A man with coughing spells for 20 years

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Introduction

Charcot-Marie-Tooth (CMT) disease or hereditary sensory motor neuropathy (HSMN) is the most common hereditary neuropathy with an estimated prevalence of 1 in 2500 people.[1] The characteristic findings in CMT include progressive sensory symptoms and weakness in the distal limbs, imbalance, and foot and ankle deformities.[2] Various atypical features of CMT have been described, including ptosis, tonic pupil, optic atrophy, deafness, diaphragmatic weakness, vocal cord palsy, chronic cough, facial or bulbar weakness, tongue atrophy, dysautonomia, cerebellar ataxia, and upper motor neuron signs.[2] The present case describes a patient with long standing numbness, imbalance, chronic cough, and a strong family history of similar symptoms.

Case Presentation

A 53-year-old man presented with complaints of daily coughing spells for the last 20 years. He described it as spells of constant intense coughing until he became lightheaded and almost passed out. The cough was always dry and could be triggered by pungent smells, temperature changes, eating or drinking. During these episodes he felt as if his throat was tightening. Hoarseness of his voice was not present in his symptomology. He was initially diagnosed with mild asthma, but pulmonary function tests were normal and the cough was not responsive to standard asthma treatment. Multiple laryngoscopy examinations were unrevealing.

He had an uneventful birth and perinatal history. He had no foot, ankle, or spine surgeries, wounds or injuries. He only participated in cross country running while in school. He first noticed imbalance when he was ice skating 10 years ago. His imbalance slowly progressed that led to his first fall approximately five years prior. More recently, he noted difficulty climbing stairs and buttoning clothes. He also reported a difficulty sensing temperature in his hands and feet, which resulted in multiple injuries in these regions.

Family history is significant on his maternal side with his mother and uncle having similar symptoms of imbalance and chronic coughing spells. His mother also had vocal cord paralysis and issues with aspiration. His brother and sister were both diagnosed with sensory neuropathy without further details.

Mental status, cranial nerves and muscle strength were all normal on the initial neurological exam. Deep tendon reflexes were hypoactive. Impaired sensation of pinprick and vibration was noted in the distal extremities, more significantly in the lower and sensation of proprioception was reduced in the toes bilaterally. Gait was unsteady and wide based. No hammer toes or high arches were observed.

Sensory nerve conduction studies showed diffusely reduced sensory nerve action potentials (SNAPs) in the upper and lower extremities. Motor nerve conductions of the upper and lower extremities were normal. Needle examination of selected muscles revealed evidence of chronic denervation in a length dependent pattern.

Laboratory workup for the aetiologies of neuropathy revealed slightly reduced B12 level that was quickly corrected with B12 supplementation, without leading to changes in his symptoms of neuropathy and coughing spells. Due to the chronic slowly progressive course and significant family history of similar symptoms, a genetic cause of neuropathy was considered. The initial testing revealed the following changes in the MFN2 gene: c.708+11_708+13delCTC (intronic). Variants of uncertain significance (VUS) were noted in the DNAJB2, MFN2NDRG1, and SPG11 genes. The changes noted above in the MFN2 gene were initially classified as being VUS but reclassified as being pathogenic and being associated with autosomal dominant or autosomal recessive CMT2A. The final diagnosis for this patient was CMT2A with involvement of laryngeal nerve causing chronic neuropathic cough. His coughing spells were relatively treatment refractory to standard asthma inhalant medications, amitriptyline, and gabapentin.

Discussion

Neuropathic cough has been associated with a variety of hereditary, nutritional, infectious/post infectious, infiltrative, and iatrogenic causes that have been summarized in **Table 1.** In hereditary neuropathies, chronic cough is hypothesized to arise from vagal neuropathy with consequent autonomic dysfunction. This may include impaired vagal control of the distal oesophageal sphincter, promoting gastroesophageal reflux and causing reflux laryngitis, and secondary laryngeal irritation–induced cough.[3] Denervation hypersensitivity is another mechanism for neuropathic cough, whereby impaired sensory function of the superior and recurrent laryngeal branches of the vagal nerve, which form the afferent limb of the sensory cough pathway, lowers the threshold required to trigger coughing. Due to the length dependent nature of CMT, the recurrent laryngeal nerve is preferentially affected, making vocal cord paralysis a well-known cause of morbidity in advanced stages of CMT.[4]

Table 1. Causes of neuropathic cough

Type	Causes	Associated features
Nutritional	B12 deficiency	Small and large fibre sensory myeloneuropathy, macrocytosis
Infection/post infectious	Post viral vagal neuropathy	Recent viral infection, dry cough, throat paraesthesia
Genetic	CMT	Imbalance, chronic pain
	HSAN	Distal sensory loss, SNHL
	CANVAS	Ataxia, vestibular areflexia
Infiltrative	Neurofibroma in vagal nerve	Cutaneous neurofibromas, family history
	Amyloidosis/sarcoidosis	Small fibre neuropathy, other cranial neuropathies, heart failure
Traumatic/iatrogenic	Post intubation/surgical	Recent surgery/instrumentation
Structural	Mediastinal mass, cervical spine disease (C2-C5)	Smoking history, myelopathic findings or radicular pain

Abbreviations: CMT: Charcot-Marie-Tooth, HSAN: Hereditary Sensory Autonomic Neuropathy, SNHL: Sensory Neural Hearing Loss, CANVAS: Cerebellar Ataxia, Neuropathy, with Vestibular Areflexia Syndrome

In clinical practice, it is essential to systematically exclude common cardiac, pulmonary, and gastrointestinal causes of chronic cough while identifying features suggestive of neuropathic cough.[5] Characteristic features of cough hypersensitivity syndrome or neuropathic cough include: (i) a persistent or intermittent irritating sensation in the pharyngeal or laryngeal region; (ii) a globus or choking sensation in the throat or chest; and (iii) cough triggered by temperature changes, laughing, talking, or exposure to pungent smells or aerosols, although triggers may be absent.[6]

Attributable to shared mechanisms, including denervation hypersensitivity and

central reflex sensitization, neuropathic cough and neuropathic pain are treated using similar therapeutic approaches. Gabapentin and amitriptyline have been tried and tested in randomized clinical trials with promising results.[7]

This case highlights the importance of periodic re-evaluation of genetic testing results in cases with VUS. The initial testing identified VUS in multiple genes, including MFN2, the most common gene associated with CMT2. Five years later, this variant was reclassified as being pathogenic.

There were certain features in this case that did not fit the common phenotype of MFN2 related CMT2. Unlike the current case, motor weakness typically predominates over sensory impairment. Most affected individuals develop symptoms in the first or second decade of life, with foot drop being a common presenting feature. Concomitantly, MFN2 associated CMT2 has several atypical features apart from chronic cough which include upper motor signs like mild increased reflexes, increased tone, extensor plantar responses without a frank spastic gait, and cranial neuropathies leading to optic atrophy, trigeminal neuralgia, facial weakness, diaphragmatic weakness, and hoarse voice.[8-10]

Conclusions

Hereditary neuropathies are common and exhibit a broad spectrum of presentations. This case underscores the importance of maintaining diagnostic vigilance in identifying neuropathic cough as an atypical manifestation of hereditary neuropathies and in periodically re-evaluating genetic testing to achieve a definitive diagnosis.

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