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TWO CASES OF CONGENITAL MYASTHENIC SYNDROME WITH VOCAL CORD PARALYSIS

Congenital myasthenic syndrome (CMS) typically presents within the first year of life with fluctuating and fatigable muscle weakness, often affecting ocular and bulbar muscles.¹ In spite of bulbar involvement, vocal cord paralysis (VCP) is an uncommon presentation of CMS,² and is most often seen in peripheral neuropathies such as *TRPV4* mutations.³ We report 2 cases of CMS with 2 novel mutations in which VCP was a major sign.

Case reports. *Case 1.* The male proband was born at term after an unremarkable pregnancy to consanguineous parents of Bangladeshi origin. Shortly after birth, he was hypotonic and stridorous and required intubation. ENT laryngoscopy examination on day 1 of life showed bilateral VCP that normalized a week later and returned the week following as unilateral VCP. A tracheostomy was done on day of life 26. He remained tachypneic and stridorous. At 3 months of age, variable and fatigable dysconjugate eye movements, bilateral ptosis, and mild facial diplegia were noted. A diagnosis of a congenital myasthenic syndrome was suspected and genetic testing was sent for a congenital myasthenic syndrome panel (Prevention Genetics, Marshfield, WI). A trial of pyridostigmine did not result in any improvement and the addition of 3,4-diaminopyridine led to minor improvements in facial movements. After the genetic testing came back positive for a *COLQ* mutation (see below), ephedrine was started and resulted in significant improvement. He became more alert, opening his eyes and moving his limbs more.

Genetic testing revealed an undocumented homozygous sequence variant in the *COLQ* gene (c.1183G>A) that led to the substitution of a highly conserved aspartic acid for asparagine at amino acid position 395 (p.D395N). The sequence variant was predicted to be “deleterious,” “probably damaging,” and “disease causing” by SIFT, PolyPhen2, and Mutation-Taster, respectively. Two nearby amino acid substitutions (p.Cys386Ser and p.Arg410Gln) are documented pathogenic (<http://www.LOVD.nl/COLQ>). There was an additional heterozygous variant identified in *MUSK* (c.2561G>A, p.G854Q) of high expected pathogenicity. Deletion/duplication

analysis on a custom designed comparative genomic hybridization platform did not reveal a deletion/duplication on the other allele.

Case 2. The female proband was born at 36 weeks gestation with hypotonia and respiratory distress. Mechanical ventilation was needed for 8 months followed by continuous positive airway pressure via tracheostomy until 18 months of age. Her condition remained relatively stable and she displayed mild global delay. At 8 years of age, she started having respiratory distress and nocturnal apnea. ENT laryngoscopy examination showed bilateral VCP and tracheostomy was completed. A history of easy fatigability and fluctuating respiratory distress raised the possibility of a congenital myasthenic syndrome. A trial of pyridostigmine mildly improved her symptoms, while 3,4-diaminopyridine resulted in a significant clinical improvement.

Whole exome sequencing completed through the Finding of Rare Disease Genes study Canada (FORGE) indicated compound heterozygosity for 2 *MUSK* mutations (c.79+2T>G and c.2158A>G). The disruption to the splice donor signal of intron 1 (rs200783529) is expected to be pathogenic. The other missense mutation led to a substitution of a highly conserved lysine for glutamic acid at position 720 (p.K720E). Parental testing confirmed that the mutations were in *trans* and the mutations were confirmed using Sanger sequencing (Prevention Genetics).

Discussion. Congenital VCP is the second most common cause of neonatal stridor and accounts for 10% of congenital laryngeal anomalies.⁴ It is rarely secondary to a neuromuscular disorder.⁵ The phenotypes of CMS are expanding with more cases diagnosed and with the discovery of new mutations. VCP has been reported as an early sign of CMS in the context of *DOK7* and *CHRNAE* mutations.⁶ Also, one member of the only 4 previously reported families with *MUSK* mutation had VCP.⁷ To our knowledge, no other cases of CMS with VCP have been reported in association with other CMS genes.

Patient 1 represents the first reported case of CMS and VCP due to synaptic basal lamina defects (*COLQ*). It is unclear if there is an added synergistic effect with the *MUSK* variant of uncertain clinical

significance also identified. If the *MUSK* variant was functioning in synergy with the *COLQ* variant, this would be the second reported patient with *MUSK*-related CMS with VCP, raising the possibility that VCP could be a feature of these gene mutations. Confirmation of this hypothesis will require further reports of *MUSK*-related CMS to determine the true prevalence.

Collectively, the above cases add novel mutation data to rare causes of CMS and emphasize that VCP and neonatal stridor should raise the suspicion of congenital myasthenic syndrome.

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