Tracheal Anomalies in Pfeiffer Syndrome

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Objective: To determine the types and frequency of airway anomalies in patients with Pfeiffer syndrome.

Design: Retrospective case series.

Setting: Academic tertiary care pediatric hospital.

Participants: Eleven patients with Pfeiffer syndrome, 6 of whom were severely affected, were identified. All were included in the study.

Main Outcome Measures: Presence of tracheal anomalies, need for tracheotomy, and length of life.

Results: The 6 severely affected patients had mutations in genes that code for fibroblast growth factor receptor 2 (S351C [3 patients]; C342S [2 patients]; and W290C [1 patient]). Five of these patients were diagnosed during bronchoscopy or tracheotomy as having a congenital tracheal cartilaginous sleeve. In 1 patient, supportive care was withdrawn at 2 weeks of life, and the patient died. The remaining 5 patients required tracheotomy because of severe upper airway obstruction. Three of these patients died (at ages 9 months and 7 and 15 years). Two are still alive at ages 23 and 18 months.

Conclusions: Patients with Pfeiffer syndrome manifest significant airway pathologic conditions. Upper airway obstruction is related to midface hypoplasia and secondary nasal obstruction. Tracheal anomalies have been infrequently reported.

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TRACHEAL CARTILAGINOUS sleeve (TCS) is an airway malformation in which distinct tracheal rings cannot be identified. In the place of normal cartilaginous arches, a continuous segment of cartilage extends from below the subglottis to the carina or, possibly, the mainstem bronchi. This rare malformation is associated with several of the craniosynostosis syndromes, most notably Apert, Crouzon, and Pfeiffer syndromes. In patients with Pfeiffer syndrome and TCS, the prognosis is poor, because of airway complications and the other significant multiorgan system anomalies.

Patients with Pfeiffer syndrome and TCS require tracheotomy, most frequently to treat obstructive sleep apnea that results from midface hypoplasia, choanal stenosis, and macroglossia. The rigidity of the trachea makes appropriate sizing of tracheostomy appliances difficult and may lead to increased formation of granulation tissue. Diagnosis of TCS in patients with Pfeiffer syndrome can alert physicians to the need for vigilant surveillance of the airway to prevent complications related to granulation tissue. The diagnosis of TCS is also a key piece of information that can aid in counseling of families regarding prognosis and quality of life.

METHODS

A retrospective medical chart review of 11 patients with Pfeiffer syndrome was performed at The Children’s Hospital of Philadelphia. Of these patients, 6 were considered to be severely affected, based on multiorgan system involvement and genetic testing or chromosomal analysis. Operative reports from tracheotomy and bronchoscopy procedures were reviewed, as well as inpatient hospital records, outpatient office records, and autopsy reports, when available. Data collected included date of birth, date of tracheotomy, and date of death (if applicable). Tracheal anomalies and other dysmorphicologic conditions were identified. Speech and swallowing...
deficits were recorded. Finally, when available, information regarding prenatal care and birth history was recorded.

RESULTS

Of the 6 severely affected patients, all had mutations in genes that code for fibroblast growth factor receptor 2 (FGFR2). Three patients (patients 1, 2, and 6) had S351C mutations, 2 (patients 4 and 5) had C342S mutations, and 1 (patient 3) had a W290C mutation. There were 4 boys and 2 girls. Four patients (patients 1, 2, 3, and 6) are deceased, with a mean age of death of 6.5 years. Two patients are still alive, patient 4 (at age 23 months) and patient 5 (at age 18 months). Four patients (patients 1, 2, 3, and 6) were diagnosed as having hydrocephalus and required ventriculoperitoneal shunting, and 2 patients (patients 1 and 2) manifested severe developmental delay and seizure disorders. Five patients (patients 1, 2, 3, and 6) had external auditory canal stenosis or atresia, and 3 (patients 2, 3, and 4) had documented hearing loss. All of the patients initially had strong cries, but speech development was affected in all patients. Hearing loss, developmental delay, and eventual need for tracheotomy likely contributed. In all patients, the prenatal courses were uneventful. In 1 patient (patient 6), hydrocephalus and absence of the corpus callosum were noted on a prenatal ultrasonogram (Table 1).

Tracheal cartilaginous sleeve was diagnosed in 5 of 6 patients (patients 1, 3, 4, 5, and 6). Diagnosis was made intraoperatively during tracheotomy, bronchoscopically, or at autopsy. Although not diagnosed as having TCS, patient 2 had tracheal stenosis and after undergoing tracheotomy had significant problems with recurrent formation of granulation tissue suprastomal and below the end of the tracheostomy tube. Rereview of video recordings taken during surveillance bronchoscopy reveals significant granulation tissue throughout the trachea, and normal tracheal rings are unidentifiable. This patient is deceased, and an autopsy was not performed. Of the 5 patients diagnosed as having TCS, 2 patients also had tracheal stenosis and 3 had short tracheas. Three patients (patients 1, 4, and 5) with TCS underwent tracheotomy. The 2 patients who did not undergo tracheotomy died. Supportive care was withdrawn from patient 6, and he died at age 16 days. Patient 3 was known to have a TCS and was having respiratory difficulty in the face of an upper respiratory tract infection. The patient died at home of respiratory failure at 9 months of age. Of the 3 patients with TCS who underwent tracheotomy, patients 4 and 5 are still alive. Patient 1 died just before age 16 years (Table 2).

COMMENT

Pfeiffer syndrome was originally described in 1964 as a disorder that combined craniosynostosis, midface hypoplasia with a beaked nasal tip, ocular proptosis, and medially deviated great toes and thumbs. The original report describes an autosomal dominant inheritance pattern. Since the original report, the disorder is better understood and includes multiple other anomalies. In 1993, Cohen classified patients with Pfeiffer syndrome into 3 groups and later added that there is overlap between the groups. Type I includes patients with mild expression of the classic findings. These patients are able to reproduce and pass the gene mutation to offspring in an autosomal dominant pattern. Types II and III are more severely affected, manifesting severe ocular proptosis and midface hypoplasia. Type II includes the cloverleaf skull deformity, whereas type III does not. Patients with types II and III are at increased risk of

Table 1. Head and Neck Manifestations

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Cloverleaf Skull</th>
<th>EAC</th>
<th>Choanae</th>
<th>Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/almost 16 y*</td>
<td>No</td>
<td>B/l stenosis</td>
<td>Normal</td>
<td>Oral and G-tube</td>
</tr>
<tr>
<td>2/F/9½ y*</td>
<td>No</td>
<td>B/l stenosis</td>
<td>Stenosis</td>
<td>G-tube</td>
</tr>
<tr>
<td>3/F/9 mo*</td>
<td>No</td>
<td>Right atresia</td>
<td>Stenosis</td>
<td>Oral and G-tube</td>
</tr>
<tr>
<td>4/M/23 mo</td>
<td>Yes</td>
<td>B/l stenosis</td>
<td>Normal</td>
<td>Jejunostomy tube</td>
</tr>
<tr>
<td>5/M/16 mo</td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Oral</td>
</tr>
<tr>
<td>6/M/16 d*</td>
<td>No</td>
<td>B/l stenosis</td>
<td>Atresia</td>
<td>Nasogastric tube</td>
</tr>
</tbody>
</table>

Abbreviations: B/l, bilateral; EAC, external auditory canal; G-tube, gastrostomy tube. *
Deceased.

Table 2. Tracheal Findings and Cause of Death

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Tracheotomy, mo</th>
<th>Tracheal Sleeve</th>
<th>Tracheal Stenosis</th>
<th>Short Trachea</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Support withdrawn resulting in respiratory failure</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Respiratory failure following upper respiratory tract infection</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Support withdrawn resulting in respiratory failure</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
neurodevelopmental abnormalities and have a shortened life expectancy. Because patients with types II and III do not reach reproductive age, these subtypes are the result of spontaneous mutations.

The understanding of Pfeiffer syndrome has increased over the last decade with respect to phenotype and genotype. Mutations in FGFR1 and FGFR2 are responsible for the disease. Multiple point mutations and splice mutations have been described, and while there is phenotypic heterogeneity, information with respect to genotype can assist in predicting clinical course. Of the 11 patients we originally identified in our study, 6 were severely affected. In all of these patients, there were significant airway anomalies. All patients had severe midface hypoplasia, and 3 had choanal stenosis or atresia. These upper airway abnormalities resulted in feeding difficulties or sleep apnea in all severely affected patients. Four patients underwent tracheotomy to overcome the apnea and feeding difficulties. The 2 patients who did not undergo tracheotomy had the shortest life spans. Although tracheotomy has aided in extending the life of patients with severe manifestations of Pfeiffer syndrome, tracheal pathologic conditions, which we found to be universal in our series, further complicate their course.

Tracheal cartilaginous sleeve is a rare malformation that is associated with the craniosynostosis syndromes. Tracheal cartilaginous sleeve may be diagnosed bronchoscopically by the conspicuous absence of tracheal rings, by direct visualization of the trachea during tracheotomy, or at autopsy. The length of the sleeve may vary from 5 rings to beyond the primary bronchi. The sleeve may be circumferential, or there may be posterior membranous septum (Figures 1, 2, and 3). The res-
piratory motion of the trachea, when viewed bronchoscopically, is also abnormal. In patients with a circumferential TCS, there is a paucity of tracheal movement with respiration, and it may appear rigid. In patients with a membranous septum, the trachea may fold in on itself or appear to tubulate with respiration. The trachea may be narrow or short, as was the case in 3 or 4 of our patients. The abnormal tracheal dimensions make appropriate sizing of tracheostomy tubes difficult, and patients may be at greater risk of formation of granulation tissue. In patient 2, we cannot confirm the diagnosis of TCS, but the patient developed massive amounts of granulation tissue refractory to all medical and surgical interventions (Figure 4).

The exact physiologic effect of TCS on airway fluid mechanics has not been elucidated, but tracheal sleeve is suspected to interfere with clearance of secretions and passive airway immunity.8 Postmortem histopathologic examination of the trachea in patient 3 demonstrated mucosal ulceration, a marked inflammatory infiltrate, and abnormally located mucinous glands (Figure 5 and Figure 6). The significance of these findings is unknown. The potential for TCS, especially the circumferential form, to react to local irritation and injury may be analogous to that of the cricoid cartilage. Furthermore, the potential for TCS to grow with patients is unknown. If these abnormal airways cannot enlarge commensurate with patient growth, patients may outgrow their airways, leading to premature death.

Treatment of tracheal anomalies associated with Pfeiffer syndrome is patient-specific. Tracheotomy has been the mainstay of airway management in this patient population and may extend the life span. Appropriate sizing of tracheotomy appliances, vigilant tracheostomy care, and frequent bronchoscopy and excision of granulation tissue are required to avoid tracheotomy-related death.9 Maximum treatment of laryngotraheal reflux disease is also recommended. In patients with very short segments of TCS, excision with end-to-end anastomosis has been described, but very short segments of TCS are uncommon.7 Longer segments of TCS may be treated with slide tracheoplasty,10 but with high morbidity and mortality. Tracheal cartilaginous sleeve portends premature death in essentially all patients, with a mean age of death of younger than 3 years.7

CONCLUSIONS

Tracheal anomalies associated with severe cases of Pfeiffer syndrome were identified universally in our study population, with 5 of 6 patients diagnosed as having TCS. To our knowledge, this is the first report of the frequency of tracheal anomalies, particularly TCS, associated with severe cases of Pfeiffer syndrome. A high index of suspicion must be maintained by clinicians in the airway evaluation of patients with Pfeiffer syndrome to diagnose tracheal anomalies and treat them appropriately.
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REFERENCES