A Potential Novel Variant of Hereditary Sensory Neuropathy in a 61-Year-Old Man With Cough-Induced Syncope and Vertebral Artery Dissection

To the Editor: A 61-year-old man with history of hereditary sensory neuropathy was admitted for severe coughing and sudden-onset worsening of chronic numbness in his extremities. He had a chronic cough of more than 30 years' duration, and his coughing occurred several times a day, often precipitated by fumes or eating. The cough was almost always accompanied by worsening of the chronic numbness and tingling in various extremities. After an episode of dizziness and syncope, he subsequently developed severe right neck pain and headache. Family history was notable for 2 sisters with hereditary sensory neuropathy with similar persistent lower extremity numbness and burning. The patient worked in road construction and thus was exposed to noxious fumes that exacerbated his cough.

Prior evaluation included nerve conduction studies that resulted in unobtainable sural and radial sensory responses, whereas median sensory responses had low amplitudes and normal distal latencies. Median and peroneal motor responses were normal. Findings on this study were consistent with a sensory neuropathy or axonal neuropathy. An extensive laboratory evaluation for acquired causes was negative; paraneoplastic work-up was also negative.

On examination of the patient, there was no evidence of sensorineural hearing loss or nystagmus. He had a length-dependent decrease to vibration, pinprick, and temperature sensation with intact proprioception. Romberg sign was positive. Laboratory values were essentially normal, including creatine kinase. Cardiac work-up and chest radiographic results were normal. Computed tomogaphy of the head showed no acute intracranial process. However, subsequent computed tomogaphic angiography revealed a right vertebral artery dissection. It was thought this was precipitated by the severe coughing spell.

After extensively ruling out common causes of syncope and cough, consideration of a mutation in the serine palmitoyltransferase gene (*SPTLC1*, formerly known as *HSN1*) was warranted. Serine palmitoyltransferase is a key enzyme in the production of sphingomyelin.[1] Deficiency or mutation of this important enzyme has been reported as a rare cause of autosomal dominant hereditary sensory neuropathy manifesting with peripheral sensory neuropathy, chronic cough, and syncope.[1-3] Mutation of *SPTLC1* leads to accumulation of ceramide, which precipitates neuronal cell degeneration and apoptosis, causing significant demyelination of axons of the ventral and dorsal roots of the spinal cord.[1] Clinically, this manifests as progressive lower limb sensory axonal neuropathy and distal muscle weakening and ulcerations.[1]

Even more rarely, *SPTLC1* in the form of distal sensory axonal deficits can present along with gastroesophageal reflux with adult onset of paroxysmal cough, which can lead to syncope. This constellation of symptoms constitutes a rare familial disorder characterized thus far in only a few case reports that include genetic analysis of a large Australian family.[3-5] The cough is attributed to denervation hypersensitivity of the upper airways and esophagus. The chromosome linkage is on 3p22-p24, which is thought to be a distinctly unique and novel variant of *SPTLC1*.[3] A study was also perfomed in 4 generations of a Japanese family that was discovered to have a motor neuropathy in addition to the sensory neuropathy with recurrent paroxysmal dry cough; other notable findings included fine postural tremors, muscle cramping with elevation of creatine kinase levels, and neurogenic bladder. Genetic testing in this family showed no evidence of linkage to 3p22-p24.[5]

We performed extensive genetic evaluation and testing of our patient and found no mutation of *SPTLC1*. Additional testing for *MPZ*, *RAB7A (*previously known as *RAB7*), *TRKA*, *NGF* (previously known as NGFB), *HSN2*, and Friedrich ataxia was also negative (Table). In the absence of mutations in any of these tested genes, it is likely that our patient had a novel, previously uncharacterized variant of hereditary sensory neuropathy that resulted in severe coughing, leading to syncope and vertebral artery dissection.

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TABLE. **Review of Genetic Tests Evaluated in 61-Year-Old Man, All of Which Were Negative**

	Explanation of gene name and function	Mutations and associated clinical symptoms
SPTLC1	Serine palmitoyltransferase 1 Mode of inheritance: autosomal dominant Chromosome location: 9q21-q22 Comprises one-half of the *SPTLC* heterodimer (with *SPTLC2*), which catalyzes condensation of serine and palmitoyl CoA, the initial step in sphingolipid synthesis	Mutations are associated with HSAN type I and degeneration of doral root ganglia Slow progression of disease, between 2nd and 4th decades of life Slow progression of disease, between 2nd and 4th decades of life Progressive lower limb sensory axonal neuropathy; distal muscle weakening and ulcerations Loss of sensation to pain and temperature, but vibration sense and proprioception are preserved Findings on electromyography may include electrical evidence of demyelination
MPZ	Myelin protein zero Mode of inheritance: autosomal dominant Chromosome location: 1q22 Protein abundant in the myelin sheath, required for myelin production and maintenance of structure	Mutations in *MPZ* have been associated with inherited demyelinating neuropathies including Charcot-Marie-Tooth disease type 1B (CMT1B), congenital hypomyelination, and Déjerine-Sottas disease; also with HSMN type II
RAB7	Endosomal protein Mode of inheritance: autosomal dominant	Mutations associated with sensory loss and mutilation Charcot-Marie-Tooth disease type 2B Leads to an ulcero-mutilating neuropathy
TRKA/NTRK1	Tyrosine kinase receptor A/neurotrophic tyrosine kinase receptor type I Mode of inheritance: autosomal recessive Chromosome location: 1q21-q22 *NTRK1* is the receptor kinase phosphorylated in response to high-affinity nerve growth factor	Mutations in this gene lead to HSAN IV (defective neural crest differentiation) or congenital insensitivity to pain with anhidrosis Onset in childhood Polyneuropathy, arthropathies, and autonomic dysfunction (anhidrosis and hyperthermia due to absence of innervation of sweat glands, decreased corneal sensation, hypolacrimia) Other symptoms include recurrent infections, prolonged wound healing, painless fractures, cognitive impairment/mental retardation, aggressive behavior, self-mutilation
NGFB	Nerve growth factor beta gene Mode of inheritance: autosomal recessive	Mutation in *NGFB* alters the nerve growth factor kinase receptor and prevents NGF-dependent neuronal growth Clinically similar to hereditary sensory and autonomic neuropathy type V Charcot arthropathy
HSN2	Hereditary sensory neuropathy 2 Mode of inheritance: autosomal recessive Chromosome location: 12p13.33 *HSN2* is located on an exon within the gene encoding WNK lysine deficient protein kinase 1 (*WNK1*)	Mutations lead to truncation of the HSN2 protein Onset of symptoms in infancy or early childhood The disease is characterized by upper and lower extremity neuropathy with numbness, absent deep tendon reflexes, diminished sensation to pain, temperature, and touch, but normal response to pressure and vibration Also involves skin (mostly foot) ulcerations Muscle bulk and strength are preserved

HSAN = hereditary sensory and autonomic neuropathy; HSMN = hereditary motor and sensory neuropathy.

CORRECTIONS

Incorrect time frame: In the article by Tosh et al entitled "Influenza Vaccines: From Surveillance Through Production to Protection," published in the March 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(3):257-273), the time frame was incorrect on page 267, lines 1 through 6, right-hand column. The sentence should read as follows: Because its safety in this population is uncertain, LAIV [live-attenuated influenza vaccine] is not currently recommended for use in people with asthma; a randomized trial found an increase in clinically relevant wheezing among those younger than 24 months in the **42 days** after receiving LAIV, regardless of whether they had asthma.[125]

Tosh et al also want to point out that this same trial found that the increase in medically wheezing was primarily seen in weeks 2 through 4 after vaccination.

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Inadvertent omission of information: In the article by Leise et al entitled "Patients Dismissed From the Hospital With a Diagnosis of Noncardiac Chest Pain: Cardiac Outcomes and Health Care Utilization, published in the April 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(4):323-330), grant support was inadvertently omitted. In a footnote on page 323, the following should have been added: **This study was made possible by the Rochester Epidemiology Project (grant No. R01-AR30582 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases).**

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Incorrect age: In the e-Residents' Clinic entitled "31-Year-Old Man With Fever, Palpitations, and Generalized Rash" by Mwirigi and Rodriguez-Porcel, which was published online-only with the April 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(4):e13-e16), the age of the patient in the first sentence after question No. 1 and the answer choices is incorrect. The sentence should read as follows: It would not be safe to send this **31**-year-old patient with a fever, rash, and third-degree heart block home without an appropriate work-up.

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