory neuronopathy, bilateral vestibular areflexia, and cerebellar impairment.[12] The disease is likely underdiagnosed as the complete clinical triad may be present in only two-thirds of patients.[7] Recent elucidation of a genetic diagnosis allowed for identification of previously unrecognized symptoms, including chronic cough, dysautonomia, and oropharyngeal dysphagia, which are now considered central features.[2,3,13,14] To our knowledge, this is the first study that characterized the CANVAS cough according to both subjective and objective dimensions.

TABLE 5 Video laryngostroboscopy results.

Patients	Supraglottic framework behavior	Supraglottic framework anatomy	Vocal fold morphology	Vocal fold motility	Symmetry of glottic vibration	Glottic closure	Profile of vocal fold edge	Mucosal wave	Final classification
1	Normal	Normal	Bilateral mid-fold atrophy	Normal	Symmetric	Complete	Straight	Normal	Mild
3	Severe supraglottic compression	Normal	Presence of lesion (granuloma on right vocal fold)	Normal	Symmetric	Complete	Straight	Small	Moderate
4	Severe supraglottic compression	Normal	Presence of lesion (bilateral mid-fold fibrovascular change)	Normal	Symmetric	Complete	Straight	Small	Moderate
5	Severe supraglottic compression	Normal	Normal	Normal	Symmetric	Complete	Straight	Normal	Mild
8	Normal	Normal	Normal	Normal	Symmetric	Complete	Straight	Normal	Normal
10	Moderate supraglottic compression	Significant interarytenoid and periarytenoid erythema	Normal	Normal	Symmetric	Complete	Straight	Normal	Mild
12	Normal	Slightly erythematous arytenoid towers	Presence of lesions (bilateral anterior varices)	Normal	Symmetric	Complete	Straight	Normal	Mild
13	Moderate supraglottic compression	Significant interarytenoid and periarytenoid edema/erythema	Normal	Normal	Symmetric	Complete	Straight	Normal	Mild

Note: Results of video laryngostroboscopy for patients who had undergone this imaging ($n = 8$). Overall video laryngostroboscopy findings were classified as normal (with 0 abnormal parameters), mild (with 1–2 abnormal parameters), moderate (with 3–4 abnormal parameters), or severe (with 5 or more abnormal parameters).

Chronic cough has been associated with several neurologic genetic disorders, including Holmes-Adie syndrome, Charcot–Marie–Tooth disease type 2 J, hereditary sensory and autonomic neuropathy, and dominant ataxia.[15–18] A recent study showed that chronic cough was present in over 60% of patients with CANVAS, which often occurred without a specific trigger and preceded neurologic symptoms by up to three decades.[4] Moreover, chronic cough is often refractory to treatment and is associated with distinct negative psychosocial impacts on QoL, particularly in patients with unclear diagnoses.[19–21] Many validated tools are utilized to measure cough-specific QoL, including the LCQ.[10]

In our study, 92% of patients with genetically confirmed CANVAS endorsed history of chronic cough that antedated gait instability by a median of 16 years. Distinct environmental and mechanical triggers were appreciated, including talking, eating, smoke, and spicy and dry foods. Associated symptoms include dysphonia, dysphagia, pain, dyspnea, rhinorrhea, urinary incontinence, and sleep disturbance, and the cough inconsistently responded to treatment. Pulmonary, esophageal, and rhinologic etiologies for the cough were evaluated and empirically treated with minimal response in most patients, including maximal reflux therapy. Interestingly, patients were treated empirically for neurogenic cough with neuromodulating medications to which most reported no effect. Despite the broad, refractory physical manifestations of CANVAS cough, patients reported significantly more negative psychosocial QoL impacts than physical QoL impacts, reflecting previous studies of cough-related QoL.[20,21]

No statistically significant correlation was found between cough duration and total LCQ scores, despite perceived cough severity either worsening or remaining the same in most patients. These findings are similar to those described by Won and Song in which diverse factors likely mediate patient experience of chronic cough with longer disease duration.[19]

Interestingly, ataxia duration and years of cough before ataxia symptoms were directly and inversely correlated with total LCQ scores, respectively. A complex circuitry mediates the cough reflex, involving interactions among neurons in the medulla, cerebellum, and peripheral ganglia.[18] Hypothesized etiological mechanisms of CANVAS cough include vagal neuronopathy, upper airway and esophagus hypersensitivity or motility abnormality due to afferent fiber impairment, and/or cerebellar circuitry dysfunction.[7,9] These findings, similar to those described in dominant ataxia with spasmodic cough, suggest that the neurodegenerative process in CANVAS progressively disrupts cerebellar neurons likely involved in the cough response.[18]

Esophagram and video laryngostroboscopy studies revealed some degree of esophageal and laryngeal dysfunction in most patients with CANVAS, including esophageal dysmotility, laryngeal penetration, supraglottic compression, arytenoid erythema, and changes to vocal fold morphology. Most patients presented with mild to moderate

laryngeal changes. While arytenoid erythema is considered to be a sign of laryngopharyngeal reflux, prior unsuccessful trials of maximal reflux therapy, with daily proton pump inhibitor and/or alginate therapy, in majority of patients suggest that these findings are separate from gastroesophageal reflux. Esophageal dysmotility, which was subjectively present in all patients according to EAT-10 survey results, could mediate laryngopharyngeal reflux. However, further dysphagia workup was limited as most patients could not pursue additional diagnostic testing, including esophageal manometry, due to time, geography, and cost constraints. No statistically significant correlation was found between QoL scores and video laryngostroboscopy scores, consistent with prior studies showing that QoL questionnaires fail to predict underlying objective physiologic impairments in neurologic diseases.[14]

Our study has several limitations. We had a limited sample size as CANVAS is a relatively rare, but likely under-diagnosed entity, and our analyses were restricted to patients with CANVAS presenting to University of Chicago Medical Center. Future studies, including multi-institutional collaborations, could allow for more robust sample sizes. Our chart review methodology limits data collection to only those diagnostic studies patients were able to undergo. In particular, our dysphagia work-up was limited as many patients chose not to pursue esophageal manometry testing due to cost and time constraints and reliance on telehealth given the ongoing COVID-19 pandemic. Lastly, as with all survey-based studies, sample bias and response bias potentially limit generalizability of our results.

5 | CONCLUSIONS

Chronic cough is a hallmark presenting symptom in CANVAS with predominantly psychosocial QoL effects and unrecognized laryngeal alterations. The absence of correlation between cough duration and cough-related QoL impairments suggests that objective studies assessing esophageal and laryngeal function must be conducted. Association of longer ataxia duration and better cough-related QoL suggests involvement of cerebellar neurons in the cough response. In cases of idiopathic, refractory chronic cough, genetic testing for CANVAS and esophageal and laryngeal evaluations should be considered, especially in association with sensory, cerebellar, and/or vestibular involvement.

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