Presence of 22q11 Deletion in Postadenoidectomy Velopharyngeal Insufficiency

Jonathan A. Perkins, DO; Kathleen Sie, MD; Steven Gray, MD

Background: Velopharyngeal insufficiency is an uncommon complication of adenoidectomy. Persistent velopharyngeal insufficiency following adenoidectomy (VIA) may occur in association with an unrecognized syndrome, such as velocardiofacial syndrome (VCFS). Although the diagnosis of VCFS is primarily a clinical one, a test has been developed to identify the underlying chromosomal abnormality, ie, deletion of 22q11.

Objective: To describe characteristics and occurrence of the 22q11 deletion in a population with VIA.

Setting: Three tertiary referral centers.

Design: Retrospective case series of 23 patients with VIA who required intervention and had follow-up for more than 1 year. These patients' medical records were reviewed for indications for adenoidectomy, the presence of 22q11 deletion and whether a 22q11 deletion test was obtained, phenotypic evidence for VCFS, presence of a submucous cleft palate, velopharyngeal closure pattern, and type of speech intervention.

Results: Of the 23 patients, 9 underwent adenoidectomy for otitis media, 9 for obstructive sleep symptoms, and 5 for sinusitis therapy. Fourteen of the 23 patients were tested for a 22q11 deletion. Of these 14 patients, 9 had a 22q11 deletion with 5 having phenotypic evidence for VCFS. Six of the 23 patients had a submucous cleft palate, 2 of whom had a 22q11 deletion.

Conclusions: Although VIA is uncommon, its occurrence should alert the otolaryngologist to the possibility of an underlying syndrome diagnosis. The 22q11 deletion test is beneficial in diagnosing patients with genotypic, but not phenotypic, VCFS in this population. In tested subjects of our patient population, 28% (4 patients) had the genotype for VCFS, without clinical evidence of VCFS.

PATIENTS AND METHODS

A retrospective chart review was conducted at Madigan Army Medical Center, Tacoma, Wash, Children's Hospital and Medical Center, Seattle, Wash, and Primary Childrens Medical Center, University of Utah, Salt Lake City, to identify patients with VIA referred to the otolaryngology clinic. Inclusion criteria were VIA that required intervention, age younger than 15 years at the time of presentation, and follow-up of at least 1 year. Exclusion criteria were known complete palatal cleft prior to adenoidectomy and other known craniofacial syndromes besides VCFS. The medical records were evaluated for the following data: patient age, type of initial procedure (adenoidectomy vs tonsillectomy and adenoidectomy), reasons for the adenoidectomy, phenotypic presence of VCFS, presence of 22q11 deletion, whether a FISH test for 22q11 deletion was obtained, presence of a submucous cleft palate, presence of associated anomalies (ie, developmental delay, chronic ear disease, sinusosal disease, etc), type of velopharyngeal evaluation and closure pattern, severity of VPI, and type of speech intervention. Velopharyngeal closure patterns were assessed as sagittal, coronal, circular, and circular with the presence of a Passavant ridge. The severity of VPI was rated as mild, moderate, and severe. Twenty-three patients met inclusion criteria.

Statistical analysis was descriptive.

RESULTS

The average age at presentation for evaluation of VIA of our study population was 5.75 years (range, 2-14 years). Five of the 23 patients were girls. The average duration between adenoidectomy and presentation for VIA evaluation was 22 months (range, 2-118 months). Initial surgery was an adenoidectomy in 8 patients and adenotonsillectomy in 15. Indications for surgery were otitis media (9 patients), sinusitis (5 patients), and obstructive sleep symptoms (9 patients). Phenotypic manifestation of VCFS (ie, congenital cardiac defects, abnormal facies, development delay) was present in 5 patients and absent in 18; 1 of those with phenotypic evidence VCFS and 5 of those without phenotypic evidence of VCFS had submucous cleft palate. Table 2 summarizes the results of 22q11 deletion testing.

Associated systemic conditions were found in our patient population. Developmental delay was present in 9 of the 23 patients, 8 of whom had the 22q11 deletion. Chronic ear disease was present in 9 of the 23 patients, with 3 of them requiring mastoidectomies. Two of these 3 patients had the 22q11 deletion. Nasal symptoms were present in 8 of the 23 patients, with 5 of them giving a history of nasal regurgitation. Of these 5 patients, 3 had the 22q11 deletion. Cardiac anomalies were present in

<table>
<thead>
<tr>
<th>Table 1. Common Clinical Features of Velocardiofacial Syndrome</th>
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<tr>
<td>Cleft of secondary palate                                       Learning disability</td>
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<tr>
<td>Retroglossia                                                    Conductive hearing loss</td>
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<tr>
<td>Vertical maxillary excess                                      Hypotonia</td>
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<tr>
<td>Prominent nose                                                  Obstructive sleep apnea</td>
</tr>
<tr>
<td>Auricular anomalies                                             Psychosis/schizophrenia</td>
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<tr>
<td>Deficient malar region                                          Hypoplastic adenoid tissue</td>
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<td>Structural heart anomalies                                      Hypocalcemia</td>
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This is because of the genetic heterogeneity of this chromosome deletion. Consequently, it is possible to have phenotypic VCFS (ie, abnormal facies, conotruncal cardiac defects, developmental delay, and submucous cleft palate) without the 22q11 deletion. The significance of the 22q11 deletion being present in the absence of phenotypic evidence for a clinical syndrome is still being determined. Critical regions within this area on chromosome 22 are being identified that will further increase diagnostic accuracy and eliminate this current discrepancy between phenotype and genotype. The ability to diagnose a syndrome that involves the head and neck, such as VCFS, with genetic analysis alone is important. Chromosomal anomalies have multisystem involvements that have a wide spectrum of clinical manifestations. The presence of the 22q11 deletion in a patient with VPI of any etiology would allow early intervention in all aspects of that patient's life, particularly when VCFS is also present.

The goal of this study was to determine the utility of fluorescent in situ hybridization (FISH) testing for the 22q11 deletion in children with VIA.

niofacial syndrome may remain undiagnosed due to subtle physical examination findings and variable clinical presentation. Recently, deletions of band 11 on the long arm of chromosome 22 have been associated with approximately 90% of patients with DiGeorge syndrome and 68% of patients with VCFS. Subsequently, this deletion has been described in conotruncal anomaly face syndrome, CHARGE association, and Smith-Lemli-Opitz (G/BBB) syndrome. As a result, a new term, “chromosome 22q11 deletion syndrome,” has been coined, as the complete clinical spectrum of this abnormality is characterized.

Many of the clinical features of VCFS (Table 1) have been reported in the presence of a 22q11 deletion. These features impact the head and neck and are of importance to the otolaryngologist. The spectrum of clinical features in patients with VCFS predisposes these individuals to chronic ear disease due to eustachian tube dysfunction and underlying immune dysfunction. Symptoms of upper airway compromise may be present secondary to muscular hypotonia, deficiencies within the facial skeleton, and anomalies of the skull base. Developmental delay and psychiatric disease are present in many of these patients. Velopharyngeal insufficiency is frequently present in varying degrees of severity.

With the ability to detect the 22q11 deletion, the clinical diagnosis of VCFS has become more variable. The clinical significance of this deletion is still being determined, but it is now possible to have VCFS and this deletion without all the clinical features of VCFS.
3 of 5 patients with the 22q11 deletion and phenotypic evidence of VCFS.

Flexible endoscopy and video fluoroscopy was used in 18 and endoscopy alone in 5 of the 23 patients to assess velopharyngeal function. The types of velopharyngeal closure pattern were as follows: sagittal (n=1), coronal (n=17), circular (n=4), and circular with Passavant ridge (n=1). Preintervention VPI severity as judged by speech intelligibility was poor in 15 of the 23 patients, fair in 5, and good in 3. This changed to good in 13, fair in 3, and poor in 1 after intervention. The interventions consisted of surgery in 13 (spinchter pharyngoplasty in 7 patients, pharyngeal flap in 3 patients, and Furlow palatoplasty in 3 patients), speech prosthesis in 2, and intensive speech therapy in 8 who declined a more invasive intervention.

**COMMENT**

Velopharyngeal insufficiency following adenoidectomy frequently occurs in the presence of known stigmata of a craniofacial syndrome or cleft palate. The stigmata of a submucous cleft palate are thought to signify an underlying derangement of velar musculature. These stigmata can be subtle and may be unrecognized prior to the adenoidectomy. When these stigmata are absent, the etiology of VPI in this setting is frequently attributed to an unknown cause or an “occult” submucous cleft palate. The occult submucous cleft palate is described as an absence or deficiency of the musculus uvulae, detected with nasopharyngoscopy, and notching of the posterior hard palate. We describe 23 patients with VIA. Seventeen (69%) of these patients did not have stigmata of an abnormal soft palate (occult or overt) and were thought to have VIA of unknown cause. Patients with palatal anomalies had the 22q11 deletion when they were tested. Four of the 9 patients with the deletion did not have a known syndromic diagnosis. Seven of the 9 patients having the 22q11 deletion did not have stigmata of abnormal palatal anatomy.

Retrospective evaluation for the presence of the 22q11 deletion in our population of children with VIA has shown a significant number of patients with this deletion. Of the tested patients, 40% with the deletion had no phenotypic evidence of an underlying craniofacial syndrome and 60% did not have stigmata of abnormal palatal anatomy. This high incidence of the 22q11 deletion within our study population reflects the tertiary referral pattern of our institutions. However, a similarly high frequency of the 22q11 deletion has been described in a population of patients with VPI, after palatoplasty and of unknown cause. Muscular dysfunction or malformation involving the velopharyngeal region could explain the etiology of persistent VPI in these patients, especially in the presence of a 22q11 deletion. It is our experience that soft palate musculature is indeed deficient in patients with the 22q11 deletion and VCFS. The exact mechanism for abnormal velar function and anatomy in this setting may be explained by a premature loss of cells within the palate and other dysfunctional structures involved in VPI. It has been hypothesized that genes within the 22q11 microdeletion locus control normal migration and function of tissues derived from neural crest cells in branchial arches 3 through 6. A gene encoding for proteins (ubiquitin-specific proteases) that regulate cell survival has been identified in the 22q11 region, which may explain the craniofacial and congenital cardiac defects seen in patients with this deletion.

Our patient population had a high incidence of associated disorders. Chronic ear disease was present in almost 40%, which is not unexpected. Abnormal palate function and muscular hypotonia are linked with poor eustachian tube function. In addition, the possibility of underlying immune dysfunction in patients with the 22q11 deletion may predispose them to chronic ear disease. The presence of nasal regurgitation with feeding is sometimes associated with abnormal palate function. Careful questioning prior to an adenoidectomy may reveal this sign. If nasal regurgitation is present, consideration for removal of superior and choanal adenoid tissue alone should be entertained. Muscular hypotonia and immune dysfunction are described in patients with VCFS and the 22q11 deletion, which may have contributed to the conditions for which they underwent adenoidectomy. Muscular hypotonia and immune dysfunction could cause symptoms of upper airway obstruction and sinusitis in young children, which are commonly treated with an adenoidectomy. A large collaborative study has demonstrated the prevalence of otolaryngologic problems in a group of patients with 22q11 deletions. The investigators found similar problems with chronic ear and nasal disease. Nasal anomalies, laryngeal anomalies, laryngomalacia, tracheomalacia, and choanal atresia also have been reported in this study and others. Developmental delay has been described in the chromosome 22q11 deletion syndrome. Our population had evidence for this as well, especially in children with the deletion. The nature of this cognitive delay appears to be a nonverbal learning disability. Further study needs to be done to determine the best therapy to improve development in affected individuals.

The management of VIA is controversial. Our goals in this setting were to restore normal velopharyngeal function tailored to the pattern of velopharyngeal closure. Since the majority of patients undergoing surgery had coronal velopharyngeal closure, a spinchter pharyngoplasty or Furlow palatoplasty were performed most frequently. Other forms of surgical management have been de-

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**Table 2. 22q11 Deletion Testing Results**

<table>
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<tr>
<th>22q11 Deletion Obtained</th>
<th>VPI Present</th>
<th>VCFS Present</th>
<th>VCFS Absent</th>
<th>Submucous Cleft Palate</th>
</tr>
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<tbody>
<tr>
<td>Present</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Absent</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>NA†</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
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*VCFS indicates velocardiofacial syndrome; NA, not applicable.
†Only 2 of 6 patients with a submucous cleft palate were tested.*
scribed, including posterior pharyngeal wall augmentation. When contemplating pharyngeal surgery in patients with VCFS, the need for routine preoperative imaging of cervical vasculature is debated. In VCFS the carotid arteries can be medially displaced, potentially increasing the risk of arterial injury during pharyngeal surgery. Regardless of whether vascular imaging is obtained, a high index of suspicion for vascular anomalies should be present in all patients undergoing pharyngeal surgery for VIA, especially since the full spectrum of the 22q11 deletion and its relationship to VCFS is being defined in patients with VIA and undiagnosed VCFS. Further study of the optimum treatment strategy for VIA is ongoing.

Detecting a 22q11 deletion is important because of the multisystem impact this chromosome deletion may have. In addition to the well-known cardiac and palatal anomalies, significant psychiatric, endocrine, immunologic, and ocular problems have been described in these patients. In some countries, prenatal testing for this deletion is being performed. Inheritance of the deletion has been demonstrated in several patterns; therefore, all affected individuals and their families should have genetic counseling. Increasingly accurate mapping of the 22q11 region, through refinements in FISH technique, has shown critical regions that may be associated with specific developmental anomalies. Deletions in these smaller areas may explain anomalies of the involved pharyngeal arches in patients previously not demonstrating a 22q11 deletion. If this occurs, specific genetic deletions may be linked with many syndromes that involve the head and neck.

Our brief report demonstrates a high incidence of the chromosome 22q11 deletion in a population of children with VIA. The retrospective nature of our study, the small study sample, and the fact that all patients did not undergo a FISH test for the 22q11 deletion limit the conclusions we can make regarding these findings. Despite these limitations, consideration for 22q11 testing should be made in all patients with VIA because of the possibility of genotypic VCFS. Moreover, strong suspicion of VCFS should be considered if palatal abnormalities or other phenotypic findings of VCFS are present. Further study of the optimum treatment strategy for VIA is ongoing.

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REFERENCES