ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Invited review

Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS): a neurogenic cough prototype

Laurent Guilleminault, Stuart B. Mazzone, Pauline Chazelas, Simon Frachet, Anne-Sophie Lia, Laurent Magy

Please cite this article as: Guilleminault L, Mazzone SB, Chazelas P, *et al*. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS): a neurogenic cough prototype. *ERJ Open Res* 2024; in press (https://doi.org/10.1183/23120541.00024-2024).

Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome (CANVAS): a Neurogenic Cough Prototype

Laurent Guilleminault[1,2]†, Stuart B. Mazzone[3]†, Pauline Chazelas[4,5], Simon Frachet[5,7], Anne-Sophie Lia[4,5,6], Laurent Magy[5,7]

1. Toulouse Institute for Infectious and Inflammatory Diseases (Infinity), INSERM UMR1291, CNRS UMR5051, University Toulouse III, 31024 Toulouse, France.
2. Department of respiratory medicine, Toulouse University Hospital, Faculty of Medicine, Toulouse, France.
3. Department of Anatomy and Physiology, University of Melbourne, Victoria, Australia
4. Service de Biochimie et Génétique Moléculaire – CHU Limoges, France
5. NeurIT-UR20218- Université de Limoges, France
6. Service de Bioinformatique – CHU Limoges, France
7. Service et Laboratoire de Neurologie, Centre de Référence 'Neuropathies Périphériques Rares, NNerf', CHU Limoges, Limoges, France

† The authors have equally contributed to the manuscript and are the co-first authors of the publication

*Corresponding author:

Laurent Guilleminault

Hôpital Larrey, CHU de Toulouse

24 chemin de Pouvourville

31059 Toulouse

Phone: 0033567771850

Fax : 0033567771472

guilleminault.l@chu-toulouse.fr

No funding

Disclosure of interest:

Prof Guilleminault reports personal fees from Bayer and MSD. He has participated in clinical trials from Bayer and MSD. He also reports grants, personal fees, and non-financial support from Astrazeneca, personal fees and non-financial support from GSK, personal fees and non-financial support from Novartis, personal fees from Chiesi, and personal fees and non-financial support from Sanofi, outside the submitted work. Prof Mazzone declares honoraria from Merck, NeRRe Therapeutics, Reckitt Benckiser and Bellus Health and grant support from Merck and Bellus Health, outside of the submitted work.

The other authors declare no disclosure of interests.

Abstract word count: 161

Word count: 3734

Take home message: 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.

Abstract

Chronic cough is a frequent disorder that is defined by a 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.

Key words: chronic cough, refractory chronic cough, CANVAS, *RFC1* gene

Introduction

Chronic cough is defined by a cough of more than eight 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 [3, 4] related to psychosocial complications with the inability to suppress cough in a quiet environment such as the theatre, church, or cinema[3] and physical complications including urinary incontinence [5]. Chronic cough can be associated with common diseases such as asthma, rhinosinusitis, and GERD (gastro-oesophageal reflux disease) [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 to 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 *RFC1* gene. Intriguingly, we observed that 25% of patients with RCC presented at least one AAGGG repeat expansion in the *RFC1* gene [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 nineties [17] (Figure 1). At that time, it was recognized that some patients with this specific disorder also presented sensory peripheral neuropathy; but 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 anterior and dorsal vermis, usually appears mild on brain magnetic resonance imaging [21]. It is estimated that around 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.* identified the first molecular cause of CANVAS, corresponding to a biallelic intronic AAGGG repeat expansion in the replication factor C subunit 1 (*RFC1*) gene [23]. Subsequently, the allele frequency of the AAGGG 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 2,000 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, 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 (4p .14) and contains 25 exons. This gene encodes for the large subunit of 140 kDa of replicator factor C (RFC). RFC is a clamp loader of 5 subunits, involved in the DNA replication fork within the proliferating cell nuclear antigen (PCNA). 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 an abnormal RFC1 protein conformation or expression [23]. However, additional

studies showed a decreased level of *RFC1* mRNA and/or RFC1 protein compared to 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 (DRG) and V, VII and VIIIth cranial nerve ganglia [19]. Observations have shown a ganglionic and nerve root atrophy with a loss of neuronal cells and their replacement by psammoma bodies areas 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 meter in length, extending from the CNS (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 optimized 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 sensory nerve action potentials (SNAPs) with preservation of compound muscle action potentials (CMAPs) 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, by contrast with 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 is 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 tests results [17]. Besides the core clinical features of CANVAS, authors have also reported that some patients may experience dysautonomia, parkinsonism, and cognitive impairment but, 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, 2 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% [21-23, 28, 44-46, 48, 49] (Figure 2). 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*. noticed that cough could precede the walking difficulties by one decade [23]. 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. GERD, which is a common cause of chronic

cough, does not explain the high prevalence of RCC in CANVAS. In a recent study, reflux disease was reported in 19 patients (31%) with CANVAS and was not significantly more prevalent either with or without cough although GERD was observed in 40% of patients with cough and 19% of those with no cough [22]. In CANVAS patients, the role of GERD in cough triggering needs to be better elucidated. Indeed, other 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 GERD even mild to moderate 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 seldom 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 ENT. In our cohort, the age of cough onset was statistically lower in patients with repeat expansions of *RFC1* compared to those with no repeat expansions of *RFC1* (44.6 ± 12.4 vs 51.2 ± 10.8, respectively, p=0.04) [16]. Moreover, apart from age, dust/smoke or food as triggering factor, 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 sensitized 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 groups: chemosensitive nociceptors (unmyelinated C-fibres) from the

jugular ganglia and low-threshold mechanosensors (myelinated A-delta 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 to 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 adenosine triphosphate (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 characterized by upregulated inflammatory cell influx into the nerve and ganglia, the activation of local glial cells, and the induction of proinflammatory 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 sensitization. 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 published guidelines on the diagnosis and treatment of chronic cough [1]. Given the neurological mechanisms in 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 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. Ten years ago, the concept of CHS emerged, with the strong impression that neurological mechanisms are involved in RCC. Data from animal models also give 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 preclinical 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.

References

1. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, Hilton Boon M, Kantar A, Lai K, McGarvey L, Rigau D, Satia I, Smith J, Song WJ, Tonia T, van den Berg JWK, van Manen MJG , Zacharasiewicz A, ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J, 2020. 55(1): 1901136.
2. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, Jo EJ, Kim MH, Plevkova J, Park HW, Cho SH , Morice AH, The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J, 2015. 45(5): 1479-1481.
3. French CL, Irwin RS, Curley FJ , Krikorian CJ, Impact of chronic cough on quality of life. Arch Intern Med, 1998. 158(15): 1657-1661.
4. Young EC , Smith JA, Quality of life in patients with chronic cough. Ther Adv Respir Dis, 2010. 4(1): 49-55.
5. Dicpinigaitis PV, Prevalence of stress urinary incontinence in women presenting for evaluation of chronic cough. ERJ Open Res, 2021. 7(1): 00012-2021.
6. Arinze JT, de Roos EW, Karimi L, Verhamme KMC, Stricker BH , Brusselle GG, Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. ERJ Open Res, 2020. 6(2): 00300-2019.
7. Palombini BC, Villanova CA, Araújo E, Gastal OL, Alt DC, Stolz DP , Palombini CO, A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. Chest, 1999. 116(2): 279-284.
8. Kaplan AG, Chronic Cough in Adults: Make the Diagnosis and Make a Difference. Pulm Ther, 2019. 5(1): 11-21.
9. Morice A, Dicpinigaitis P, McGarvey L , Birring SS, Chronic cough: new insights and future prospects. Eur Respir Rev, 2021. 30(162): 210127.
10. Chung KF , Pavord ID, Prevalence, pathogenesis, and causes of chronic cough. The Lancet, 2008. 371(9621): 1364-1374.
11. Chung KF, Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. J Thorac Dis, 2014. 6(Suppl 7): S699-707.
12. Chung KF, McGarvey L , Mazzone SB, Chronic cough as a neuropathic disorder. Lancet Respir Med, 2013. 1(5): 414-422.
13. Driessen AK, Devlin AC, Lundy FT, Martin SL, Sergeant GP, Mazzone SB , McGarvey LP, Perspectives on neuroinflammation contributing to chronic cough. Eur Respir J, 2020. 56(4): 2000758.
14. Kimber J, Mitchell D , Mathias CJ, Chronic cough in the Holmes-Adie syndrome: association in five cases with autonomic dysfunction. J Neurol Neurosurg Psychiatry, 1998. 65(4): 583-586.
15. Spring PJ, Kok C, Nicholson GA, Ing AJ, Spies JM, Bassett ML, Cameron J, Kerlin P, Bowler S, Tuck R , Pollard JD, Autosomal dominant hereditary sensory neuropathy with chronic cough and gastro-oesophageal reflux: clinical features in two families linked to chromosome 3p22-p24. Brain, 2005. 128(Pt 12): 2797-2810.
16. Guilleminault L, Chazelas P, Melloni B, Magdelaine C, Villeneuve T, Brouquières D, Lia AS , Magy L, Repeat Expansions of RFC1 in Refractory Chronic Cough: A Missing Piece of the Puzzle? Chest, 2022: 911-915.
17. Rinne T, Bronstein AM, Rudge P, Gresty MA , Luxon LM, Bilateral loss of vestibular function: clinical findings in 53 patients. J Neurol, 1998. 245(6-7): 314-321.

18. Szmulewicz DJ, Waterston JA, Halmagyi GM, Mossman S, Chancellor AM, McLean CA , Storey E, Sensory neuropathy as part of the cerebellar ataxia neuropathy vestibular areflexia syndrome. Neurology, 2011. 76(22): 1903-1910.
19. Szmulewicz DJ, Waterston JA, MacDougall HG, Mossman S, Chancellor AM, McLean CA, Merchant S, Patrikios P, Halmagyi GM , Storey E, Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS): a review of the clinical features and video-oculographic diagnosis. Ann N Y Acad Sci, 2011. 1233: 139-147.
20. Cazzato D, Bella ED, Dacci P, Mariotti C , Lauria G, Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome: a slowly progressive disorder with stereotypical presentation. J Neurol, 2016. 263(2): 245-249.
21. Cortese A, Tozza S, Yau WY, Rossi S, Beecroft SJ, Jaunmuktane Z, Dyer Z, Ravenscroft G, Lamont PJ, Mossman S, Chancellor A, Maisonobe T, Pereon Y, Cauquil C, Colnaghi S, Mallucci G, Curro R, Tomaselli PJ, Thomas-Black G, Sullivan R, Efthymiou S, Rossor AM, Laurá M, Pipis M, Horga A, Polke J, Kaski D, Horvath R, Chinnery PF, Marques W, Tassorelli C, Devigili G, Leonardis L, Wood NW, Bronstein A, Giunti P, Züchner S, Stojkovic T, Laing N, Roxburgh RH, Houlden H , Reilly MM, Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain, 2020. 143(2): 480-490.
22. Traschütz A, Cortese A, Reich S, Dominik N, Faber J, Jacobi H, Hartmann AM, Rujescu D, Montaut S, Echaniz-Laguna A, Erer S, Schütz VC, Tarnutzer AA, Sturm M, Haack TB, Vaucamps-Diedhiou N, Puccio H, Schöls L, Klockgether T, van de Warrenburg BP, Paucar M, Timmann D, Hilgers RD, Gazulla J, Strupp M, Moris G, Filla A, Houlden H, Anheim M, Infante J, Basak AN , Synofzik M, Natural History, Phenotypic Spectrum, and Discriminative Features of Multisystemic RFC1 Disease. Neurology, 2021. 96(9): e1369-e1382.
23. Cortese A, Simone R, Sullivan R, Vandrovcova J, Tariq H, Yau WY, Humphrey J, Jaunmuktane Z, Sivakumar P, Polke J, Ilyas M, Tribollet E, Tomaselli PJ, Devigili G, Callegari I, Versino M, Salpietro V, Efthymiou S, Kaski D, Wood NW, Andrade NS, Buglo E, Rebelo A, Rossor AM, Bronstein A, Fratta P, Marques WJ, Züchner S, Reilly MM , Houlden H, Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet, 2019. 51(4): 649-658.
24. Rafehi H, Szmulewicz DJ, Bennett MF, Sobreira NLM, Pope K, Smith KR, Gillies G, Diakumis P, Dolzhenko E, Eberle MA, Barcina MG, Breen DP, Chancellor AM, Cremer PD, Delatycki MB, Fogel BL, Hackett A, Halmagyi GM, Kapetanovic S, Lang A, Mossman S, Mu W, Patrikios P, Perlman SL, Rosemergy I, Storey E, Watson SRD, Wilson MA, Zee DS, Valle D, Amor DJ, Bahlo M , Lockhart PJ, Bioinformatics-Based Identification of Expanded Repeats: A Non-reference Intronic Pentamer Expansion in RFC1 Causes CANVAS. Am J Hum Genet, 2019. 105(1): 151-165.
25. Akçimen F, Ross JP, Bourassa CV, Liao C, Rochefort D, Gama MTD, Dicaire MJ, Barsottini OG, Brais B, Pedroso JL, Dion PA , Rouleau GA, Investigation of the RFC1 Repeat Expansion in a Canadian and a Brazilian Ataxia Cohort: Identification of Novel Conformations. Front Genet, 2019. 10: 1219.
26. Gisatulin M, Dobricic V, Zühlke C, Hellenbroich Y, Tadic V, Münchau A, Isenhardt K, Bürk K, Bahlo M, Lockhart PJ, Lohmann K, Helmchen C , Brüggemann N, Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes. Neurology, 2020. 95(21): e2912-e2923.

27. Boesch SM , Nance MA, Intronic pentanucleotide expansion in the replication factor 1 gene (RFC1) is a major cause of adult-onset ataxia. Neurol Genet, 2020. 6(3): e436.
28. Beecroft SJ, Cortese A, Sullivan R, Yau WY, Dyer Z, Wu TY, Mulroy E, Pelosi L, Rodrigues M, Taylor R, Mossman S, Leadbetter R, Cleland J, Anderson T, Ravenscroft G, Laing NG, Houlden H, Reilly MM , Roxburgh RH, A Māori specific RFC1 pathogenic repeat configuration in CANVAS, likely due to a founder allele. Brain, 2020. 143(9): 2673-2680.
29. Tsuchiya M, Nan H, Koh K, Ichinose Y, Gao L, Shimozono K, Hata T, Kim YJ, Ohtsuka T, Cortese A , Takiyama Y, RFC1 repeat expansion in Japanese patients with late-onset cerebellar ataxia. J Hum Genet, 2020. 65(12): 1143-1147.
30. Miyatake S, Yoshida K, Koshimizu E, Doi H, Yamada M, Miyaji Y, Ueda N, Tsuyuzaki J, Kodaira M, Onoue H, Taguri M, Imamura S, Fukuda H, Hamanaka K, Fujita A, Satoh M, Miyama T, Watanabe N, Kurita Y, Okubo M, Tanaka K, Kishida H, Koyano S, Takahashi T, Ono Y, Higashida K, Yoshikura N, Ogata K, Kato R, Tsuchida N, Uchiyama Y, Miyake N, Shimohata T, Tanaka F, Mizuguchi T , Matsumoto N, Repeat conformation heterogeneity in cerebellar ataxia, neuropathy, vestibular areflexia syndrome. Brain, 2022. 145(3): 1139-1150.
31. Scriba CK, Beecroft SJ, Clayton JS, Cortese A, Sullivan R, Yau WY, Dominik N, Rodrigues M, Walker E, Dyer Z, Wu TY, Davis MR, Chandler DC, Weisburd B, Houlden H, Reilly MM, Laing NG, Lamont PJ, Roxburgh RH , Ravenscroft G, A novel RFC1 repeat motif (ACAGG) in two Asia-Pacific CANVAS families. Brain, 2020. 143(10): 2904-2910.
32. Ronco R, Perini C, Currò R, Dominik N, Facchini S, Gennari A, Simone R, Stuart S, Nagy S, Vegezzi E, Quartesan I, El-Saddig A, Lavin T, Tucci A, Szymura A, Novis De Farias LE, Gary A, Delfeld M, Kandikatla P, Niu N, Tawde S, Shaw J, Polke J, Reilly MM, Wood NW, Crespan E, Gomez C, Chen JYH, Schmahmann JD, Gosal D, Houlden H, Das S , Cortese A, Truncating Variants in RFC1 in Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome. Neurology, 2023. 100(5): e543-e554.
33. Benkirane M, Da Cunha D, Marelli C, Larrieu L, Renaud M, Varilh J, Pointaux M, Baux D, Ardouin O, Vangoethem C, Taulan M, Daumas Duport B, Bergougnoux A, Corbillé AG, Cossée M, Juntas Morales R, Tuffery-Giraud S, Koenig M, Isidor B , Vincent MC, RFC1 nonsense and frameshift variants cause CANVAS: clues for an unsolved pathophysiology. Brain, 2022. 145(11): 3770-3775.
34. Weber S, Coarelli G, Heinzmann A, Monin ML, Richard N, Gerard M, Durr A , Huin V, Two RFC1 splicing variants in CANVAS. Brain, 2023. 146(3): e14-e16.
35. King KA, Wegner DJ, Bucelli RC, Shapiro J, Paul AJ, Dickson PI , Wambach JA, Whole-Genome and Long-Read Sequencing Identify a Novel Mechanism in RFC1 Resulting in CANVAS Syndrome. Neurol Genet, 2022. 8(6): e200036.
36. Arteche-López A, Avila-Fernandez A, Damian A, Soengas-Gonda E, de la Fuente RP, Gómez PR, Merlo JG, Burgos LH, Fernández CC, Rosales JML, Martínez JFG, Quesada-Espinosa JF, Corton M , Guerrero-Molina MP, New Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome cases are caused by the presence of a nonsense variant in compound heterozygosity with the pathogenic repeat expansion in the RFC1 gene. Clin Genet, 2023. 103(2): 236-241.
37. França MC, Jr., D'Abreu A, Zanardi VA, Faria AV, Lopes-Cendes I, Nucci A , Cendes F, MRI shows dorsal lesions and spinal cord atrophy in chronic sensory neuronopathies. J Neuroimaging, 2008. 18(2): 168-172.

38. Szmulewicz DJ, McLean CA, Rodriguez ML, Chancellor AM, Mossman S, Lamont D, Roberts L, Storey E , Halmagyi GM, Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology, 2014. 82(16): 1410-1415.
39. Beaudin M, Manto M, Schmahmann JD, Pandolfo M , Dupre N, Recessive cerebellar and afferent ataxias - clinical challenges and future directions. Nat Rev Neurol, 2022. 18(5): 257-272.
40. Hirakawa H, Okajima S, Nagaoka T, Kubo T, Takamatsu T , Oyamada M, Regional differences in blood-nerve barrier function and tight-junction protein expression within the rat dorsal root ganglion. Neuroreport, 2004. 15(3): 405-408.
41. Zhang G, Gibbs E, Kelman Z, O'Donnell M , Hurwitz J, Studies on the interactions between human replication factor C and human proliferating cell nuclear antigen. Proc Natl Acad Sci U S A, 1999. 96(5): 1869-1874.
42. Szmulewicz DJ, Seiderer L, Halmagyi GM, Storey E , Roberts L, Neurophysiological evidence for generalized sensory neuronopathy in cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome. Muscle Nerve, 2015. 51(4): 600-603.
43. Burke D , Halmagyi GM, Normal tendon reflexes despite absent sensory nerve action potentials in CANVAS: a neurophysiological study. J Neurol Sci, 2018. 387: 75-79.
44. Huin V, Coarelli G, Guemy C, Boluda S, Debs R, Mochel F, Stojkovic T, Grabli D, Maisonobe T, Gaymard B, Lenglet T, Tard C, Davion JB, Sablonnière B, Monin ML, Ewenczyk C, Viala K, Charles P, Le Ber I, Reilly MM, Houlden H, Cortese A, Seilhean D, Brice A , Durr A, Motor neuron pathology in CANVAS due to RFC1 expansions. Brain, 2021: 2121-2132.
45. Montaut S, Diedhiou N, Fahrer P, Marelli C, Lhermitte B, Robelin L, Vincent MC, Corti L, Taieb G, Gebus O, Rudolf G, Tarabeux J, Dondaine N, Canuet M, Almeras M, Benkirane M, Larrieu L, Chanson JB, Nadaj-Pakleza A, Echaniz-Laguna A, Cauquil C, Lannes B, Chelly J, Anheim M, Puccio H , Tranchant C, Biallelic RFC1-expansion in a French multicentric sporadic ataxia cohort. J Neurol, 2021. 268(9): 3337-3343.
46. Wu TY, Taylor JM, Kilfoyle DH, Smith AD, McGuinness BJ, Simpson MP, Walker EB, Bergin PS, Cleland JC, Hutchinson DO, Anderson NE, Snow BJ, Anderson TJ, Paermentier LA, Cutfield NJ, Chancellor AM, Mossman SS , Roxburgh RH, Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome. Brain, 2014. 137(Pt 10): 2649-2656.
47. Szmulewicz DJ, McLean CA, MacDougall HG, Roberts L, Storey E , Halmagyi GM, CANVAS an update: clinical presentation, investigation and management. J Vestib Res, 2014. 24(5-6): 465-474.
48. Matos P, Rezende TJR, Schmitt GS, Bonadia LC, Reis F, Martinez ARM, de Lima FD, Bueno MGA, Tomaselli PJ, Cendes F, Pedroso JL, Barsottini OGP, Marques W, Jr. , França M, Jr., Brain Structural Signature of RFC1-Related Disorder. Mov Disord, 2021. 36(11): 2634-2641.
49. Beijer D, Dohrn MF, De Winter J, Fazal S, Cortese A, Stojkovic T, Fernández-Eulate G, Remiche G, Gentile M, Van Coster R, Dufke C, Synofzik M, De Jonghe P, Züchner S , Baets J, RFC1 repeat expansions: A recurrent cause of sensory and autonomic neuropathy with cough and ataxia. Eur J Neurol, 2022: 2156-2161.
50. Turner RD, Hirons B, Cortese A , Birring SS, Chronic Cough as a Genetic Neurological Disorder? Insights from Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS). Lung, 2023. 201(6): 511-519.

51. Morice AH, The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung, 2010. 188 Suppl 1: S87-90.
52. Morice AH, Chronic cough hypersensitivity syndrome. Cough, 2013. 9(1): 14.
53. Chung KF, McGarvey L, Song WJ, Chang AB, Lai K, Canning BJ, Birring SS, Smith JA , Mazzone SB, Cough hypersensitivity and chronic cough. Nat Rev Dis Primers, 2022. 8(1): 45.
54. Chung KF, Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough. Pulm Pharmacol Ther, 2011. 24(3): 267-271.
55. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, Dal Negro RW, Dicpinigaitis P, Kantar A, McGarvey LP, Pacheco A, Sakalauskas R , Smith JA, Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J, 2014. 44(5): 1132-1148.
56. Carr MJ, Hunter DD, Jacoby DB , Undem BJ, Expression of tachykinins in nonnociceptive vagal afferent neurons during respiratory viral infection in guinea pigs. American journal of respiratory and critical care medicine, 2002. 165(8): 1071-1075.
57. Chuaychoo B, Hunter DD, Myers AC, Kollarik M , Undem BJ, Allergen-induced substance P synthesis in large-diameter sensory neurons innervating the lungs. Journal of Allergy and Clinical Immunology, 2005. 116(2): 325-331.
58. Mazzone SB, An overview of the sensory receptors regulating cough. Cough, 2005. 1(1): 2.
59. Mazzone SB , Undem BJ, Vagal Afferent Innervation of the Airways in Health and Disease. Physiol Rev, 2016. 96(3): 975-1024.
60. Farrell MJ, Bautista TG, Liang E, Azzollini D, Egan GF , Mazzone SB, Evidence for multiple bulbar and higher brain circuits processing sensory inputs from the respiratory system in humans. J Physiol, 2020. 598(24): 5771-5787.
61. Driessen AK, McGovern AE, Behrens R, Moe AAK, Farrell MJ , Mazzone SB, A role for neurokinin 1 receptor expressing neurons in the paratrigeminal nucleus in bradykinin-evoked cough in guinea-pigs. J Physiol, 2020. 598(11): 2257-2275.
62. Bautista TG, Leech J, Mazzone SB , Farrell MJ, Regional brain stem activations during capsaicin inhalation using functional magnetic resonance imaging in humans. J Neurophysiol, 2019. 121(4): 1171-1182.
63. Canning BJ , Mori N, Encoding of the cough reflex in anesthetized guinea pigs. Am J Physiol Regul Integr Comp Physiol, 2011. 300(2): R369-377.
64. Mazzone SB , Farrell MJ, Heterogeneity of cough neurobiology: Clinical implications. Pulm Pharmacol Ther, 2019. 55: 62-66.
65. Shapiro CO, Proskocil BJ, Oppegard LJ, Blum ED, Kappel NL, Chang CH, Fryer AD, Jacoby DB, Costello RW , Drake MG, Airway Sensory Nerve Density Is Increased in Chronic Cough. Am J Respir Crit Care Med, 2021. 203(3): 348-355.
66. Dicpinigaitis PV, Enilari O , Cleven KL, Prevalence of Arnold nerve reflex in subjects with and without chronic cough: Relevance to Cough Hypersensitivity Syndrome. Pulm Pharmacol Ther, 2019. 54: 22-24.
67. Dicpinigaitis PV, Kantar A, Enilari O , Paravati F, Prevalence of Arnold Nerve Reflex in Adults and Children With Chronic Cough. Chest, 2018. 153(3): 675-679.
68. Sykes DL, Zhang M , Morice AH, Treatment of chronic cough: P2X3 receptor antagonists and beyond. Pharmacol Ther, 2022. 237: 108166.
69. Patil MJ, Sun H, Ru F, Meeker S , Undem BJ, Targeting C-fibers for peripheral acting anti-tussive drugs. Pulm Pharmacol Ther, 2019. 56: 15-19.

70. Verzele NAJ, Chua BY, Law CW, Zhang A, Ritchie ME, Wightman O, Edwards IN, Hulme KD, Bloxham CJ, Bielefeldt-Ohmann H, Trewella MW, Moe AAK, Chew KY, Mazzone SB, Short KR , McGovern AE, The impact of influenza pulmonary infection and inflammation on vagal bronchopulmonary sensory neurons. Faseb j, 2021. 35(3): e21320.
71. Mazzone SB, Yang SK, Keller JA, Simanauskaite J, Arikkatt J, Fogarty MJ, Moe AAK, Chen C, Trewella MW, Tian L, Ritchie ME, Chua BY, Phipps S, Short KR , McGovern AE, Modulation of Vagal Sensory Neurons via High Mobility Group Box-1 and Receptor for Advanced Glycation End Products: Implications for Respiratory Viral Infections. Front Physiol, 2021. 12: 744812.
72. Kaelberer MM, Caceres AI , Jordt SE, Activation of a nerve injury transcriptional signature in airway-innervating sensory neurons after lipopolysaccharide-induced lung inflammation. Am J Physiol Lung Cell Mol Physiol, 2020. 318(5): L953-l964.
73. North RY, Odem MA, Li Y, Tatsui CE, Cassidy RM, Dougherty PM , Walters ET, Electrophysiological Alterations Driving Pain-Associated Spontaneous Activity in Human Sensory Neuron Somata Parallel Alterations Described in Spontaneously Active Rodent Nociceptors. J Pain, 2022: 1343-1357.
74. Tan AM, Samad OA, Dib-Hajj SD , Waxman SG, Virus-Mediated Knockdown of Nav1.3 in Dorsal Root Ganglia of STZ-Induced Diabetic Rats Alleviates Tactile Allodynia. Mol Med, 2015. 21(1): 544-552.
75. Dalal A, Tata M, Allègre G, Gekiere F, Bons N , Albe-Fessard D, Spontaneous activity of rat dorsal horn cells in spinal segments of sciatic projection following transection of sciatic nerve or of corresponding dorsal roots. Neuroscience, 1999. 94(1): 217-228.
76. Hanakawa T, Neural mechanisms underlying deafferentation pain: a hypothesis from a neuroimaging perspective. J Orthop Sci, 2012. 17(3): 331-335.
77. Mazzone SB , Geraghty DP, Respiratory actions of tachykinins in the nucleus of the solitary tract: effect of neonatal capsaicin pretreatment. Br J Pharmacol, 2000. 129(6): 1132-1139.
78. Moe AAK, Singh N, Dimmock M, Cox K, McGarvey L, Chung KF, McGovern AE, McMahon M, Richards AL, Farrell MJ , Mazzone SB, Brainstem processing of cough sensory inputs in chronic cough hypersensitivity. EBioMedicine, 2024. 100: 104976.
79. James A , Williams J, Basic Opioid Pharmacology - An Update. Br J Pain, 2020. 14(2): 115-121.

Figure 1: Clinical characteristics of patients with CANVAS

Figure 2: Prevalence of chronic cough in patients with CANVAS (i.e. RFC1 repeat expansion) in the literature. *Cough was an inclusion criterion

Figure 3: Pathophysiology of cough and 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 A-delta 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, seems to be confined to the inferior olivary nuclei, with evidence of a loss of neurons and gliosis at this location.

Figure 4: Algorithm of chronic cough management in CANVAS patients

Table 1: Clinical characteristics of cough hypersensitivity syndrome according to Chung *et al*. [11]

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 breaths: mechanical activation - Changes in temperature, cold air: thermoactivation - Aerosols, scents, odours: chemoactivation - Supine position, eating - Exercise

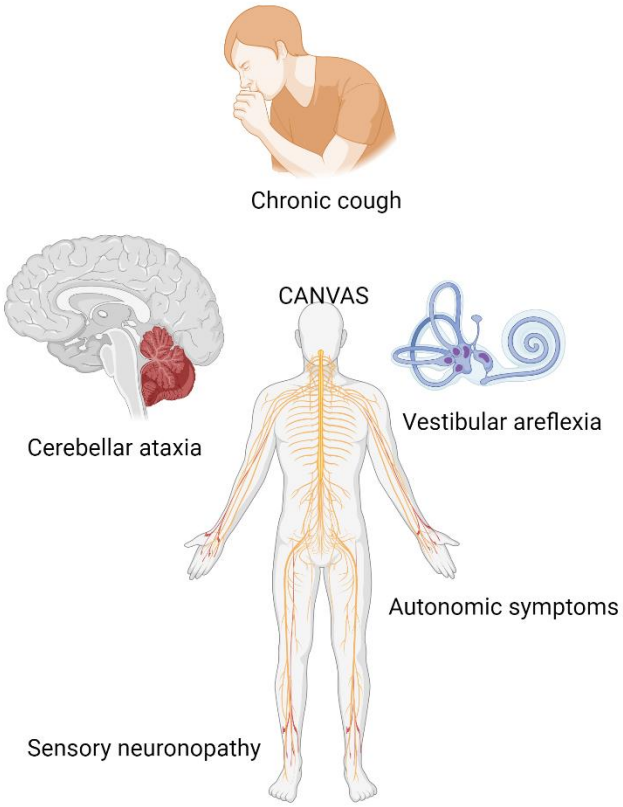
Chronic cough
CANVAS
Cerebellar ataxia
Vestibular areflexia
Autonomic symptoms
Sensory neuronopathy

Figure 1

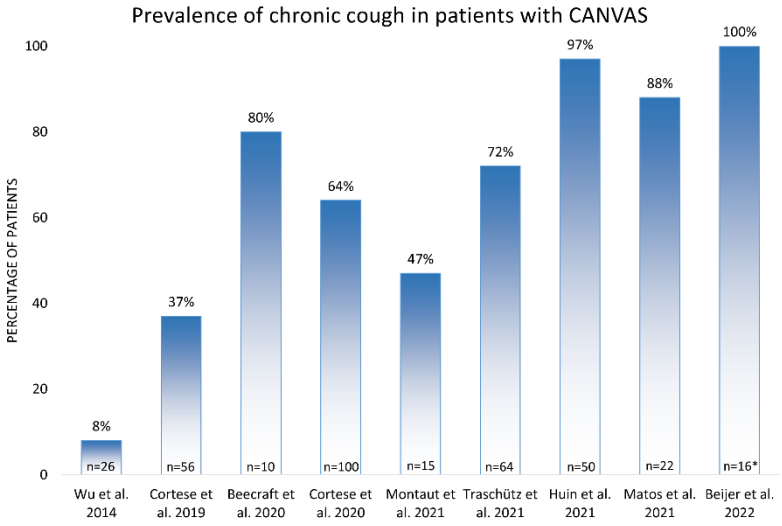
Prevalence of chronic cough in patients with CANVAS
PERCENTAGE OF PATIENTS
100
80
60
40
20
0
8%
37%
80%
64%
47%
72%
97%
88%
100%
n=26
n=56
n=10
n=100
n=15
n=64
n=50
n=22
n=16*
Wu et al. 2014
Cortese et al. 2019
Beecraft et al. 2020
Cortese et al. 2020
Montaut et al. 2021
Traschütz et al. 2021
Huin et al. 2021
Matos et al. 2021
Beijer et al. 2022

Figure 2

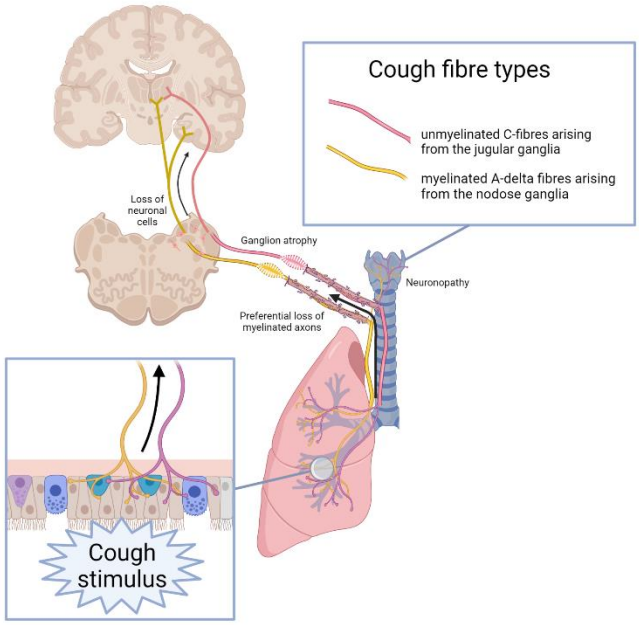
Cough fibre types
unmyelinated C-fibres arising from the jugular ganglia
myelinated A-delta fibres arising from the nodose ganglia
Loss of neuronal cells
Ganglion atrophy
Neuronopathy
Preferential loss of myelinated axons
Cough stimulus

Figure 3

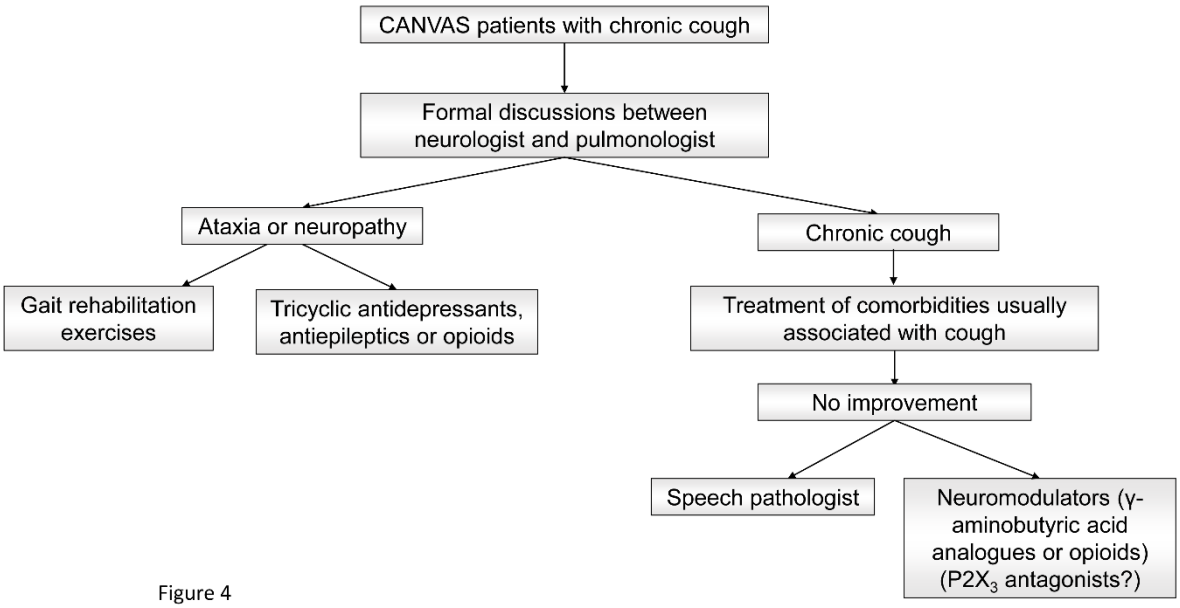
CANVAS patients with chronic cough
Formal discussions between neurologist and pulmonologist
Ataxia or neuropathy
Chronic cough
Gait rehabilitation exercises
Tricyclic antidepressants, antiepileptics or opioids
Treatment of comorbidities usually associated with cough
No improvement
Speech pathologist
Neuromodulators (γ-aminobutyric acid analogues or opioids) ($P2X_3$ antagonists?)

Figure 4