Structural Airway Anomalies in Patients with DiGeorge Syndrome: A Current Review

Robert Y. Huang, MD, and Nina L. Shapiro, MD

DiGeorge Syndrome is a genetic disorder characterized by either absence or hypoplasia of the thymus and the parathyroid glands. Patients with this syndrome also have a high incidence of cardiovascular malformations and facial dysmorphism. Structural airway anomalies have also been described, albeit infrequently. Tracheoesophageal fistula, short trachea with reduced numbers of tracheal rings, abnormal thyroid cartilage, laryngomalacia, tracheomalacia, and bronchomalacia have been recognized in these patients. We review all previously reported patients with DiGeorge syndrome and lower airway anomalies. In addition, we present 2 patients with DiGeorge syndrome who were each found to have an aberrant right tracheal bronchus. Structural airway anomalies can be a cause of morbidity and mortality in patients with DiGeorge syndrome. Prompt, thorough evaluation of the upper and lower airway in these patients is essential.

(*Editorial Comment:* The authors report 2 children with DiGeorge Syndrome who present with aberrant tracheal bronchi.)

DiGeorge syndrome is a disorder with a broad spectrum of clinical expression and varying severity. Although the syndrome primarily involves the thymus and parathyroids, other organs can also be affected. Congenital cardiac malformations and facial dysmorphism are frequently associated with DiGeorge syndrome.[1-3] Other commonly seen abnormalities in DiGeorge syndrome include thyroid agenesis, esophageal atresia, gastroesophageal reflux, failure to thrive, respiratory failure, and hydronephrosis. The head and neck manifestations in DiGeorge patients are also well recognized. These include abnormalities of the external ear, middle ear and inner ear, as well as upper airway anomalies such as cleft lip and palate, short philtrum, and choanal atresia.[1,2]

Cardiopulmonary failure is not uncommon in DiGeorge patients, particularly in the setting of complex heart disease. Despite the fact that many patients suffer from respiratory insufficiency or failure, structural airway anomalies have been rarely described. Tracheoesophageal fistula, short trachea with reduced numbers of tracheal rings, abnormal thyroid cartilage, laryngomalacia, tracheomalacia, and bronchomalacia have been recognized in these patients.[4-9] All previous reported anomalies of the structural airway in DiGeorge patients are summarized. Moreover, 2 cases of tracheal bronchus in patients with DiGeorge syndrome are presented to show the wide spectrum of structural airway anomalies seen with this disorder.

DIGEORGE SYNDROME

Congenital absence of thymus and parathyroids were first reported in 1959.[1,2] It was initially termed III-IV pharyngeal pouch syndrome because of the common embryologic origin of the affected structures.[1] In 1965, Angelo DiGeorge described the association of thymic aplasia, congenital hypoparathyroidism, and facial anomalies in 3 infants.[1,2] Since then, the association of congenital hypopara-

From the Department of Surgery, Division of Head and Neck Surgery, UCLA School of Medicine, Los Angeles, CA.
Presented at the Meeting of the Southern California Chapter of the American College of Surgeons, January 23, 1999, Santa Barbara, CA.
Address reprint requests to Nina L. Shapiro, MD, Division of Head and Neck Surgery, UCLA School of Medicine, 10833 Le Conte Ave, Room 62-158 CHS, Los Angeles, CA 90095-1624.

0196-0709/00/2105-0008$10.00
doi:10.1053/ajot.2000.16166

thyroidism with thymic aplasia became referred to as ''DiGeorge syndrome.''[1]

Most cases of DiGeorge syndrome occur sporadically, but autosomal recessive and autosomal dominant inheritance have also been documented. Various chromosomal aberrations have been reported, including deletion of chromosome 22q11 or 10p13.[1-3] Coloboma (of eyes), hearing deficit, choanal atresia, retardation of growth, genital defects (male only), and endocardial cushion defect (CHARGE) association may also be present.[4] The incidence of DiGeorge syndrome is estimated to be approximately 1 in 5,000 live births.[2]

The pathophysiology involves an embryologic defect in the 3rd and 4th pharyngeal pouch development from which the parathyroid and thymus normally evolve.[1-9] The embryologic event may affect not only the 3rd and 4th branchial pouches but also the 4th, 5th, and 6th branchial arches, thereby resulting in a contiguous field defect.[5] The etiology of this embryologic defect, however, is unclear and is perhaps heterogeneous.[3] Because the embryologic defects are not well understood, the extent of the phenotypic manifestation of these defects remains unclear.[6] Clinical features associated with DiGeorge syndrome continue to evolve.

A broad spectrum of severity is seen with DiGeorge syndrome and is related to the amount of thymic and parathyroid tissue that is present. Lischner[7] was the first to categorize DiGeorge syndrome as ''complete'' and ''incomplete.''[1,◦] Complete DiGeorge syndrome was designated as total thymic and parathyroid aplasia.[1,8] Partial DiGeorge syndrome indicates presence of some thymic or parathyroid tissue. Patients with the complete forms of the syndrome have a poor prognosis attributable to severe hypocalcemia and immune deficiency.[3,6]

The wide clinical variability of DiGeorge syndrome has been well recognized. Malformations of other structures derived from the 3rd and 4th branchial pouches can occur concurrently. Congenital cardiac malformations and facial dysmorphism are particularly associated with DiGeorge Syndrome. Musculoskeletal, gastrointestinal, urogenital, and developmental anomalies may also be seen (Table 1).[1-3]

TABLE 1. Findings Commonly Associated with DiGeorge Syndrome[1-3]

Organ/System	Findings
Parathyroids	Hypocalcemia
Thymus	Defective cell-mediated immunity with increased susceptibility to infection
Cardiovascular anomalies	Interrupted aortic arch
	Persistent truncus arteriosus
	Tetralogy of Fallot
	Double aortic arch
	Endocardial cushion defects
Craniofacial anomalies	Microcephaly
	Micrognathia
	Hypertelorism
	Short palpebral fissures
	Broad nasal bridge
	Short philtrum
	Cleft palate or bifid uvula
	Choanal atresia
	Abnormalities of the external ear (deep-set, small, malformed ears, atresia)
	Abnormalities of the middle ear
	Absence of malleus, incus, stapes
	Small facial nerve
	Absence of the stapedial muscle
	Absence of the oval window
	Atresia of the tympanic cavity
	Abnormalities of the inner ear
	Absence of the horizontal semicircular canal
	Hypoplastic seventh and eighth CN
	CNS malformations
Other abnormalities	Failure to thrive
	Mental retardation
	Absent thyroid lobe
	Esophageal atresia
	Gastroesophageal reflux disease
	Meckel diverticulum
	Imperforate anus
	Urinary malformations
	Hydronephrosis

STRUCTURAL AIRWAY ANOMALIES

Structural airway anomalies in DiGeorge syndrome were first described in 1968. Dische[9] presented a neonate with DiGeorge syndrome, tracheoesophageal fistula, esophageal atresia, and choanal atresia. This infant died at the 4th day of life shortly after a cardiac ballooning procedure.

Sein and colleagues[8] examined tracheal

anatomy in 14 patients with DiGeorge syndrome. Of the 14 patients, there were 6 specimens with tracheas permitting ring counts. The number of tracheal rings in all 6 patients was low, ranging from 13 to 16 rings (14.7 ± 0.9) compared with that of a control series of 17 patients that ranged from 16.5 to 19.5 (17.5 ± 1.4). In addition, 7 of the 14 patients with DiGeorge syndrome had some degree of extrinsic tracheal compression. These tracheal compressions were mild and had not produced stridor or other respiratory difficulties associated with tracheal obstruction.[8]

Wells et al[5] analyzed laryngeal anatomy in patients with DiGeorge syndrome. They compared the larynges of 17 patients who had DiGeorge syndrome with those of 69 normal infants. DiGeorge patients were noted to have small thyroid cartilages with increased anterior angle and abnormally short superior cornu. The epiglottis in all of these children was normal.[5] It was not reported whether any of the 17 patients had clinically significant airway obstruction secondary to their laryngeal abnormalities.

Muller[6] described the signs and symptoms in 16 patients with DiGeorge syndrome. One neonate with complete DiGeorge syndrome had laryngomalacia and required a tracheotomy. Another neonate with the partial form of the syndrome had cricopharyngeal dysfunction.[6]

Markert and colleagues[4] presented 2 patients with DiGeorge syndrome. Both patients had recurrent respiratory difficulties. One patient had an abnormal larynx with a normal tracheobronchial tree. There was a leftward torsion of the epiglottis that obstructed the glottis. A tracheotomy bypassed the airway abnormality. The second patient was noted to have laryngomalacia, right laryngeal fullness, moderate tracheomalacia, anterior fullness to the carina, and moderate right bronchomalacia to the segmental level. Despite placement of a tracheotomy, the patient later died of sepsis and respiratory failure secondary to lower airway anomalies.[4]

Deerojanawong and colleagues[10] examined the pulmonary manifestations in 19 children with DiGeorge syndrome. Bronchomalacia was present in 4 of 19 children. In children with DiGeorge syndrome, bronchomalacia with recurrent infection was an important cause of morbidity and mortality. Immunologic suppression secondary to T-cell deficiency in the setting of bronchopulmonary disease placed these children at even higher risk for severe infection. All patients who had bronchomalacia had recurrent or persistent respiratory tract infections that, in association with their complex heart disease and immunocompromised state, contributed to their death.[10]

Two patients with DiGeorge syndrome seen at our institution were also found to have structural airway anomalies. The first case is that of a male DiGeorge infant who required multiple intubations for respiratory distress. Direct laryngoscopy and bronchoscopy showed moderate extrinsic collapse of the left mainstem bronchus, which was likely related to his cardiac disease. There was an early takeoff of the right upper lobe consistent with an aberrant tracheal bronchus. This tracheal bronchus was probed with the suction catheter and appeared to be a blind pouch. The patient developed progressive respiratory insufficiency secondary to pulmonary hypertension and pulmonary edema. He eventually progressed to respiratory failure at 7 months of age and subsequently died of cardiopulmonary failure at 8 months of age.

The second case is that of a male infant with DiGeorge syndrome who developed recurrent episodes of apnea, bradycardia, and desaturation requiring intermittent intubation and mechanical ventilation. On direct laryngoscopy and tracheobronchoscopy, he was noted to have an aberrant right tracheal bronchus emanating from the posterolateral right tracheal wall (Fig 1). Pulmonary evaluation showed bronchopulmonary dysplasia, restrictive lung disease, and reactive airway disease. He eventually underwent a tracheotomy for long-term ventilatory support.

DISCUSSION

The above case reports and previous studies of DiGeorge syndrome have documented that structural airway abnormalities can extend from the supraglottis to the segmental bronchi. Table 2 summarizes all previous reported anomalies of the structural airway. Although great vessel and cardiac malformation may lead to extrinsic compression of the tracheobronchial tree, the pathogenesis of intrinsic

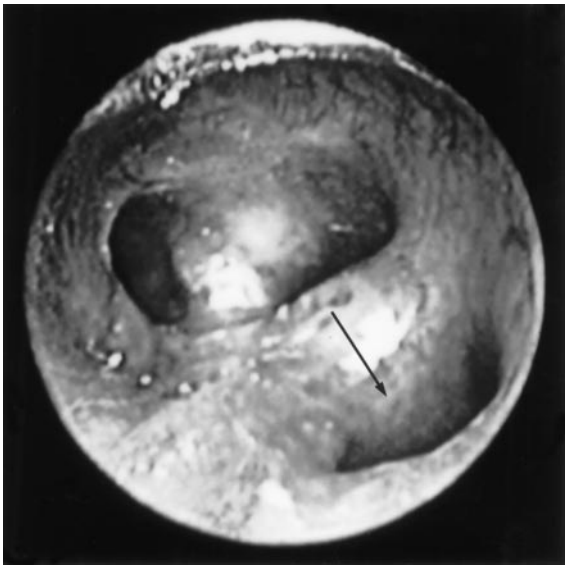

Fig 1. Endoscopic photograph from the bronchoscopy in patient 2 with aberrant right tracheal bronchus (arrow).

structural anomalies in DiGeorge syndrome, such as a shortened trachea and tracheal bronchus, is unclear.

The larynx is predominantly a derivative of the 4th branchial arch.[5] Given that the primary defects associated with DiGeorge syndrome lie within the 3rd and 4th pharyngeal pouches, laryngeal deformities can simultaneously occur because of the proximity of the 4th pouch and 4th arch.[5] Sein and colleagues[8] proposed that abnormal cardiogenesis and angiogenesis with compromised blood supply to the region of the 3rd and 4th pharyngeal arches may play a role in the pathogenesis of the short trachea. Similarly, Wells et al[5] have suggested that this syndrome involves not only the 3rd and 4th branchial pouches, but also derivatives of the 4th to 6th branchial arches as a contiguous field defect. The short trachea and tracheal bronchus in DiGeorge syndrome therefore showed that the affected field may involve midline pharyngeal derivatives as well as those of the lateral branchial arches and pouches.[5]

Both patients in our series had complete DiGeorge syndrome and underwent rigid tracheobronchial examination for respiratory distress. A thorough evaluation of the airway in both patients showed an aberrant right tracheal bronchus. The location of the tracheal bronchus in both cases was above the carina on the right lateral wall. Under endoscopic visualization, the lumen of the anomalous bronchus was noted to be incomplete and did not serve the upper lobe. It was not associated with tracheal stenosis and was not complicated by infection. Presence of a tracheal bronchus did not significantly contribute to the patients' respiratory insufficiencies; their respiratory failure resulted from bronchopulmonary dysplasia and congenital pulmonary vascular hypoplasia.

Tracheal bronchus is an anomalous condition with an incidence ranging between 0.1% and 5%.[11] It may occur in conjunction with other anomalies, including Down syndrome, cystic lung lesions, and cardiovascular malformations.[11] It presents almost exclusively on the right side, approximately 2 cm above the carina. It usually does not cause airway symptomatology and is often diagnosed incidentally. Some patients with an aberrant tracheal bronchus may have a hypofunctional right upper lobe, predisposing them to right upper lobe pneumonia. Lobectomy may be indicated in these cases.[11]

TABLE 2. Laryngeal and Tracheobronchial Anomalies in DiGeorge Syndrome

Authors	Number of Patients	Structural Airway Abnormalities
Dische[9]	1	Tracheoesophageal fistula
Sein et al[8]	14 patients (6 tracheal specimens)	Reduced number of tracheal rings Shortened trachea Tracheal compression
Wells et al[5]	17	Small thyroid cartilages Increased anterior angle Short superior cornu
Muller et al[6]	2	Laryngomalacia
Markert et al[4]	2	Abnormal epiglottis in patient 1 Laryngomalacia, tracheomalacia, and bronchomalacia in patient 2
Deerojanawong et al[10]	19	Bronchomalacia Recurrent pulmonary infections
Our cases	2	Tracheal Bronchus

These 2 cases are the first reports of aberrant tracheal bronchus in patients with DiGeorge syndrome. In both patients, the tracheal bronchi did not contribute to airway compromise and did not require direct treatment. Tracheal bronchus may need to be added to the continually evolving spectrum of phenotypic expression that defines DiGeorge syndrome.

CONCLUSION

Because the underlying embryonic defect in DiGeorge syndrome is still unclear and is likely heterogeneous, the extent of the phenotypic expression of this event remains manifold.[6] The manifestation of DiGeorge syndrome is continuously being redefined. Our reports of tracheal bronchus will add to the list of phenotypic expressions.

Although rarely reported in the literature, laryngeal and tracheobronchial anomalies are not uncommon findings in the DiGeorge patient population. It appears that many of these structural anomalies do not contribute to airway symptoms and, as a result, most patients did not undergo a thorough visualization of the lower airway. Therefore, the incidence of lower airway anomalies may be underreported. Some structural airway anomalies are more clinically significant. Bronchomalacia in the setting of complex cardiac disease can lead to severe morbidity and mortality. This clearly becomes even more evident in the immunocompromised patient. It is important to be aware of the various airway anomalies associated with DiGeorge syndrome. Prompt, thorough evaluation is necessary in any patient with DiGeorge syndrome who is having respiratory difficulties. Early visualization of the airway to determine the extent of airway abnormalities can facilitate early intervention and therapy.

REFERENCES

1. Demczuk S, Aurias A: DiGeorge Syndrome and related syndromes associated with 22q11.2 deletions. Ann Genet 38:59-76, 1995

2. Thomas JA, Graham JM: Chromosome 22q11 Deletion Syndrome: An update and review for the primary pediatrician. Clin Pediatr 36:253-266, 1997

3. Gorlin RJ, Cohen MM, Levin LS (eds): Syndromes of the Head and Neck. New York, NY, Oxford, 1990

4. Markert ML, Majure M, Harville TO, et al: Severe laryngomalacia and bronchomalacia in DiGeorge syndrome and CHARGE association. Pediatr Pulmonal 24:364-369, 1997

5. Wells TR, Landing BH, Galliani CA, et al: Abnormal growth of the thyroid cartilage in the DiGeorge syndrome. Pediatr Pathol 6:209-225, 1986

6. Muller W, Peter HH, Wilken M, et al: The DiGeorge syndrome. I. Clinical evaluation and course of partial and complete forms of the syndrome. Eur J Pediatr 147:496-502, 1988

7. Lischner HW: DiGeorge Syndrome. J Pediatr 81: 1042, 1972

8. Sein K, Wells TR, Landing BH: Short Trachea, with reduced number of cartilage rings—a hitherto unrecognized feature of DiGeorge syndrome. Pediatr Pathol 4:81-88, 1985

9. Dische MR: Lymphoid tissue and associated congenital malformations in thymic agenesis. Arch Pathol 86:312-316, 1968

10. Deerojanawong J, Chang AB, Eng PA, et al: Pulmonary diseases in children with severe combined immune deficiency and DiGeorge syndrome. Pediatr Pulm 24:324-330, 1997

11. Barat M, Konrad HR: Tracheal bronchus. Am J Otolaryngol 8:118-122, 1987