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Association of airway abnormalities with 22q11.2 deletion syndrome

Rosalba Sacca [a, b, 1], Karen B. Zur [c, d], T. Blaine Crowley [b], Elaine H. Zackai [b, e], Kathleen D. Valverde [a], Donna M. McDonald-McGinn [b, e, *]

[a] Genetic Counseling Master's Program, Arcadia University, Glenside, PA, USA
[b] 22q and You and Clinical Genetics Centers, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[c] Pediatric Voice Program and The Center for Pediatric Airway Disorders, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[d] Department of Otolaryngology: Head & Neck Surgery, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[e] Department of Pediatrics, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Introduction: 22q11.2 deletion syndrome (22q11.2DS) presents with complex but variable symptoms, including cardiac, immune, palatal, endocrine, cognitive, and psychiatric issues. However, an association of 22q11.2DS with structural airway abnormalities has not been formally described. The aim of this study was to document the frequency of this association.

Methods: We retrospectively reviewed medical records of patients with 22q11.2DS evaluated in the 22q and You Center at the Children's Hospital of Philadelphia between 1999 and 2015 referred to otolaryngology for an airway assessment. Type of airway abnormality and presence of comorbidities, such as congenital heart disease, tracheostomy, and association with prenatal symptomatology such as polyhydramnios, were noted.

Results: Of the 104 patients who underwent an otolaryngology procedure (microlaryngoscopy or bronchoscopy), 71% (n = 74) had airway abnormalities. Patients with airway abnormalities ranged in age from 5 months to 37 years, with similar prevalence among males and females. Observed airway abnormalities included tracheomalacia (36%), subglottic stenosis (28%), laryngomalacia (26%), glottic web (21%), and bronchomalacia (16%). Most patients with airway abnormalities (91%) had an associated congenital heart defect, with ventricular septal defect and Tetralogy of Fallot being the most prevalent. Importantly, 30% of patients required a tracheostomy, and overall polyhydramnios was noted in 16% of pregnancies.

Conclusion: Airway abnormalities are a common feature of 22q11.2DS, leading to substantial morbidity, particularly when combined with complex cardiac disease. Polyhydramnios may be an important prenatal clue to both the diagnosis of 22q11.2DS and airway anomalies. Postnatal assessment of airway structure and function among patients with 22q11.2DS is an important component of overall evaluation and will help guide long-term management.

1. Introduction

22q11.2 deletion syndrome (22q11.2DS), now known to be etiologically associated in the vast majority of cases with DiGeroge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, and Cayler Cardiofacial syndrome, as well as a subset of patients with Opitz G/BBB syndrome, is the most common microdeletion syndrome with an estimated prevalence of ~1:4000 children; however, recent prenatal reports have identified a 22q11.2 deletion in ~1:1000 unselected fetuses [1] perhaps reflecting the well documented broad phenotypic variability [2]. Chromosome 22q11.2 deletions typically result from *de novo* non-homologous meiotic recombination, although ~10% of cases are familial [3,4]. Approximately 85% of individuals diagnosed with 22q11.2DS have a common recurrent 3-Mb deletion encompassing about 50 functional genes. The remaining 15% have an "atypical nested" deletion within the common 3-Mb deletion region.

* Corresponding author. The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA.
E-mail addresses: rosalba_sacca@dfci.harvard.edu (R. Sacca), mcginn@email.chop.edu (D.M. McDonald-McGinn).
[1] Present address: Rosalba Sacca, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215.

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22q11.2DS presents clinically as a complex multisystem set of symptoms that vary widely, even within families [3] often including some combination of congenital heart disease (CHD), palatal abnormalities such as velopharyngeal incompetence, immunodeficiency, gastrointestinal dysfunction such as gastroesophageal reflux disease, endocrine abnormalities including hypocalcemia, growth hormone deficiency and autoimmune thyroid disease, genitourinary anomalies such as renal agenesis and hypospadias, thrombocytopenia, conductive and sensorineural hearing loss occasionally with cochlear abnormalities, developmental delay, learning disabilities, and variable behavioral differences including Attention Deficit Hyperactivity Disorder (ADHD), autism, anxiety, and psychiatric illness, specifically schizophrenia [2,4–6]. Some but not all patients have a recognizable pattern of dysmorphic craniofacial features most often including hooded eyelids, a bulbous nasal tip with hypoplastic alae nasi, and auricular anomalies including protuberant and cupped ears with attached lobes and helical differences with microtia, anotia, and preauricular pits/tags observed less frequently.

As approximately three-quarters of patients with 22q11.2DS have cardiovascular, immune, and/or palatal abnormalities, these features have been well described in the literature, together with clear management guidelines [4,7]. In contrast, structural airway abnormalities are generally not included in these descriptions and are rarely discussed in the literature.

Congenital airway abnormalities include structural changes in the upper or lower respiratory tract. Upper airway abnormalities may be diagnosed as a result of stridor, respiratory distress, or failure to thrive [8,9]. The extant literature on 22q11.2DS and airway abnormalities includes descriptive case studies and chart reviews involving limited numbers of patients ranging from 1 to 19 individuals. Reported abnormalities have included tracheoesophageal fistula (TEF), reduced number of tracheal rings, laryngomalacia, tracheomalacia, and bronchomalacia but even within the largest study, descriptions of specific airway abnormalities was limited [10–15].

Airway abnormalities in patients with 22q11.2DS can result in significant morbidity and some mortality, especially in combination with complex CHD. Assessing the prevalence of airway abnormalities in 22q11.2DS will help guide patient management and minimize future respiratory complications. Accordingly, we sought to document the frequency of the association between 22q11.2DS and airway abnormalities. This objective was achieved by evaluating a large, well-characterized patient population within a multidisciplinary clinic that focuses on clinical management of children with 22q11.2DS.

2. Methods

The study was conducted within the 22q and You Center at The Children's Hospital of Philadelphia (CHOP) under IRB Protocol 07-005352. We retrospectively reviewed the medical records of patients with 22q11.2DS who were evaluated at CHOP between 1999 and 2015 and referred to otolaryngology for an airway assessment. The study population included only patients with a confirmed 22q11.2 microdeletion using standard laboratory methodologies including fluorescence *in-situ* hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (CGH), or SNP microarray analysis. Evaluation within the 22q and You Center, housed within the Division of Human Genetics at CHOP, includes multidisciplinary examination by numerous subspecialists generally including but not limited to genetics, otolaryngology, speech pathology, audiology, plastic surgery, cardiology, immunology, endocrinology, gastroenterology,

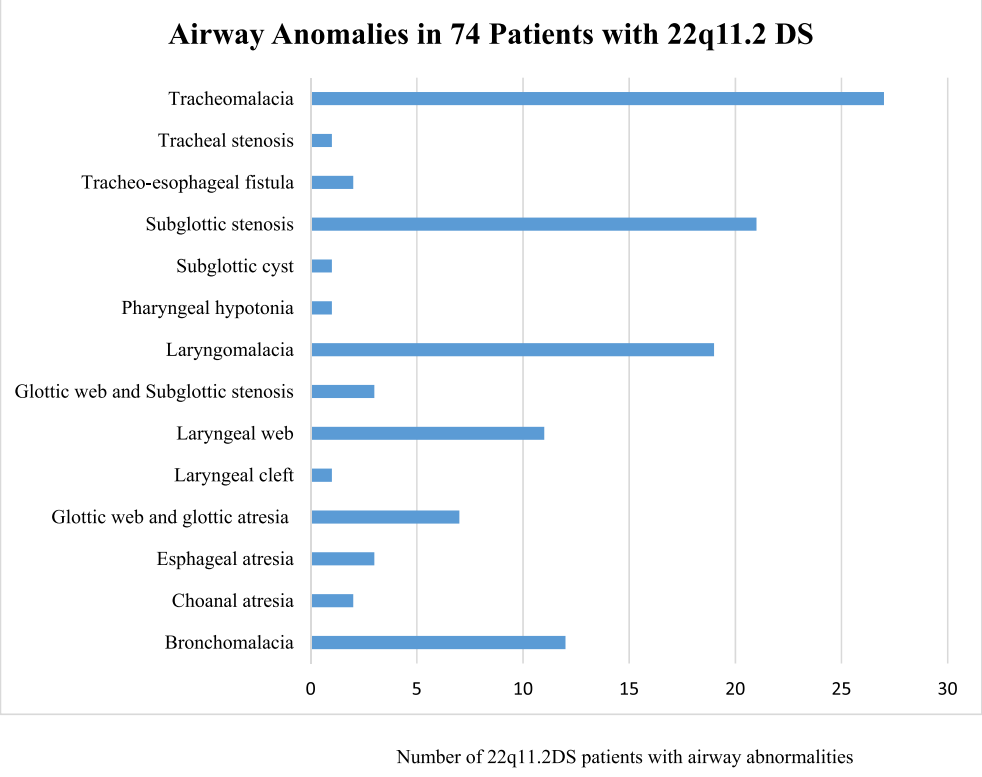

Fig. 1. Airway anomalies in 74 patients with 22q11.2DS. Evaluation included examination by a pediatric otolaryngologist +/− visualization procedures such as microlaryngoscopy and bronchoscopy.
Number of 22q11.2DS patients with airway abnormalities.