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Isolated vocal cord paralysis in two siblings with compound heterozygous variants in *MUSK*: Expanding the phenotypic spectrum

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Abstract

The congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders caused by perturbations in signal transduction at the neuromuscular junction. Defects in muscle, skeletal, receptor tyrosine kinase (MuSK) cause two distinct phenotypes: fetal akinesia with multiple congenital anomalies (Fetal akinesia deformation sequence [MIM:208150]) and early onset congenital myasthenia (myasthenic syndrome, congenital, 9, associated with acetylcholine receptor deficiency [MIM:616325]). Myasthenia due to MuSK deficiency has variable clinical features, ranging from a milder presentation of isolated late-onset proximal muscle weakness; to a severe presentation of prenatal-onset diffuse weakness, ophthalmoplegia, respiratory failure, and vocal cord paralysis (VCP). Here, we propose to expand the phenotypic spectrum for MuSK deficiency to include isolated VCP with the absence of other classical myasthenic symptoms. We evaluated two brothers who presented in the neonatal period with respiratory failure secondary to isolated VCP. Research-based exome sequencing revealed biallelic likely pathogenic variants in *MUSK* (MIM:601296). Both children had normal gross motor and fine motor development. One brother had speech delay, likely due to a combination of tracheostomy status and ankyloglossia. This case report suggests that CMS should be on the differential diagnosis for familial recurrence of VCP.

Keywords

congenital myasthenic syndromes; Dok-7 deficiency; MuSK deficiency; phenotypic expansion; vocal cord paralysis

1 | INTRODUCTION

The congenital myasthenic syndromes (CMS) are a broad group of disorders due to dysfunction of the proteins involved in signal transduction at the neuromuscular junction. To

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date, over 30 CMS disease genes have been identified (Engel, 2018). The severity, affected muscle groups, and age of onset vary across these genetic etiologies, but the vast majority of CMS present in the neonatal period or early in life with myasthenic symptoms, including fatigable muscle weakness, ptosis, and oculoparesis (Engel et al., 2015).

Muscle, skeletal receptor tyrosine kinase (MuSK) is a postsynaptic transmembrane protein that plays a crucial role in the creation of the postsynaptic scaffold (Ben Ammar et al., 2013). To our knowledge, 20 patients with biallelic loss-of-function variants in *MUSK* have been reported (Owen et al., 2018). All of these patients have presented with some combination of classical myasthenia symptoms, including weakness, neonatal hypotonia, oculoparesis, and respiratory failure. Congenital vocal cord paralysis (VCP) has been reported in CMS caused by *COLQ* and *DOK7* mutations as well as CMS caused by MuSK deficiency (Al-Shahoumi, et al., 2015; Chevessier et al., 2004; Giarrana et al., 2015; Jephson et al., 2010; Klein et al., 2013; Maggi et al., 2013). While congenital stridor or VCP has been reported in isolation in *DOK7*-related CMS, isolated VCP has not been reported in association with biallelic *MUSK* variants (Klein et al., 2013).

Here, we present two brothers of Asian origin who presented with VCP and feeding difficulty, without other symptoms of myasthenia. Research-based exome sequencing identified compound heterozygous likely pathogenic variants in *MUSK*, which were clinically confirmed. These patients represent an expansion of the phenotypic spectrum of MuSK deficiency, and raise the possibility that this CMS may not always present with classical symptoms of myasthenia.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Informed verbal consent to publish this report was obtained from the patients' mother.

2.2 | Patient 1

Patient 1 is an Asian male born full-term to a nonconsanguineous couple. At birth, he exhibited no respiratory distress, but subsequently developed stridor. Direct laryngoscopy diagnosed bilateral VCP in the neonatal period. As he was stable without respiratory support, he was discharged home. He presented back to medical attention at age 2 months, with worsened stridor, as well as failure to thrive and feeding intolerance, thought secondary to respiratory distress.

Initial examination was notable only for increased head lag for age. He otherwise had normal tone, strength, reflexes, eye movements, and facial expressions. There was no ptosis, oculoparesis, or fatigable weakness. Repeat direct laryngoscopy confirmed bilateral VCP.

He underwent cricoid split, laryngoplasty, and balloon dilation, which relieved the stridor and obviated the need for tracheostomy or extended mechanical ventilation beyond the perioperative period. Repeat laryngoscopy at 4 months of age revealed persistent bilateral VCP. Most recent flexible laryngoscopy at 15 months of age revealed bilateral vocal fold

paresis with some abduction. He continues to have stridor when active, crying, or ill, but breathes quietly when calm. Feeding difficulty resolved postsurgically, in the infancy period.

He met his early gross motor milestones on time, and began to walk independently at 13 months of age. His last examination with neurology was at 18 months of age, after confirmation of the molecular diagnosis. His facial movements were strong and symmetric, his muscle strength and deep tendon reflexes were normal throughout the body, and he had laxity of the bilateral ankles. Repetitive stimulation and stimulation single fiber electromyography (StimSFEMG) testing were not performed. He has not received medical therapy for myasthenia. He is now 22 months of age.

2.3 | Patient 2

Patient 2 is the older brother of Patient 1, also born full-term to the same nonconsanguineous couple. His course was more severe than that of his brother. At birth, he exhibited respiratory distress and severe stridor requiring intubation. Direct laryngoscopy revealed bilateral VCP. He failed extubation to noninvasive positive pressure ventilation, and thus underwent tracheostomy. He did not require mechanical ventilation after hospital discharge. Due to respiratory problems, he required enteral feedings in the neonatal period, but transitioned to full oral bottle feeding after tracheostomy.

His breathing improved with growth of the larynx, and he was decannulated at age 3 years 5 months. Flexible laryngoscopy at age 3 years 6 months revealed good vocal cord abduction.

He is growing and developing well. He met his early developmental milestones on time, walked independently at 13 months, learned well in preschool, and is currently in kindergarten. He has experienced speech delay and articulation problems, likely due to history of tracheostomy as well as ankyloglossia.

His last examination with neurology was at 5 years 9 months of age, after confirmation of molecular diagnosis. His examination was notable for no fatigability with upward gaze for 2 min, intact facial strength (able to elevate eyebrows equally, smile equally, and bury eyelashes), and normal deep tendon reflexes of patella, bicep, and brachioradialis. Strength was 4/5 throughout, possibly because of poor patient effort, and there was mild bilateral ankle laxity. Repetitive stimulation and StimSFEMG testing were not performed. He has not received medical therapy for myasthenia.

His medical history is notable for eosinophilic esophagitis, food allergy, asthma, and obstructive sleep apnea. His surgical history is notable for tracheostomy and subsequent decannulation, repair of tracheocutaneous fistula, tonsillectomy and adenoidectomy, and frenotomy for ankyloglossia. He is now 6 years of age.

2.4 | Genetic analysis

We performed exome sequencing on Patient 1 to identify the etiology of isolated bilateral VCP. The parents provided written consent, and all work was performed under a research protocol approved by the Institutional Review Board of the Children’s Hospital of Philadelphia. Variants previously reported in dbSNP, the 1,000 Genomes Project, and the

National Heart, Lung, and Blood Institute Exome Sequencing Project Exome Variant Server with a minor allele frequency >1% were excluded. Anticipating that synonymous variants are far less likely to be pathogenic, we focused our variant analysis primarily on nonsynonymous variants, nonsense variants, splice-acceptor and -donor site variants, and coding insertions/deletions (indels). Emphasis was placed on identifying homozygous, compound heterozygous, or X-linked variants.

3 | RESULTS

Exome sequencing followed by confirmatory Sanger sequencing identified compound heterozygous variants, c.2287G > A:p.A763T and c.2446C > T:p.R816X, in exon 15 of *MUSK* (MIM:601296; NM_005592.3) in both affected siblings. The c.2446C > T:p.R816X variant, which was rated likely pathogenic based on ACMG guidelines, was carried by the healthy mother. While the father is currently not available for testing, c.2287G > A:p.A763T is presumed to be paternally inherited, and was predicted to be deleterious by SIFT, PolyPhen-2, LRT, and MutationTaster. This variant resides in the tyrosine kinase domain of MuSK, similar to a majority of reported *MUSK* missense mutations, making it also likely pathogenic based on ACMG guidelines (Al-Shahoumi et al., 2015; Ben Ammar et al., 2013; Chevessier et al., 2004; Luan, Tian, & Cao, 2016; Maggi et al., 2013; Maselli et al., 2010). Both variants were present in the gnomAD dataset with a minor allele frequency of 8.165e-6 (c.2446C > T:p. R816X) and 1.01e-4 (c.2287G > A:p.A763T) without any homozygous state, but analysis of the 1,000 Genomes Project and our existing in-house dataset of more than 5,000 subjects did not reveal other occurrences of either variant or homozygous state for either variant.

4 | DISCUSSION

Our patients expand the number of reported individuals with biallelic *MUSK* mutations to 22. Both variants occur in exon 15 of the gene, and several other patients with MuSK deficiency had pathogenic variants in exon 15 of *MUSK*. Based on this evidence, we believe that the biallelic *MUSK* variants are the genetic etiology for our patients' isolated vocal cord palsy, despite the fact that they exhibit no other classical features of myasthenia.

With the advent of clinical exome sequencing, this diagnostic capability has expanded the phenotype of numerous previously characterized genetic conditions (Blumkin et al., 2014; Chang et al., 2018; Prada et al., 2014; Szafranski et al., 2016). In some cases, conditions with heterogeneous phenotypes are found to have new symptomatology that further diversifies the phenotype (Blumkin et al., 2014). In others, patients missing classical symptoms of known inherited disorders are nevertheless diagnosed with these disorders through exome sequencing, thus expanding the phenotypic spectrum in a milder direction (Prada et al., 2014). We feel that our familial case report represents a similar expansion of the phenotypic spectrum of MuSK deficiency to include isolated VCP without classical myasthenia symptoms. There is precedent for this in MuSK deficiency, when Owen et al. (2018) suggested that late-onset congenital myasthenia may represent a distinct, milder phenotype, with evidence of genotype–phenotype correlation.

Owen et al. posit that null alleles in *MUSK* predict a severe respiratory phenotype, and missense variants in the tyrosine kinase region predict a late-onset predominantly limb-girdle weakness. Our patients' mutations occur within the tyrosine kinase domain of the protein. One is a null allele, which has not been reported within this domain in affected patients. A number of other reported patients, both with and without respiratory involvement including VCP, have had mutations within the tyrosine kinase domain (Al-Shahoumi et al., 2015; Ben Ammar et al., 2013; Chevessier et al., 2004; Luan et al., 2016; Maggi et al., 2013; Maselli et al., 2010). There does not seem to be a clear correlation between location of the *MUSK* variant and presence of VCP. Due to our patients' mutations being located in the tyrosine kinase domain, as well as their young age, it is possible that they will develop fatigable proximal weakness in the second decade of life, like the patients described by Owen et al. However, none of the patients described by Owen et al. presented with VCP in the neonatal period, marking our patients' clinical course as distinct from these others'.

Our patients' neurological evaluation revealed mild bilateral ankle laxity in both brothers. This likely falls within the range of normal childhood joint laxity. Initial examination of Patient 1 revealed increased head lag for age, which may have been a subtle sign of the underlying diagnosis. The younger brother, examined by neurology at 18 months of age, could not cooperate for repetitive stimulation testing or sustained upward gaze. The older brother, examined by neurology at 5 years 9 months of age, exhibited 4/5 strength throughout the body, which may have reflected poor patient cooperation. Notably, his bulbar strength was intact. He, too, did not undergo repetitive stimulation, due to the young age. Neither child has undergone StimSFEMG, though this may be a consideration for future evaluation.

Both individuals in our report presented with feeding intolerance in addition to VCP. The feeding problems were attributed to the vocal fold paralysis, as feeding difficulty is a common comorbidity of laryngotracheal malformations. In fact, this may have been a sign of bulbar weakness, as combined VCP and feeding problems in the neonatal period have been reported in many individuals with *DOK7*-related congenital myasthenia. Notably, some children with *DOK7*-related CMS had feeding problems severe enough to require prolonged nasogastric feeding or gastrostomy, whereas our patients resumed normal oral feeding after correction of the underlying respiratory problem (Jephson et al., 2010; Klein et al., 2013). Nevertheless, our patients' presentation mirrors that of several patients with *DOK7*-related CMS, further underlining that patients with CMS can present with isolated VCP and feeding problems in the neonatal period. The index of suspicion for an underlying neuromuscular diagnosis should remain high in these clinical scenarios, especially as feeding problems are often attributed to laryngotracheal malformations.

Of note, the Dok-7 protein has been shown to interact with MuSK to activate it to form the postsynaptic apparatus, which is essential for neurotransmission (Okada et al., 2006). A report by Maselli et al. (2010) showed that in a patient with biallelic *MUSK* mutations of p.M605I and p.A727V, both variants caused moderate to severe impairment of MuSK interaction with Dok-7. This protein interaction may underlie the overlapping phenotypes of *DOK7*-related CMS patients with VCP and feeding difficulty, and our *MUSK*-related CMS

patients with VCP and feeding difficulty. Additionally, some patients with *DOK7*-related CMS, like our patients, met early motor milestones on time.

While most reported individuals with *MUSK*-related CMS presented with symptoms in the neonatal or toddler period, there have been reports of patients who presented with weakness as late as 18 years of age (Ben Ammar et al., 2013; Luan et al., 2016; Owen et al., 2018). However, individuals who had onset of symptoms in childhood or the second decade of life, did not exhibit VCP at birth. Conversely, individuals who exhibited VCP at birth, did not exhibit otherwise normal early motor development. Thus, our patients are unique in this respect. It is possible that both of the brothers will begin to exhibit fatigable weakness and other classical myasthenia symptoms later in life. They will be followed closely to monitor for such symptoms. Notably, both brothers have shown improvement or resolution in their VCP. As suggested in similar cases of *DOK7*-related CMS, this may be a reflection of fatigable laryngeal muscles or transient VCP (Jephson et al., 2010). In this report, we have presented a familial case of two brothers who presented with isolated VCP and associated feeding difficulty in the neonatal period. The feeding difficulty resolved upon treatment of the VCP, and both brothers exhibited otherwise normal gross motor development with no other signs of classical myasthenia. Exome sequencing revealed biallelic variants in *MUSK*, which has previously been associated with a CMS. Recent literature posits the possibility of a second, distinct phenotype of late-onset limb-girdle muscle weakness. We propose that isolated VCP with associated feeding difficulty is also a unique phenotype of MuSK deficiency, and this diagnosis should be considered in such cases, especially in familial presentations.

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