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A Sodium Channel Myotonia Presenting with Intermittent Dysphagia as a Manifestation of a Rare *SCN4A* Variant

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Abstract The voltage gated sodium channel *SCN4A* mutations account for non-dystrophic myotonia and include a heterogeneous group of conditions that include hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, and hypokalemic periodic paralysis type 2. This case report proposes that a rare variant p.Pro1629Leu in *SCN4A* can cause a skeletal muscle deficit with intermittent dysphagia.

Keywords *SCN4A* · Myotonia · Dysphagia

Introduction

Nondystrophic myotonia, defined as an abnormal muscle relaxation, has been attributed to multiple voltage-gated sodium channelopathies. *SCN4A*, which encodes the α -subunits of skeletal muscle sodium channels, is one of these channelopathy genes with sub-phenotypes including potassium-aggravated myotonia (PAM), hypokalemic or hyperkalemic periodic paralysis, and paramyotonia congenita. Patients with PAM, previously termed sodium channel myotonia, suffer symptoms characterized by spontaneous but intermittent potassium-induced weakness secondary to the inexcitability

of skeletal muscle fibers. PAM includes the following conditions: myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia, all of which share mutations on the *SCN4A* gene. Over 30 missense mutations have been reported with a phenotypic spectrum ranging from fatigue to paramyotonia (Kokunai et al. 2012). For example, PAM patients with G1306A mutation on the *SCN4A* gene suffer from “subclinical” myotonia, whereas those with G1306V mutation exhibit a severe myotonia. Here, we describe a rare variant in the *SCN4A* gene in a patient with intermittent dysphagia and acquired myasthenia gravis.

Case Report

We report the case of a 62 year-old female patient of Ashkenazi-Jewish ancestry who presented to the gastrointestinal clinic with symptoms of fatigue, lethargy, and anemia. She describes intermittent unilateral blurriness of vision, difficulty ambulating due to the sense of imbalance, and evidence of subacute cognitive decline with memory and concentration difficulties. In addition, the patient reported intermittent dysphagia after ingesting potassium-rich foods. The past medical history is significant for Hashimoto’s thyroiditis, controlled with thyroid supplement. The social history is negative for smoking or alcohol, and her family history is negative for neurological, autoimmune, and genetic disorders. On physical examination, the patient was noted to have eyelid weakness which led to a workup for myasthenia gravis. The patient had evidence of motor dystonia affecting the eyelids. The neurological examination demonstrated intact motor function, muscle tone, and strength in all four extremities; however, there was a mild decreased vibration at the toes. Slowed heel-knee-shin was exhibited; otherwise, the patient had a normal neurological exam. Her mini-mental status examination received a score of 22/30

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with loss of points for recall, serial 7's, and spatial awareness with intersecting pentagons. Because of the anemia and dysphagia, the patient underwent an upper endoscopy and was found to have atrophic gastritis by biopsy. The laboratory studies were significant for a B12 level of 332 after subcutaneous B12 repletion, serum gastrin 2075, and a positive parietal cell antibody. The magnetic resonance imaging (MRI) of the brain was significant for an incidental meningioma, which was stable on serial imaging.

Electromyography was significant for single fiber jitter study with a confirmation of myasthenia gravis; however, the patient had negative anti-MuSK antibodies. Medical therapy was deferred due to marginal symptoms of isolated fatigue and continued gastrointestinal (GI) discomfort with a history of multiple small bowel ulcers seen on past endoscopy. Extensive GI workup included grossly normal hydrogen breath test and octreotide scan. Upper endoscopy confirmed atrophic gastric mucosa consistent with atrophic gastritis with intestinal metaplasia on biopsy, in addition to post-bulbar ulcerations. The endoscopy revealed a lack of peristalsis of the proximal esophagus, the presence of a dilated proximal esophagus and a lack of coordinated antroduodenal contractility. Capsule endoscopy was significant for nonbleeding angiodysplasia and multiple small to medium sized ulcers in the proximal to distal small bowel, sparing the jejunum. The patient underwent a gastric emptying study wherein 1 mCi Tc-99 m sulfur colloid was ingested with half of a chicken sandwich and 4 oz. of apple juice. Planar images of the abdomen were obtained at 15-min intervals out to 90 min. Delayed gastric emptying was observed with only 18% of the meal emptying from the stomach at 90 min (A half emptying time of 90 min or less is considered normal for a solid meal). A side branch intraductal mucinous neoplasm (IPMN) was identified on endoscopic ultrasound, which remained stable in size of 3 mm on repeat ultrasounds. Further workup for Zollinger-Ellison syndrome was negative. Esophageal impedance manometry was performed which showed a lack of cricopharyngeal peristalsis.

In the setting of multiple autoimmune conditions and concern for underlying endocrinopathies, the patient was evaluated by medical genetics and underwent clinical exome sequencing at the UCLA Clinical Genomics Center (Fogel et al. 2014; Lee et al. 2014). A single heterozygous variant p.Pro1629Leu in the *SCN4A* gene was reported as a variant of uncertain significance (VUS) (Table 1). The variant is rarely observed in the population exome database (Exome Aggregation Consortium (ExAC)), Cambridge, MA (URL:

<http://exac.broadinstitute.org>) [accessed on 11/4/2015]) in 13 individuals as heterozygous (0.02%). Proline is highly conserved at this amino acid position across other species. However, because segregation analysis could not be performed in the absence of parents or other family members and the variant has not been reported in patients with similar conditions, the variant was reported as a VUS.

Discussion

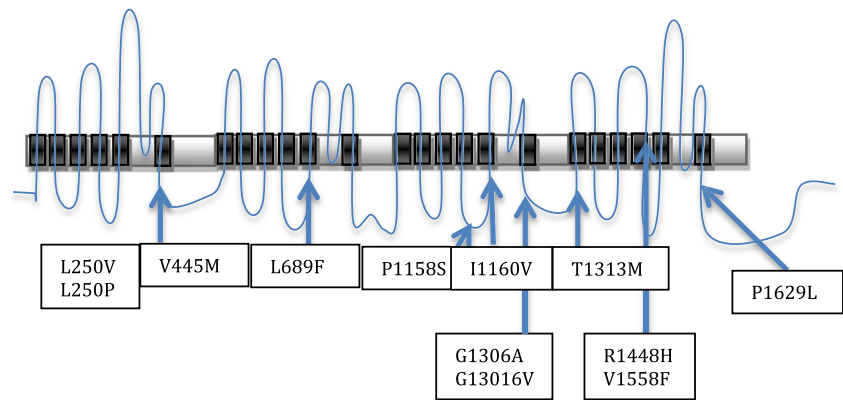
The amino acid sequence of the human *SCN4A* gene was deduced by Wang et al. (Wang et al. 1992). The *SCN4A* gene is localized to chromosome 17 (17q23.1-q25.3) and is closely linked to the growth hormone gene on 17q (Fontaine et al. 1990). Subsequently, the gene structure was determined to consist of 24 exons (McClatchey et al. 1992). The protein consists of 1836 residues and shows 93% sequence identity to the alpha subunit from rat adult skeletal muscle and 70% identity to the alpha subunit from other mammalian tissues (Fig. 1).

Mutations in the *SCN4A* gene are shown to be associated with a heterogeneous group of nondystrophic myotonias and include hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, and hypokalemic periodic paralysis type 2. These nondystrophic myotonias are relatively rare (incidence <1:1,000,000) conditions that result from mutations in the skeletal muscle sodium *SCN4A* channel. Although not life-threatening, these heterogeneous conditions can result in significant loss in the quality of life for these patients due to the fatigue and weakness (Wang et al. 1992). In one study, the authors demonstrated that among 34 patients with *SCN4A* mutations that had nondystrophic myotonia, there is a significant phenotypic overlap with mutations in other sodium and chloride channel genes, which has implications for both diagnosis and management (Trip et al. 2008). In this study, the authors identified facial stiffness, higher frequency of eye closure myotonia, and paradoxical myotonia in those patients with *SCN4A* variants. The mean age of diagnosis of *SCN4A* mutations was 46 years, and 100% of the patients reported white, non-Hispanic ethnicity. The most common presenting symptoms were stiffness, weakness, pain, and fatigue. The most common presenting signs included eye closure myotonia, grip myotonia, and episodic weakness triggered by cold or potassium-rich diet. Dysphagia was not reported to be present in this series. None of the patients with *SCN4A* mutations had the p.Pro1629Leu variant as our patient did. The most common mutation reported (32%) was a Thr1313Met

Table 1 *SCN4A* variant identified in the patient

Genomic position (hg19)	Zygosity	DNA change	Protein change	SIFT prediction	PolyPhen2 prediction
chr17: 62018756	Heterozygous	NM_000334.4: c.4886C > T	p.Pro1629Leu	Deleterious	Probably damaging

Fig. 1 Schematic representation of the SCN4A skeletal muscle sodium channel. Previous sites of known mutations are demonstrated for both paramyotonia congenital and sodium channel myotonia. The location of the mutation in this case report is shown as “P1629L”. Adapted from Ref. 7



mutation followed by Arg1448His (21%) and Gly1306Ala (15%). In another study, the authors demonstrated that a G1292D mutation results in a mutation near the intracellular face of the segment S6 in domain III of the SCN4A protein. This mutation and another one reported at V1293 L are near the intracellular mouth of the ion conduction pore, resulting in an impairment of fast activation and causing muscle hyperexcitability (Trivedi et al. 2014). A third study described 22 families with SCN4A mutations reported in the Netherlands (Trip et al. 2008). They discovered three novel mutations in SCN4A: L250 V; L250P; L689F. These mutations were distant from the location in our case report. In all of the probands with SCN4A mutations, there were clinical signs of myotonia especially involving the eyelids; however, none of the reported probands were reported to have dysphagia.

In summary, we report here a rare variant in the SCN4A skeletal muscle sodium channel gene in a patient who experienced ocular manifestations of myotonia, similar to other patients reported in the literature, but also presented with intermittent dysphagia. A plausible explanation is that the mutation noted in our patient affected the C terminal tail of the gene (P1629L) that resulted in only a partial loss of function. Confirmation of this would require in vitro or in vivo animal studies. Evaluation of the dysphagia by both esophageal endoscopy and esophageal motility study revealed an abnormal motility and coordination, so we suspect this symptom as well owed to the SCN4A mutation, thus potentially expanding the phenotype. There are limitations to our case report since other confirmatory cases with the same mutation could not be identified in the ExAC database and since 0.02% of the population has mutations in SCN4A and given that the incidence of the disease is less than one in a million. However, the symptoms of myotonia in the case reported here is subtle and manifested by a proximal cricopharyngeal motility disorder phenotype which can be discovered only after careful examination of the upper aerodigestive system using impedance manometry studies. Motility disorders involving the cricopharyngeus and upper esophagus also require a high index of suspicion because the scheme for performing esophageal manometry studies is mainly focused on the distal esophageal smooth muscle rather than

the proximal striated muscle. Our case report exhibits some signs of myasthenia gravis, which is included among the subtypes of PAM, and dysphagia can be a feature of that condition. In summary, we report a de novo mutation of the SCN4A gene with a negative family history and some characteristics of myotonia, including the development of dysphagia manifested by a lack of cricopharyngeal motility.

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