Cerebellar ataxia, neuropathy and vestibular areflexia syndrome: a neurogenic cough prototype

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Chronic cough in patients with cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS), a rare neurological disorder with a repeat expansion in the *RFC1* gene, shares similar characteristics with cough hypersensitivity syndrome https://bit.ly/42Hd8Pv

Cite this article as: Guilleminault L, Mazzone SB, Chazelas P, *et al*. Cerebellar ataxia, neuropathy and vestibular areflexia syndrome: a neurogenic cough prototype. *ERJ Open Res* 2024; 10: 00024-2024 [DOI: 10.1183/23120541.00024-2024].

Received: 8 Jan 2024
Accepted: 8 Feb 2024

Abstract

Chronic cough is a frequent disorder that is defined by cough of more than 8 weeks duration. Despite extensive investigation, some patients exhibit no aetiology and others do not respond to specific treatments directed against apparent causes of cough. Such patients are identified as having unexplained or refractory chronic cough. Recently, a high proportion of patients with chronic cough in the context of cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) was highlighted. CANVAS is a rare neurological disorder with a biallelic variation in the replication factor C subunit 1 (*RFC1*) gene corresponding mostly to an intronic AAGGG repeat expansion. Chronic cough in patients with CANVAS shares similar characteristics with cough hypersensitivity syndrome. The high prevalence of chronic cough in CANVAS gives the opportunity to better understand the neurogenic mechanism of chronic cough. In this review, we will describe the characteristics and mechanisms of CANVAS. We will also address the potential mechanisms responsible for chronic cough in CANVAS. Finally, we will address chronic cough management in the context of CANVAS.

Introduction

Chronic cough is defined by cough of more than 8 weeks duration [1] and affects around 9.6% of people worldwide [2]. This disease is commonly associated with a deterioration in the patient's quality of life related to psychosocial complications with the inability to suppress cough in a quiet environment such as a theatre, church or cinema and physical complications including urinary incontinence [3–5]. Chronic cough can be associated with common diseases such as asthma, rhinosinusitis and gastro-oesophageal reflux disease (GORD) [6–8]. However, its management is sometimes difficult because some patients exhibit no aetiology despite extensive investigation or do not respond to specific treatments directed against apparent causes of cough [9]. Such patients are identified as having unexplained or refractory chronic cough (RCC) [9]. The prevalence of RCC has not been extensively studied, but may represent 7–40% of patients with chronic cough [10].

A current proposition is that RCC could be the consequence of neurological dysfunction, possibly related to neuropathy impacting the peripheral nerve fibres mediating cough [11, 12]. However, although the concept of RCC as a neuropathic disorder has largely been investigated in animal models [13], there is little evidence to show that humans with RCC present comparable nerve alterations.

In papers published in the 1990s and 2000s, genetic neurological conditions such as Holmes–Adie syndrome have been associated with chronic cough [14, 15]. However, the clinical implications of those conditions in patients with RCC remain limited given the small number of patients. RCC is also common in cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS), a genetic neurological disorder due to a repeat expansion in the replication factor C subunit 1 (*RFC1*) gene. Intriguingly, we observed that 25% of patients with RCC presented at least one AAGGG repeat expansion in *RFC1* [16]. In this review, we will describe the characteristics of RCC in the CANVAS context and investigate the potential mechanisms responsible for this trait.

History and clinical description of CANVAS

The description of a rare syndrome combining bilateral vestibular areflexia and progressive cerebellar ataxia was published in the late 1990s (figure 1) [17]. At that time, it was recognised that some patients with this specific disorder also presented sensory peripheral neuropathy; however, the first full description of the complete disorder and use of the acronym CANVAS did not appear until 2011 [18]. Since 2019 and the first recognition of an AAGGG biallelic intronic expansion in the *RFC1* gene in this disorder, several series have been published that outline the phenotypic spectrum of CANVAS [19, 20].

As with many slowly advancing diseases, it is difficult to determine the exact date of symptom onset in CANVAS patients. Nevertheless, with the notable exception of RCC, patients start to complain of sensory symptoms and/or ataxia at a median age of 52–53 years [21, 22]. Cerebellar ataxia is of variable severity and cerebellar atrophy, predominating on the anterior and dorsal vermis, usually appears mild on brain magnetic resonance imaging [21]. It is estimated that approximately 50% of patients need to use at least a walking stick after 10 years of disease progression [22]. The peripheral neuropathic characteristics of CANVAS are best described as a sensory "neuronopathy", resulting from the selective destruction of peripheral sensory neurons culminating in a combination of numbness, ataxia and neuropathic pain with no motor involvement [18]. Although CANVAS patients rarely complain of vertigo, some of them describe oscillopsia and video-oculography may reveal vestibular areflexia or hyporeflexia [19].

Genetic anomalies in CANVAS

In 2019, Cortese *et al.* [23] identified the first molecular cause of CANVAS, corresponding to a biallelic intronic AAGGG repeat expansion in the *RFC1* gene. Subsequently, the allele frequency of the AAGGG

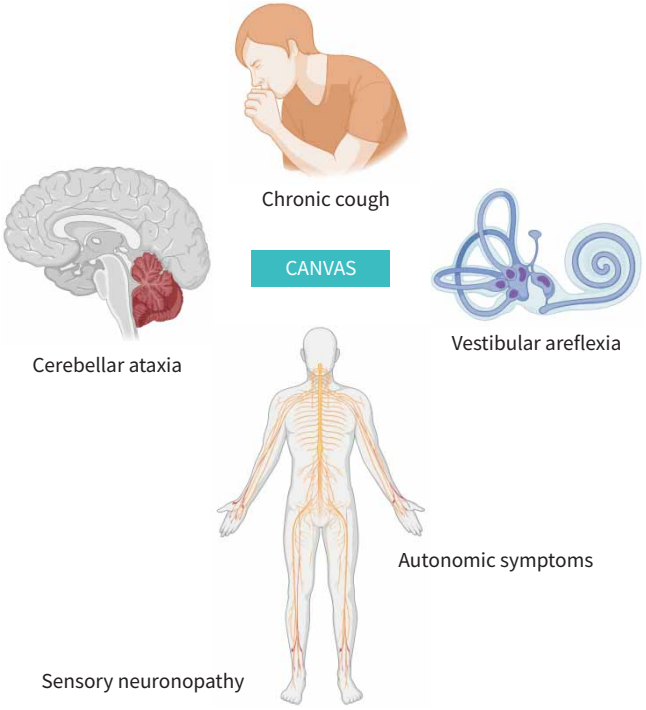

FIGURE 1 Clinical characteristics of patients with cerebellar ataxia, neuronopathy and vestibular areflexia syndrome (CANVAS).

repeat expansion was estimated at 2.3% in the general population [24]. This intronic expansion located between exons 2 and 3 differs from those initially described in controls, both in size and nucleotide sequence. Indeed, the mutated sequence was described as a large expansion (ranging from around 400 to 2000 repeats) of AAGGG pentanucleotides, also named $(AAGGG)_{exp}$, while the initial reference sequence corresponds to 11 repeats of the AAAAG motif $(AAAAG)_{11}$. In addition, the size of this "normal" motif in controls can be large $(AAAAG)_{exp}$ and the motif can be different $(AAAGG)_{exp}$ [23]. Other repeated motifs in this *RFC1* intronic region have been identified, including AAGAG and AGAGG, but their pathological impacts need to be studied further [25–28]. More recently, the large expansion of the new motif $(ACAGG)_{exp}$ has been identified in Japanese patients [29–31], and a few groups have described that in some patients with a typical phenotype of CANVAS and a heterozygous *RFC1* expansion, a truncating nucleotide variation is present on the other allele of the gene, explaining why these people develop the disease [32–36]. To date, CANVAS is considered an autosomal recessive disease, in which patients present two alleles mutated in *RFC1*. To confirm the diagnosis, long-range PCR and gene sequencing is needed to check the size of the repeats [23].

The *RFC1* gene is located on chromosome 4 (4p14) and contains 25 exons. This gene encodes for the large subunit of 140 kDa of replication factor C (RFC). RFC is a clamp loader of five subunits, involved in the DNA replication fork within the proliferating cell nuclear antigen. It is involved in nuclear DNA replication, and in telomere maintenance, mismatch repair and base excision repair. Variations in the *RFC1* gene had initially been described to not result in abnormal RFC1 protein conformation or expression [23]. However, additional studies showed a decreased level of *RFC1* mRNA and/or RFC1 protein compared with controls [32, 33, 35, 36]. Thus, the relationship between the variations in the *RFC1* gene and the clinical phenotype of CANVAS has not been fully elucidated.

Pathophysiology of CANVAS

Neuropathological and neurophysiological observations in CANVAS patients clearly point to a ganglionopathy (sensory neuronopathy) involving the dorsal root ganglion (DRG) and cranial nerve ganglia V, VII and VIII [19]. Observations have shown a ganglionic and nerve root atrophy with a loss of neuronal cells and their replacement by areas of psammoma bodies and areas of satellite (glial) cell proliferation. DRG atrophy is accompanied by pathological changes in the spinal cord [37], with atrophy of the dorsal columns reflecting a significant loss of myelinated axons secondary to the degeneration of the central projections of DRG neurons. Gross examination of the brain shows cerebellar atrophy with loss of Purkinje cells, while pathological changes in the medulla oblongata where cranial ganglia neurons terminate are confined to a loss of neurons and gliosis in the inferior olivary nuclei. Notably, the cranial nerve nuclei appear normal without signs of gliosis [38].

The molecular mechanisms underpinning the progressive loss of neurons in CANVAS are not known but may involve alterations in mitochondrial function [39]. Sensory neurons can have long axonal projections, sometimes greater than 1 m in length, extending from the central nervous system (spinal cord or brainstem) to distal tissue sites. Consequently, sensory neurons have a high metabolic demand for homeostatic production and transport of materials over long distances. Oxygenated blood delivery to sustain metabolic demands of DRG neurons is optimised by a local, highly fenestrated capillary network [40]. Cerebellar Purkinje cells, also comparatively larger neurons, similarly have high metabolic demands. Accordingly, mitochondrial dysfunction would be expected to interrupt energy supply and lead to the progressive demise of susceptible neurons. How mitochondria dysfunction could occur in CANVAS is unclear, but possibilities include changes in iron metabolism or decrease in vitamin B6 or E levels. Alternative hypotheses explaining why neuronopathy occurs in CANVAS include possible neuronal DNA damage, as RFC1 is needed for DNA damage recognition and recruitment of repair enzymes [41]. These putative mechanisms require further validation given that RFC1 protein production may be unaffected in CANVAS [23].

The functional impacts of neuronopathy in CANVAS reflect the neural systems involved. Progressive imbalance likely stems from both cerebellar dysfunction and sensory involvement, since ataxia is almost always worse without visual control in these patients [22]. Sensory neuronopathy evolves towards a complete disappearance of "SNAPs" (sensory nerve action potentials) with preservation of "CMAPs" (compound muscle action potentials) on nerve conduction studies [42]. All types of sensory fibres are affected in CANVAS, as exemplified by sensory loss in all modalities with some variability among patients [22]. Strikingly, many patients complain of neuropathic pain, in contrast to most patients with hereditary neuropathy, including those with Friedreich's ataxia who also have cerebellar involvement. Otherwise, patients with CANVAS have mostly preserved tendon jerks, which are probably explained by the less severe involvement of sensory neurons transmitting muscle afferent signals [43]. Recent findings suggest the possible involvement of motor neurons in CANVAS patients, a feature seemingly devoid of

significant clinical consequences [44]. CANVAS patients may also present with vestibular areflexia, which partly explains oculomotor disorders and abnormal head impulse test results [17]. Besides the core clinical features of CANVAS, authors have also reported that some patients may experience dysautonomia, parkinsonism and cognitive impairment; however, at this stage, the prevalence of these additional features is unknown [45]. Autonomic dysfunction is also common in CANVAS patients. In one study cohort undergoing a battery of autonomic tests, all patients displayed at least one autonomic symptom and 91% displayed more than two autonomic symptoms [46]. The cause of autonomic dysfunction may relate to the peripheral spinal and cranial nerve ganglionopathies or the brainstem pathological changes in regions involved in cranial nerve control.

Chronic cough in CANVAS patients

Cough in CANVAS patients was first described in 2014 [46, 47]. Wu *et al*. [46] reported two out of 26 patients with clinical CANVAS had chronic cough. Interestingly, in one of them, chronic cough was the initial symptom, appearing 5 years before the onset of ataxia. Persistent chronic cough was also described in a retrospective study published in the same year, but no details on patient numbers were provided [47]. According to the literature, the prevalence of chronic cough in CANVAS patients with *RFC1* repeat expansion varies from 8% to 100% (figure 2) [21–23, 28, 44–46, 48, 49]. It is remarkable to see that the prevalence of cough reported in studies of CANVAS patients increases over time. The reason for this is not known but it is likely that cough was more systematically documented in the latest cohorts due to an increased acceptance that cough is particularly prevalent in CANVAS. Cortese *et al*. [23] noticed that cough could precede the walking difficulties by one decade. Indeed, chronic cough can apparently be described by patients up to three decades before the onset of neurological symptoms and is the initial symptom in two-thirds of CANVAS patients [21].

We recently identified that 25% of RCC patients had homozygous (16.2%) or heterozygous (8.8%) AAGGG repeat expansions in *RFC1* [16]. The pathogenic role of heterozygous AAGGG repeat expansions in *RFC1* is still debated in chronic cough [50]. The cough characteristics were quite homogeneous among the CANVAS patients reported in the literature and those in our study. Most patients describe a persistent, irritating, dry, spasmodic cough [28, 44] potentially triggered by a variety of factors such as emotion, stress, speaking, ear cleaning with a cotton bud or swallowing. GORD, which is a common cause of chronic cough, does not explain the high prevalence of RCC in CANVAS. In a recent study, GORD was reported in 19 patients (31%) with CANVAS and was not significantly more prevalent either with or

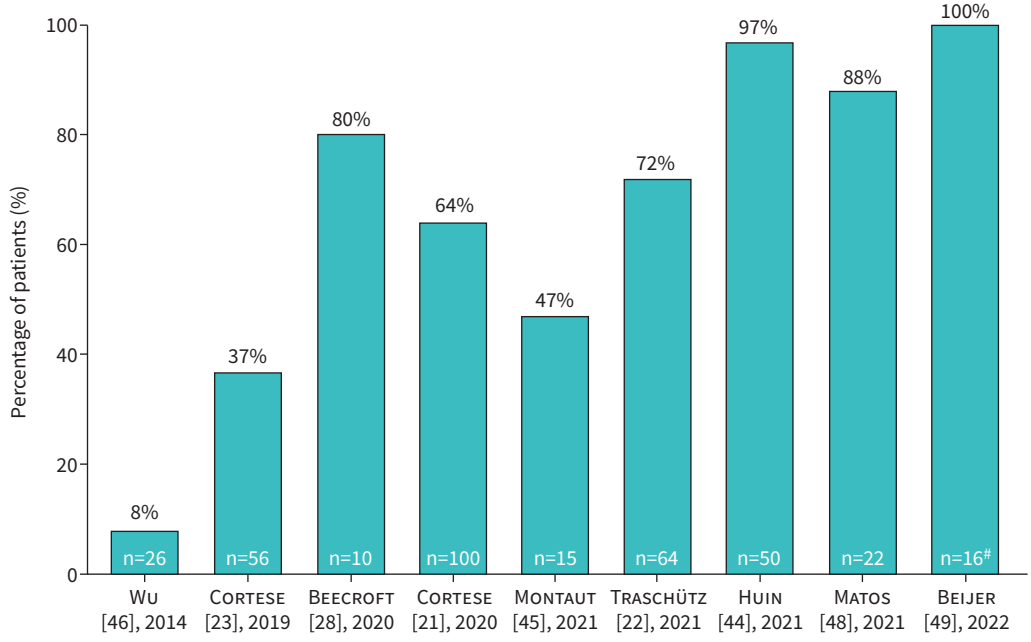

FIGURE 2 Prevalence of chronic cough in patients with cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) (*i.e.* replication factor C subunit 1 (*RFC1*) gene repeat expansion) in the literature. #: cough was an inclusion criterion.

without cough, although GORD was observed in 40% of patients with cough and 19% of those with no cough [22]. In CANVAS patients, the role of GORD in cough triggering needs to be better elucidated. Indeed, mechanisms other than acid reflux could be involved in cough. For example, non-acid reflux seems to be more closely associated with cough. Moreover, oesophageal dysmotility is commonly seen in patients with chronic cough. Interestingly, in CANVAS patients with brainstem atrophy, 100% report dysphagia [22]. The effect of even mild to moderate GORD on cough triggering in a context of cough hypersensitivity in CANVAS patients should be considered. Although there are no data on the flexible endoscopic evaluation of swallowing in CANVAS patients, swallowing difficulties are not generally commonplace in these patients. In our experience, coughing mainly occurs during the daytime, but seldomly at night or in the supine position. Otherwise, it has a relentless clinical course with no seasonal fluctuations. Chronic cough in CANVAS patients has the characteristics of RCC and repeat consultations take place across numerous disciplines including pulmonology, gastroenterology and ear/nose/throat. In our cohort, the age of cough onset was statistically lower in patients with repeat expansions of *RFC1* compared with those with no repeat expansions of *RFC1* (44.6±12.4 *versus* 51.2±10.8 years, respectively; p=0.04) [16]. Moreover, apart from age, dust/smoke or food as triggering factors remain strongly associated with repeat expansions of *RFC1* after adjustment.

In the context of late-onset ataxia, chronic cough is a strong, positive, discriminative predictor of CANVAS [48]. Otherwise, the prevalence of intronic *RFC1* expansions is particularly high in patients with hereditary sensory and autonomic neuropathies accompanied by chronic cough [49].

Cough hypersensitivity syndrome: the clinical expression of neurological dysfunction

A common feature of adult patients with chronic cough is hypersensitivity in which the vagal sensory neural pathways responsible for cough are more readily activated by airway stimuli. This has led to the adoption of the unifying concept of cough hypersensitivity syndrome (CHS) to facilitate the understanding and management of chronic cough [51, 52]. CHS is defined as troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure, reflecting both the clinical observation that patients with chronic cough mostly complain of coughing triggered by a change in atmosphere, strong smells, perfumes, speaking or singing and the experimental observation that cough reflex thresholds are lowered [53]. The introduction of CHS provides a clearer explanation of the occurrence of RCC, particularly in patients with no obvious cough aetiology [54]. This approach was endorsed by opinion leaders as a valid and useful concept in 2014 [55].

In clinical practice, many patients with chronic cough display allotussia (cough triggered by ordinarily innocuous stimuli), hypertussia (increased sensitivity to cough-evoking stimuli) and other sensory disturbances including laryngeal paraesthesia and perceptions of irritation and obstruction in the throat, all of which contribute to the experience of an increased urge to cough and excessive coughing (table 1). These symptoms are consistent with impaired or sensitised airway neural function. In CHS, sensory nerves may show altered patterns in signals encoding responses to irritant stimuli [56, 57]. CHS may also be induced through central amplification of normal sensory signals or through loss of central inhibitory controls [58].

Why do CANVAS patients have chronic cough?

Cough is dependent on sensory nerves in the airway epithelium originating from neurons in the cranial ganglia of the vagus nerve (figure 3). The vagal sensory neurons mediating cough are divided into two

TABLE 1 Clinical characteristics of cough hypersensitivity syndrome

1) Irritation in the throat or upper chest: laryngeal/pharyngeal/upper airway paraesthesia
2) Cough triggered by non-tussive stimulus, *e.g.* talking, laughing: allotussia
3) Increased cough sensitivity to inhaled stimuli and number of triggers: hypertussia
4) Cough paroxysms that are difficult to control
5) Trigger factors:
Singing, talking, laughing, deep breath: mechanical activation
Changes in temperature, cold air: thermoactivation
Aerosols, scents, odours: chemoactivation
Lying supine
Eating
Exercise

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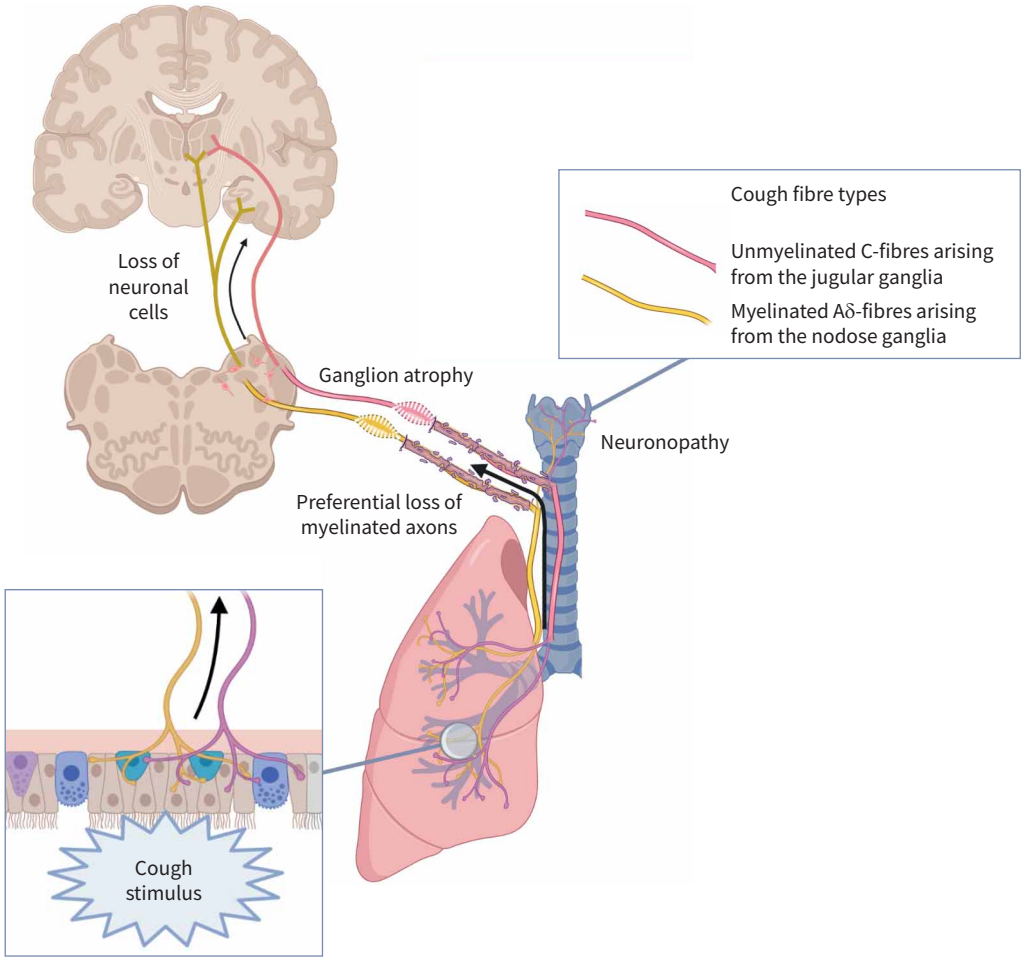

FIGURE 3 Pathophysiology of cough and cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS). The vagal sensory neurons mediating cough are divided into two groups of neurons arising from the cranial ganglia of the vagus nerves: the chemosensitive nociceptors (unmyelinated C-fibres) arising from the jugular ganglia and the low-threshold mechanosensors (myelinated Aδ-fibres) arising from the nodose ganglia. Collectively, these two sensory neuron types terminate in the mucosa of laryngeal and conducting airways, monitoring the local environment for noxious and potentially damaging chemical and mechanical airway stimuli, including inhaled gases, particulates, aspirated foodstuffs and gastric contents, mucus, and locally produced inflammatory mediators. Centrally, these nerve fibre types terminate in the nucleus of the solitary tract and paratrigeminal nucleus in the medulla oblongata, brainstem regions that have been shown to be integral to the initiation of cough and the accompanying sensory manifestations of airway noxious stimuli. CANVAS is characterised by ganglionic and nerve root atrophy with a loss of neuronal cells. Dorsal root ganglion (DRG) atrophy is accompanied by pathological changes in the spinal cord architecture, with atrophy of the dorsal columns reflecting a significant loss of myelinated axons, presumably secondary to the degeneration of the central projections of DRG neurons. Pathological changes in the medulla oblongata where cranial ganglia neurons terminate seem to be confined to the inferior olivary nuclei, with evidence of a loss of neurons and gliosis at this location.

groups: chemosensitive nociceptors (unmyelinated C-fibres) from the jugular ganglia and low-threshold mechanosensors (myelinated Aδ-fibres) from the nodose ganglia [59]. These two sensory neuron types terminate in the mucosa of laryngeal and conducting airways, where they monitor the local environment for noxious and potentially damaging inhaled gases, particulates, aspirated foodstuffs and gastric contents, mucus, and locally produced inflammatory mediators. Centrally, these nerve fibre types terminate in the nucleus of the solitary tract and paratrigeminal nucleus in the medulla oblongata, brainstem regions that have been shown to be integral to the initiation of cough and the accompanying sensory manifestations of airway noxious stimuli [60–63]. Additionally, the activity of several populations of extrapulmonary

sensory nerve fibres, including those innervating the oesophagus, nasal airways and external ear, can functionally facilitate cough through convergent interactions with primary cough-evoking sensory pathways in the brainstem [64].

The clinical presentation of cough in CANVAS is characteristic of CHS in RCC. Patient reports of throat irritation and cough triggered by emotion, stress, speaking or swallowing are consistent with the allotusia and hypertussia in RCC. Recently, it has been described that airway epithelial sensory nerve density is increased in chronic cough [65], suggesting that changes in neural innervation can contribute to the pathophysiology of cough disorders. There have been no studies of airway nerve fibre density in CANVAS patients, although airway denervation due to the extensive ganglionopathies is more likely a feature rather than hyperinnervation. This may call into question the relative involvement of peripheral airway causes of chronic cough in these patients. Up to one-third of adult RCC and CANVAS patients (compared with 1–2% of healthy individuals) display an upregulated Arnold's nerve cough reflex whereby mechanical stimulation of the external ear canal, a region innervated by the auricular branch of the vagus nerve, triggers coughing. This is consistent with a generalised hypersensitivity along vagal sensory neural pathways in RCC [66, 67] and CANVAS. However, in our cohort, the proportion of patients with Arnold's reflex was similar between chronic cough patients with (29.4%) and with no (21.1%) repeat expansions of *RFC1* [16].

The potential mechanisms leading to vagal hypersensitivity in CANVAS are unclear. Similarly, why cough presents as an early symptom in many CANVAS patients is equally perplexing. In RCC, epithelial-derived and other inflammatory mediators, notably including ATP, may be important for the development of vagal hypersensitivity [68, 69]. However, there is no evidence that pulmonary inflammation exists in CANVAS. Instead, the development of cough is more likely related to progressive neuronopathy in these patients. One possibility is that the early processes leading to vagal sensory neuron damage establish a state of neuroinflammation within the vagal nerves and ganglia. This has been shown to occur following pathogen exposure in animal models of vagal hypersensitivity and is characterised by upregulated inflammatory cell influx into the nerve and ganglia, the activation of local glial cells, and the induction of pro-inflammatory genes [70–72]. Such a phenomenon might be expected to promote a state of sensory hypersensitivity in the period prior to sensory neuron destruction. Similarly, in other neuropathies, injured sensory neurons commonly generate ectopic activity, independent of peripheral stimuli, due to changes in the ion channel composition and activity along their membranes [73, 74]. However, these possible mechanisms are only plausible in the short term, while the sensory neurons maintain some functionality and connectivity with the central nervous system.

The substantial loss of sensory neurons seen in the later stages of CANVAS would minimise any potential effects of peripheral neuroinflammation or plasticity. Instead, the denervation of brainstem neurons normally in receipt of sensory inputs may result in spontaneous activity along central cough-evoking pathways. Deafferentation hypersensitivity [75] is a cause of chronic pain in some patients with peripheral neuropathies or following surgical denervation of peripheral nerves [76]. Phantom limb pain is also thought to represent reorganisation of the central pain pathways in the absence of sensory inputs normally conveyed from the missing limb nerves. Consistent with this, neonatal destruction of nociceptive primary sensory neurons in rodents dramatically upregulates the responsivity of neurons in the nucleus of the solitary tract to local injections of neurotransmitters [77], suggestive of a state of denervation-induced sensitisation. Nevertheless, whether this is a mechanism leading to RCC in CANVAS requires further investigation and validation. Recent studies have demonstrated the utility of employing functional brain imaging to investigate brainstem activity in response to inhaled cough challenges, and such investigations may provide an avenue to understand the intactness and vagal cough nerve fibre inputs and mechanisms of hypersensitivity in CANVAS patients [78].

Therapeutic options in patients with CANVAS and chronic cough

To date, there is no disease-modifying therapy for patients with CANVAS-related neurological symptoms. Gait rehabilitation exercises must be proposed and physicians should exercise caution when using drugs that may cause vestibular (aminoglycoside), cerebellar (phenytoin) or peripheral nervous system (chemotherapies) toxicities (figure 4). Otherwise, pain in CANVAS patients is of neuropathic origin and the treatment regimen may include, as in any patient with neuropathic pain, tricyclic (and other) antidepressants, antiepileptics and opioids.

Patients with CANVAS seek medical help for cough more than for other neurological symptoms due to the high impact of cough on quality of life. Recently, the European Respiratory Society (ERS) published guidelines on the diagnosis and treatment of chronic cough [1]. Given the neurological mechanisms in

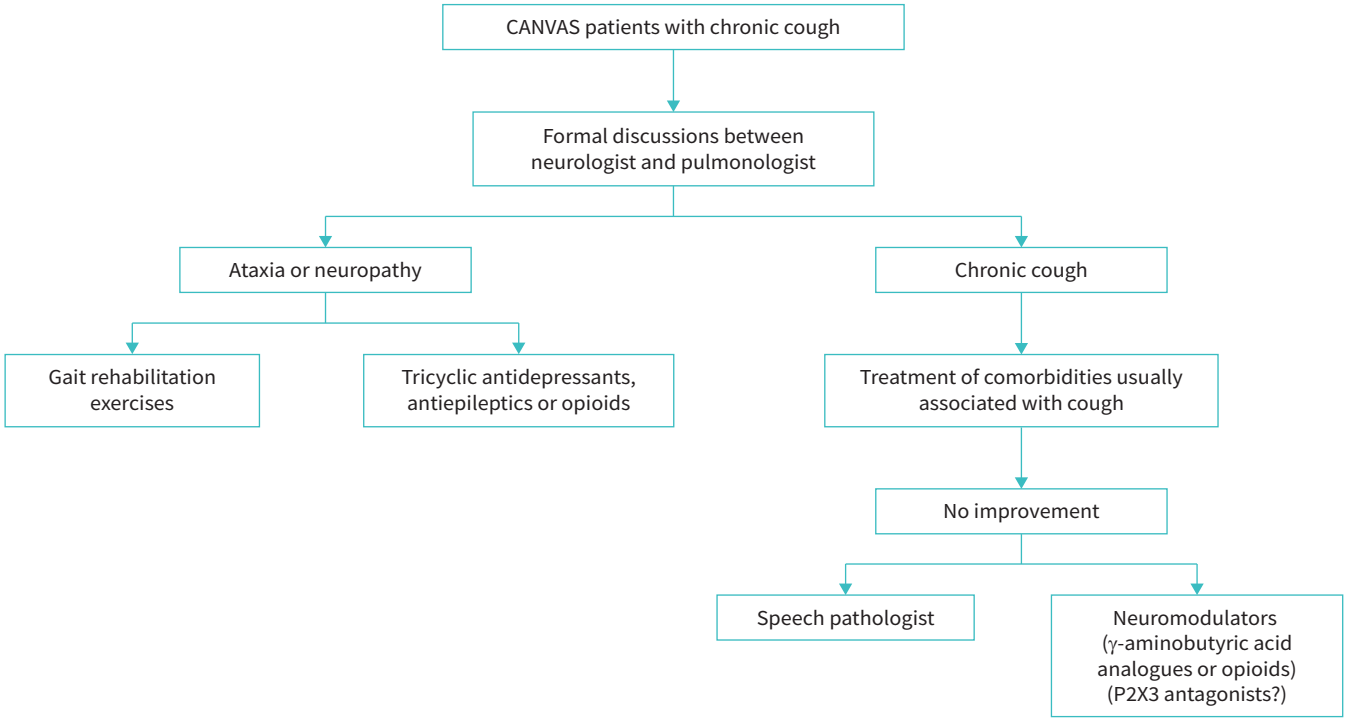

FIGURE 4 Algorithm of chronic cough management in cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) patients.

CHS, the use of neuromodulators was recommended in a situation of RCC. Given the potential combination of neuropathic pain and RCC in patients with CANVAS, a discussion between the pulmonologist and the neurologist is essential to determine the best therapeutic option [21]. Two major therapeutic classes are recommended by the ERS for the treatment of RCC: morphine and γ-aminobutyric acid analogues [1]. The classical opioid receptors (δ, κ and μ) are distributed widely within the central nervous system and, to a lesser extent, throughout the periphery [79]. γ-aminobutyric acid analogues could also act on the cerebral cortex, which might both modulate and initiate cough by acting on the respiratory area of the brainstem or at the spinal level. The effect of P2X3 antagonists on cough in CANVAS patients is still unknown.

Conclusion

RCC management is entering a new era. 10 years ago, the concept of CHS emerged, with the strong impression that neurological mechanisms are involved in RCC. Data from animal models also provide proof that the cough dysfunction is mainly neurogenic. However, conclusive evidence regarding a neurogenic origin of RCC in humans has been difficult to obtain, but may be exemplified by the RCC that commonly associates with CANVAS. However, a range of future studies are needed to unravel the mechanisms of cough hypersensitivity in CANVAS in comparison to RCC, including assessments of responsiveness through cough challenge testing, functional brain imaging to investigate central mechanisms of cough amplification, vagus nerve microneurography and airway biopsy analysis to understand the functional and structural degree of peripheral cough axon denervation, and pre-clinical studies employing patient stem cell-derived sensory neurons which may help link the varied genetic mutations with sensory neuron function. The ongoing development of new antitussive therapies for RCC provides hope for CANVAS patients and physicians, and it will be important to assess the efficacy of these (and existing therapies) in controlled trials to understand their clinical utility for treating cough in CANVAS.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: L. Guilleminault reports grants from AstraZeneca, outside the submitted work; consulting fees from Bayer, MSD, AstraZeneca, GSK, Novartis, Sanofi and Chiesi, outside the submitted work; fees for lectures from Bayer, MSD, AstraZeneca, GSK, Novartis, Sanofi and Chiesi, outside the submitted work; consulting fees for expert testimony from Bayer, MSD and Sanofi, outside the submitted work; and fees for attending meetings and/or travel

from MSD, AstraZeneca, GSK, Novartis and Sanofi, outside the submitted work. S.B. Mazzone reports grants from the National Health and Medical Research Council of Australia, Australian Research Council, Reckitt Benkiser, Bellus Health Inc. and MSD (Australia) Pty Ltd, outside the submitted work; consultancy fees from Reckitt Benkiser, NeRRe Therapeutics, Trevi Therapeutics, Merck and Chiesi, outside the submitted work; payment for writing manuscripts from Reckitt Benkiser and Chiesi, outside the submitted work; and advisory board fees received from Reckitt Benkiser, outside the submitted work. S.B. Mazzone is an Associate Editor of *ERJ Open Research*. P. Chazelas reports personal fees from Pfizer for lectures, presentations, speakers' bureaus, manuscript writing or educational events, outside the submitted work. S. Frachet reports receiving support for attending meetings and/or travel from SOS Oxygène, outside the submitted work. A-S. Lia reports receiving support from Alnylam for attending meetings and/or travel, outside the submitted work. L. Magy reports receiving personal fees for consultancy from Alnylam, Biogen and Pfizer, outside the submitted work; personal fees for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ARGENX, Pfizer and Alnylam, outside the submitted work; personal fees for expert testimony from ARGENX and LFB, outside the submitted work; support for attending meetings and/or travel from CSL Behring, outside the submitted work; and personal fees for participation on a data safety monitoring or advisory board for CSL Behring, outside the submitted work.

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