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Pantothenate Kinase-Associated Neurodegeneration Causing Paradoxical Vocal Fold Motion

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Summary: We report a patient with paradoxical vocal fold motion (PVFM) due to pantothenate kinase-associated neurodegeneration, a rare neurodegenerative disease and a subclass of neurodegeneration with brain iron accumulation disorders. PVFM is marked by normal vocal fold anatomy and physiology with intermittent adduction during the respiratory cycle. Many etiologies have been reported and include laryngeal hypersensitivity such as asthma and gastroesophageal reflux, functional disorders, and neurologic disorders such as focal respiratory dystonia. This case highlights the occasional association of PVFM with underlying neurologic disorders, especially those that disrupt autonomic functioning.

Key Words: Paradoxical vocal fold motion–Pantothenate kinase-associated neurodegeneration–Neurodegeneration with brain iron accumulation.

INTRODUCTION

Paradoxical vocal fold motion (PVFM) is a condition characterized by the inappropriate adduction of the true vocal folds during the inspiratory phase of respiration. Although PVFM primarily afflicts healthy persons, it can be a sign of underlying neurologic disorders such as central nervous system lesions.¹ Here, we report a patient with PVFM attributed to pantothenate kinase-associated neurodegeneration (PKAN), a subclass of disorders termed neurodegeneration with brain iron accumulation.² To our knowledge, PKAN as the underlying cause of PVFM has not been previously reported.

CASE REPORT

A 32-year-old female patient suffering from PKAN with a pantothenate kinase 2 (PANK2) mutation was referred to our laryngology clinic with an 8-month history of intermittent stridor. The stridor worsened during activity or anxiety, never occurred during sleep, and was not associated with respiratory distress, syncope, or cyanosis. Manifestations of her PKAN included cognitive impairment, ataxia, and progressive dysarthria. She had undergone a therapeutic pallidotomy as a teenager. On examination, a loud inspiratory stridor occurred occasionally, lasting less than 1 minute, and without evident distress. Voice quality was normal although with severe impairment of speech and language. Laryngeal examination captured a period of paradoxical vocal fold adduction during inspiration, producing audible stridor (Figure 1). This occurred for at most a few respiratory cycles before abducting completely. Generalized mild laryngeal edema was also observed. Normal vocal fold adduction occurred during voluntary phonation. The patient was diagnosed with PVFM due to her neurologic dysfunction from PKAN. Because this patient's respiratory dysfunction was not causing functional impairment, her family elected expectant observation.

However, the future possibilities of botulinum toxin injection or a tracheostomy for disorganized ventilatory drive were considered.

DISCUSSION

PKAN is a rare genetic disorder characterized by brain iron accumulation chiefly in the basal ganglia.³ There are a number of mutations leading to PKAN, most commonly a mutation in PANK2, the rate-limiting enzyme in mitochondrial coenzyme A biosynthesis. Therefore, pathways that use this enzyme are expected to be defective. Such metabolic pathways include citric acid cycle, amino acid synthesis, β -oxidation, steroid biosynthesis, and heme biosynthesis.^{2–4} Most cases are transmitted with autosomal recessive inheritance, although uncommon mutations may occur with autosomal dominant inheritance, and penetrance is variable. Classic PKAN patients present in the first decade of life with dystonia, dysarthria, rigidity, bulbar dysfunction, and neuropsychiatric features. Limb spasticity, pigmentary retinal degeneration, and spinal deformities have also been reported.³ This constellation of symptoms has warranted its classification as a “parkinsonism-plus” syndrome, which is capable of causing neurologic manifestations in the larynx.⁵ Patients typically expire before age 20 years, most commonly due to malnutrition and pneumonia. Atypical PKAN patients present in the second or third decade of life and decline more slowly.²

Laryngeal dyskinesia or PVFM has not been specifically reported in PKAN patients, although it is a feature of numerous other neurologic disorders including central nervous system lesions, movement disorders, and autonomic dysfunction.^{1,6,7} Clinical presentation does vary with etiology; for example, multiple system atrophy is associated with nocturnal PVFM while cerebral palsy produces stridor only during wakefulness, as in this patient.^{8,9} Other prevalent causes of PVFM specifically include laryngeal hypersensitivity from such diseases such as asthma or gastroesophageal reflux, focal respiratory dystonia, and anxiety or psychosocial disorders.⁶ Diagnosis of PVFM requires confirmation of otherwise normal vocal fold mobility, as unilateral or bilateral VF paralysis is a more common disorder that may produce similar stridor. Laryngomalacia, a structural laryngeal collapse without inappropriate vocal fold adduction, should also be excluded.

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FIGURE 1. Supraglottic hyperconstriction during inspiration causing vibration of arytenoid cartilage mucosa.

Treatment of PVFM typically includes respiratory retraining exercises for those patients able to comprehend and cooperate with such therapy.⁶ An interactive therapy approach is not feasible for many patients with neurologic etiologies, such as in this case. Even for those patients who may be capable of therapy, no data have been published regarding the efficacy of respiratory therapy on PVFM of organic neurologic cause.¹⁰ Botulinum toxin injection into the thyroarytenoid muscles is a common treatment for PVFM recalcitrant to speech therapy, but again little analysis of the technique has been published since its original description for adductor breathing dystonia.¹¹ For more advanced stages, CPAP, tracheostomy, and laryngeal surgery have proven efficacious.¹²

CONCLUSION

We present a patient with an inherited neurodegenerative disorder, PKAN, exhibiting intermittent PVFM. This case underscores that laryngeal dyskinesia can be a sign of a movement disorder, an association that was recognized in early descriptions of PVFM.^{1,8} As diagnosis of PVFM has increased, focus

has been on the more prevalent “primary” form of the disease. Given the dramatically different clinical presentations of primary and secondary PVFM, it is unclear how much of our current understanding is applicable to neurogenic “secondary” PVFM.

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