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Familial congenital bilateral vocal fold paralysis: A novel gene translocation☆

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ABSTRACT

Objectives: True vocal fold (TVF) paralysis is a common cause of neonatal stridor and airway obstruction, though bilateral TVF paralysis is seen less frequently. Rare cases of familial congenital TVF paralysis have been described with implied genetic origin, but few genetic abnormalities have been discovered to date. The purpose of this study is to describe a novel chromosomal translocation responsible for congenital bilateral TVF immobility.
Methods: The charts of three patients were retrospectively reviewed: a 35 year-old woman and her two children. The mother had bilateral TVF paralysis at birth requiring tracheotomy. Her oldest child had a similar presentation at birth and also required tracheotomy, while the younger child had laryngomalacia without TVF paralysis. Standard karyotype analysis was done using samples from all three patients and the parents of the mother, to assess whether a chromosomal abnormality was responsible.
Results: Karyotype analysis revealed the same balanced translocation between chromosomes 5 and 14, *t*(5;14) (p15.3, q11.2) in the mother and her two daughters. No other genetic abnormalities were identified. Neither maternal grandparent had the translocation, which appeared to be a spontaneous mutation in the mother with autosomal dominant inheritance and variable penetrance.
Conclusions: A novel chromosomal translocation was identified that appears to be responsible for familial congenital bilateral TVF paralysis. While there are other reports of genetic abnormalities responsible for this condition, we believe this is the first describing this particular translocation.

1. Introduction

Congenital true vocal fold (TVF) paralysis is a well documented phenomenon. While unilateral TVF paralysis is one of the most common causes of neonatal stridor, congenital bilateral TVF paralysis is a relatively rare cause of airway obstruction in the infant. Whether it presents as an isolated finding or as part of a complex set of abnormalities in multiple organ systems, it has a profound impact on a newborn's health. One recent systematic review found that 59% of patients with congenital bilateral TVF paralysis required tracheotomy, although 61% of patients did see some degree of functional improvement [1].

A number of different etiologies for congenital TVF paralysis have been described including neurologic injury, iatrogenic insult, and idiopathic causes. Once the airway is secured and stabilized, patients with congenital TVF paralysis typically undergo magnetic resonance imaging scan and other diagnostic testing to rule out central etiologies, as correction of a central lesion (e.g., Chiari malformation) can potentially lead to improvement in vocal fold function. In patients without a central etiology, the cause of TVF paralysis often remains unknown. However, in certain patients the occurrence of familial propagation of TVF paralysis implies a genetic origin.

Genetic causes of TVF paralysis represent an appealing area of study, as advance knowledge that a newborn is at risk for this condition can lead to potentially life-saving preparedness for securing a compromised airway as well as allow for improved prenatal counseling for the parents. Also, if other congenital anomalies

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should be found to be associated with a given case of TVF paralysis, these can have significant implications for other family members. To date, few such genetic abnormalities have been discovered.

We present a case series of familial congenital bilateral TVF paralysis, with genetic analysis identifying a unique chromosomal abnormality. A comprehensive literature review is also conducted to summarize the presently known genetic abnormalities causing this condition.

2. Methods

2.1. Chart review and genetic analysis

Institutional review board approval was obtained from Weill Cornell Medical College for this study. Charts and stored digital images were reviewed for pertinent patient history. After informed consent was given, blood samples were obtained from the three patients as well as the maternal grandparents. Karyotype studies of the patients' blood specimens were performed using standard cytogenetic techniques and analyzed with G banding at the 550 to 750 band level.

2.2. Literature review

Articles from 1965 to 2014 were searched by means of a Medline database query performed using the search string "(vocal cord OR vocal fold OR laryngeal) AND (paralysis OR palsy OR immobility) AND (genetic OR chromosome OR chromosomal OR mutation)". A total of 117 articles were initially returned. Of these, 82 were excluded as they were not original clinical reports on genetic or chromosomal abnormalities resulting in TVF paralysis. This left a total of 35 articles, the contents of which are summarized in Table 1. Of these 35 articles, only 15 described true congenital TVF paralysis, with neonatal onset and either a known chromosomal or genetic cause. The remaining articles detailed childhood or adult-onset TVF paralysis resulting from a genetic derangement.

2.3. Case review and Karyotype analysis

Patient no. 1: A 35 year old female presented with a history of traumatic delivery, as well as significant stridor and cyanosis at birth. She was intubated shortly after birth and unable to be weaned from mechanical ventilation. A tracheotomy was performed at 4 days of age. She was examined by an otolaryngologist and noted to have bilateral TVF paralysis, which was initially thought to be iatrogenic. She later developed tracheal stenosis and underwent multiple operations including placement of a T-tube at age 4. She was eventually decannulated at age 6. She currently has a paralyzed right vocal fold and has limited exercise tolerance (Fig. 1). She has no other medical conditions.

Patient no. 2: A 16 month old female, daughter of Patient 1, was delivered at 35 weeks gestational age. At birth she was noted to have a nuchal cord that was easily removed, but she continued to have bluish discoloration. She had significant stridor with her initial breaths. She was intubated at birth and noted to have bilateral vocal fold paralysis. Tracheotomy was performed at two weeks of age after failed extubation. At 1 year of age, the patient failed a decannulation attempt. Flexible laryngoscopy was significant for bilateral vocal fold hypomobility with inadequate

Table 1
Summary of comprehensive literature review of articles detailing genetic or chromosomal causes of TVF paralysis.

Year	Authors	Syndrome	Chromosomal alteration	Gene affected	Type of TVF paralysis	Age of onset
2014	Peterson	Congenital clubfoot and other anomalies	17q23.1–q23.2	TBX4	Bilateral	Neonatal
2014	Suh	Hereditary sensory and autonomic neuropathy Type 1	–	SPTLC1	Bilateral	Adult
2013	Gandomi	Mandibulofacial dysostosis with microcephaly	17q21.31	EFTUD2	Unilateral	Neonatal
2013, 2010	Klein, Jephson	Congenital myasthenic syndrome	–	DOK7	Bilateral	Neonatal
2013	Chew	Novel syndrome	–	TUBB3	Bilateral	Neonatal
2013	Leshinsky-Silver	Hereditary neuralgic amyotrophy	–	SEPT9	Bilateral	Neonatal
2013	Hida	Alexander syndrome	–	GFAP	Bilateral	Adult
2013, 2010	Fiorillo, Chen, Zimon	Charcot–Marie–Tooth 2	–	TRPV4	Both	Childhood
2012	Leopold	22q11 microdeletion syndrome	22q11	–	Unilateral	Neonatal
2012, 2011, 2005, 2004	Origone, Hermann, Fukae, Tan	Amyotrophic lateral sclerosis	–	SOD1	Bilateral	Adult
2011	Nouioua	Charcot–Marie–Tooth 4	–	PRX, MTMR2	Not described	Childhood
2010	Li	Charcot–Marie–Tooth X	–	GJB1	Both	Adult
2010	Benson	Charcot–Marie–Tooth 1, 1b, 2	–	PRX, NEFL, MPZ	Both	Adult
2009	Moroni	Charcot–Marie–Tooth 4a	–	GDAP1	Unilateral	Childhood
2008, 2001	Dick, McEntegart	Distal hereditary motor neuropathy	2q14.2	–	Both	Childhood
2008, 2003	Sevilla, Sevilla	Charcot–Marie–Tooth 2	–	GDAP1	Both	Adult
2005	McEntegart	Hereditary motor sensory neuropathy	12q23–24	–	Bilateral	Childhood
2004	Stojkovic	Charcot–Marie–Tooth 4a	8q21.1	GDAP1	Not described	Childhood
2003	Berkowitz	Robinow syndrome, 22q deletion	22q	–	Bilateral adductor	Neonatal
2003	Vaux	Williams syndrome	7q11.23	ELN	Bilateral	Neonatal
2002	Raza	–	Paracentric inversion of chromosome 13	–	Bilateral	Neonatal
2002	Santoro	Charcot–Marie–Tooth 2c	–	–	Bilateral	Adult
2002	Kovach	Charcot–Marie–Tooth 1, 1b, 2	17p11.2–12	PMP22	Bilateral	Neonatal
2001	Hahn	Congenital hypomyelination neuropathy	–	–	Bilateral	Neonatal
2001	Manaligod	–	6q16	–	Bilateral	Neonatal
2001	Berkowitz	Trisomy 21, 22q deletion	14;18 rearrangement, 5;11 transposition, trisomy 21, 22q deletion	–	Bilateral	Neonatal
1978	Mace	–	6p21?	HLA?, GLO?	Bilateral adductor	Neonatal, adult