# Increased Medical Interventions in Children with 22q11.2 Deletion Syndrome (Velocardiofacial Syndrome)

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**Abstract**

Velocardiofacial syndrome (VCFS) or 22q11.2 deletion syndrome has a wide range of associated features including congenital heart defects, palate abnormalities, and learning disabilities. Medical interventions in infants and young children with VCFS have been described in the literature, but information diminishes as children reach school age. It was anticipated that children with VCFS would experience an increased number of surgical procedures and hospitalizations compared to children with isolated congenital heart defect (CHD), isolated cleft palate (CP), and children with no genetic syndromes or birth defects. To test this we conducted a retrospective medical record review of 77 children with VCFS, 35 children with CHD, 30 children with CP, and 32 from the local community. Numbers and types of surgical procedures and hospitalizations were compared between the groups using analysis of variance methods. Children with VCFS had a significantly greater number of surgical procedures (adjusted $p<0.001$ each comparison) and hospitalizations (adjusted $p<0.01$ each comparison) than children with CHD, CP, and the LC. Overall, 81% of the VCFS cohort had at least one surgical procedure and 53% had at least one hospitalization. Forty-five percent of children with VCFS and a palate defect had at least one surgical procedure on the palate between the ages of 5-10 compared to only 17% with CP. The results of this study indicate that children with VCFS had a significantly increased need for medical interventions between the ages of 5-10 compared to children with non-syndromic CP, CHD, and from the LC. Information from this study can be used to create management protocols for health care providers and to provide anticipatory guidance to caregivers of children with VCFS.

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## Introduction

Velocardiofacial syndrome or 22q11.2 Deletion Syndrome is one of the most common genetic syndromes in humans and is associated with congenital heart defects, palatal abnormalities, and characteristic facial features[1-3]. It is caused by a deletion of chromosomal region 22q11.2 and has a prevalence of 1:2,000 to 1:7,000 live births[2]. Clinical management for those with VCFS is complex due to the wide range of phenotypic variability. In infancy and preschool years, acute medical problems such as congenital heart disease, immune disorders, feeding problems, and cleft palate occupy management. Management shifts to cognitive and behavioral disorders during school years, and then to the potential for psychiatric disorders including psychosis in late adolescence and adult years[2]. Infants with VCFS are hospitalized more often than other children, and those with and without a heart defect are equally likely to be hospitalized[4]. Among individuals with VCFS, there is a large percentage of those with significant speech problems or language delay, the most common speech abnormality being velopharyngeal insufficiency (VPI)[5]. School age children with VCFS are less likely than infants to be evaluated using echocardiogram, serum calcium, renal ultrasound, and lymphocyte count[6], even though school age children continue to have significant morbidity associated with the condition. Because of the wide range of birth defects and clinical features associated with VCFS, we wished to investigate the needs of children with VCFS compared to their peers with similar major malformations. In this study, we investigated the hypothesis that children with VCFS will require an increased number of hospitalizations and invasive procedures than children of similar age with isolated congenital heart defects (CHD), isolated cleft palate (CP), and a community cohort. Information from this study can be used by health care providers to create management protocols for school-age children with VCFS. In addition, the results from this study can be used to provide

anticipatory guidance to parents of children with VCFS, helping them feel better prepared to cope with their child's needs.

**Methods**

We conducted a retrospective chart review of four independent cohorts of pediatric patients who received health care services between the ages of 5 and 10 at Cincinnati Children's Hospital Medical Center (CCHMC). The four cohorts included 174 patients: 77 children with VCFS, 35 children with isolated CHD, 30 children with isolated CP, and 32 children with no known birth defects, chronic illnesses, or genetic conditions (community cohort). All children were at least 10 years old at the time the study began and lived within 40 miles from CCHMC between the ages of 5 and 10. CCHMC is the only hospital within this region where children could be admitted for a hospitalization or have a surgery performed. After approval by the Institutional Review Board, medical records of all individuals were reviewed for the time period from their fifth birthday to their tenth birthday. Demographic information, admission and discharge dates, diagnoses, procedures performed, information on medical conditions and birth defects, and genetic testing information were recorded for each patient. To estimate the proportion of those with low socioeconomic status, insurance information was recorded and patients with Medicaid were considered low socioeconomic status.

Inclusion Criteria

VCFS cohort: All individuals in the VCFS cohort had a documented 22q11.2 chromosome deletion confirmed by fluorescence *in situ* hybridization (FISH). To ensure completeness of medical records, patients were included only if they had at least one visit before the age of 5 and

at least one visit after the age of 10. One child passed away between the ages of 5 and 10, and this child's records were included from the age of 5 until his death.

CHD cohort: Individuals in the CHD cohort were selected to match those in the VCFS cohort with a heart defect based on type and severity of heart defect and birth year. Individuals in the CHD cohort either had no genetic testing ordered or had a FISH test confirming that they did not have a 22q11.2 deletion.

CP cohort: Individuals who were suspected to have syndromic cleft palate were excluded with the exception of Stickler syndrome. Individuals with Pierre Robin sequence were included in the CP cohort only if they did not require tracheostomies for airway complications, as most individuals with VCFS do not require tracheostomy.

Community cohort: Individuals in the community cohort were patients who received pediatric primary care services at CCHMC.

All individuals in the CHD, CP, and community cohorts were screened for features of VCFS and other genetic syndromes and were excluded if records noted dysmorphic features any additional birth defects.

**Results**

Study participant characteristics are summarized in Table 1. The patients in the VCFS cohort were slightly older on average than participants in the other cohorts, with a median birth year of 1995 and birth years as early as 1980. The four cohorts also differed with regard to ethnicity—the VCFS cohort was 95% Caucasian and the community cohort was 75% Caucasian. Insurance information was available for 88.5% of the total study population. Children in the community cohort had a higher rate of Medicaid use (78%) than the VCFS cohort (31%), the

CHD cohort (6%) and the CP cohort (13.3%). There was no significant difference in gender among the four cohorts.

Among the 77 individuals with VCFS, 52 (68%) had a congenital heart defect, the most common types being Tetralogy of Fallot and Ventricular Septal Defect. Among the VCFS cohort, 53 children (69%) had a palate defect, including 7 with CP (9%), 19 with sub-mucous CP (25%), and 43 with velopharyngeal insufficiency (VPI) occurring in isolation or in combination with another palate defect (56%). In the VCFS cohort, 33 individuals (43%) had both a congenital heart defect and a palate defect.

**Table 1. Study participant characteristics by cohort**

| | **VCFS** n(%) | **CHD** n(%) | **CP** n(%) | **Community** n(%) | **p value**[1] |
|---|---|---|---|---|---|
| **Number** | 77 | 35 | 30 | 32 | |
| **Gender (% male)** | 37 (48) | 14 (40) | 13 (43) | 16 (50) | 0.8182* |
| **Ethnicity (% Caucasian)** | 73 (95) | 28 (80) | 27 (90) | 24 (75) | 0.0008* |
| **Birth year median, (min-max)** | 1995 (1980-2000) | 1996 (1991-2000) | 1998 (1984-2000) | 1996.5 (1996-2000) | 0.0011** |
| **Medicaid use (% used)** | 24 (31) | 2 (6) | 4 (13) | 25 (78) | <.0001* |

[1]For differences among all four cohorts
*Fisher's exact test
**Kruskal-Wallis (Nonparametric) test, $\chi^2$=16.0449, df=3

Surgical Procedures

A surgical procedure was defined as a medical intervention requiring anesthesia. The total study population required 208 surgical procedures between the ages of 5 and 10, thirteen of which were performed for more than one reason (for example, a surgery for both correction of VPI and dental rehabilitation). Overall, 81% of the VCFS cohort had at least one surgical procedure. Individuals with VCFS required an average of 2.17 surgical procedures (Figure 1).

Children with VCFS experienced a significantly greater number of surgical procedures than children with CHD, CP, and children in the community (adjusted p<0.0001 each comparison, Figure 1).

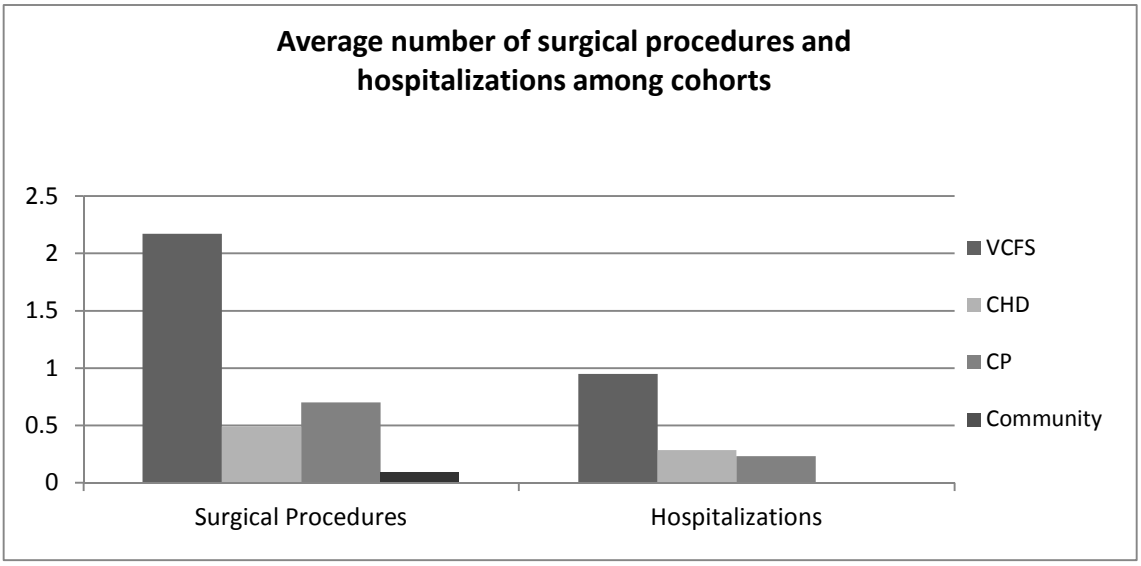


**Figure 2. Average number of surgical procedures and inpatient hospitalizations from age 5-10 for each cohort. Children with VCFS experienced a greater number of surgical procedures (adjusted p<0.0001 each comparison) and hospitalizations (adjusted p<0.01 each comparison) than children with CHD, CP, and children in the community.**

All surgical procedures were categorized by type using admitting and discharge diagnoses and type of procedure performed. The percentage of individuals undergoing at least one type of each surgical procedure for each cohort is represented in Table 2. The proportion of children who required at least one surgical palate procedure among the VCFS cohort (31%) was nearly twice that of those with CP (17%), however this difference did not reach statistical significance (p=0.149). The VCFS cohort also experienced more non-palate related ENT procedures with 47% of the VCFS cohort experiencing at least one compared to 27% of the CP cohort (p=0.057). There were 20% of children in the CHD cohort who experienced at least one surgical heart procedure compared to 13% of those in the VCFS cohort (p=0.98).

**Table 2. Number and percentage of children in each cohort requiring at least one surgical procedure by type.**

| | VCFS 77 n(%) | CHD 35 n(%) | CP 30 n(%) | Community 32 n(%) | p value[1] |
|---|---|---|---|---|---|
| **Palate procedure** | 24 (31.2) | -* | 5 (16.7) | -* | <.0001 |
| **ENT, Non-palate** | 36 (46.8) | 2 (5.7)* | 8 (26.7) | -* | <.0001 |
| **Cardiac procedure** | 10 (13.0) | 7 (20.0) | - | - | 0.0076 |
| **Dental procedure** | 15 (19.5) | -* | -* | 3 (9.4) | 0.0020 |
| **Respiratory Illness** | 2 (2.6) | 1 (2.9) | - | - | 0.6429 |
| **Illness, Non-Respiratory** | 4 (5.2) | 1 (2.9) | - | - | 0.3497 |
| **Trauma** | 2 (2.6) | 1 (2.9) | - | - | 0.6429 |
| **Hernia repair** | 6 (7.8) | 1 (2.9) | 1 (3.3) | - | 0.3019 |
| **Other** | 2 (2.6) | 1 (2.9) | - | - | 0.6429 |

**Comparisons among all four cohorts were made using ANOVA. For those types of surgical procedures that were statistically different among the four cohorts at p<0.05, Dunnett's test was used to compare each non-VCFS cohort to the VCFS cohort.**

**[1]For difference among all four cohorts (ANOVA)**

***Significant difference versus VCFS at p<0.05 (Dunnett's test)**

The types of surgical procedures required for the VCFS cohort is represented in Figure 2. Of all surgical procedures performed among individuals with VCFS, 9.4% were cardiac procedures and 19.4% were for correction of the palate or VPI. A number of surgical procedures among the VCFS cohort (51.1%) were for ear, nose, or throat (ENT) procedures that were unrelated to palate or VPI, such as microlaryngoscopy and/or bronchoscopy, the placement of

pressure equalizing tubes, or tympanoplasty. Of 41 surgical procedures among the non-VCFS cohorts, the most common reason was for non-palate related ENT procedures (41.5%).

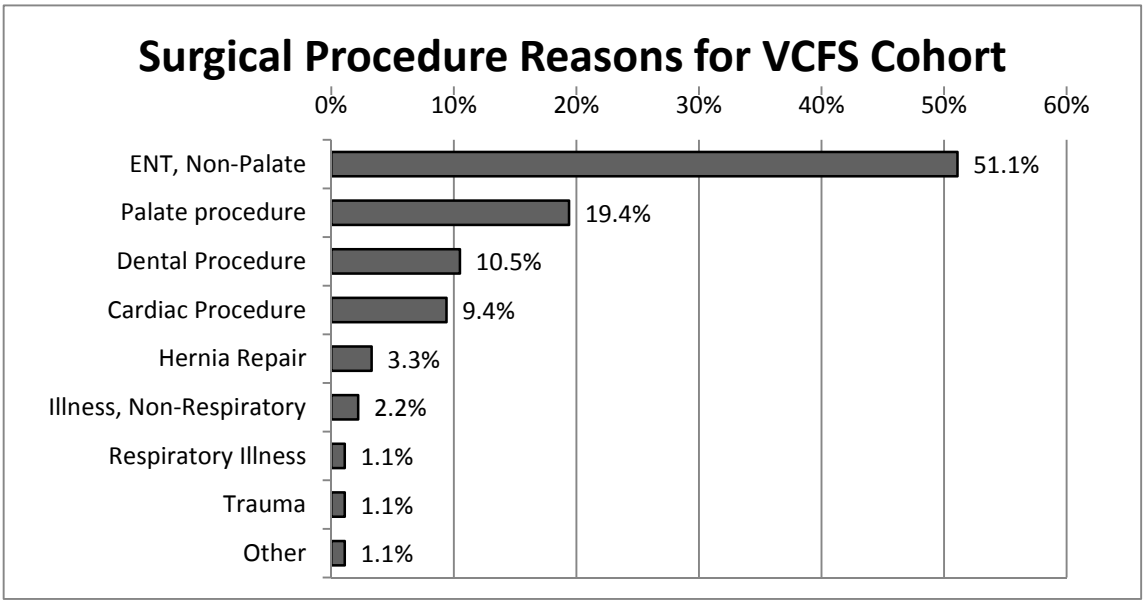


**Figure 2. Proportion of surgical procedures required for each reason among the VCFS cohort.**

Hospitalizations

A hospitalization was defined as any admission that required a minimum of one overnight stay. The total study population required a total of 90 hospitalizations—73 among children with VCFS and 17 among the non-VCFS cohorts. Over half (53.2%) of the VCFS cohort required at least one hospitalization between the ages of 5 and 10. Table 3 represents the average number of hospitalizations, lengths of hospitalizations, and the average time each patient spent hospitalized for each cohort. Children with VCFS had an average of 0.95 hospitalizations, which was significantly greater than individuals with CHD, CP, and children in the general population (Table 3). Among all children in the VCFS cohort, the average length of stay was 3.10 +/- 0.42 days, which was significantly longer than children in the other cohorts.

**Table 3. Numbers and lengths of hospitalizations for each cohort.**

| | VCFS 77 | CHD 35 | CP 30 | Community 32 |
|---|---|---|---|---|
| **Number of hospitalizations, mean** | 0.95 | 0.29 | 0.23 | 0 |
| **p value vs VCFS** | - | 0.0018* | 0.0013* | <.0001* |
| **Length of each hospitalization, mean days (SE)** | 3.26 (0.36) | 2.7 (0.99) | 3.14 (1.18) | - |
| **p value vs VCFS** | - | 0.83 | 0.99 | - |
| **Hospitalization time per patient, mean days (SE)** | 3.10 (0.42) | 0.77 (0.62) | 0.73 (0.67) | 0 |
| **p value vs VCFS** | - | 0.0064 * | 0.0093 * | 0.0003 |

***Significant difference at p<0.05**

All hospitalizations were categorized by type using admitting and discharge diagnoses. Hospitalization types among the VCFS cohort are represented in Figure 3. The most common reasons for hospitalizations in the VCFS cohort were for surgical palate procedures, ENT complications not involving the palate, and cardiac procedures which included cardiac catheterizations. A significant number of inpatient hospitalizations among children with VCFS were unrelated to a heart condition or palate dysfunction (23%).

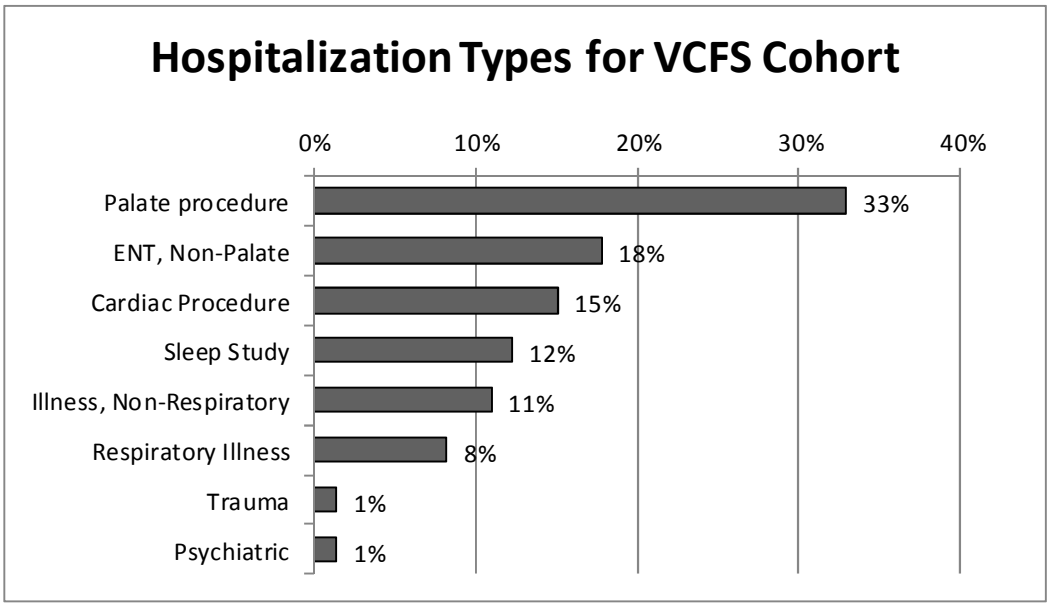


**Figure 3. Proportion of inpatient hospitalizations required for each reason among the VCFS cohort.**

Cardiac and Palatal Interventions

To compare interventions required specifically for cardiac and palatal reasons, the VCFS cohort was subdivided into those with VCFS and a heart defect (n=52), VCFS and a palate defect (n=53), and those with VCFS, a heart defect, and a palate defect (n=33). Table 4 compares the number and proportion of children requiring at least one intervention, defined as a surgical procedure or a hospitalization, for the subdivided cohort of those with VCFS and a heart defect compared to the CHD cohort. Table 5 compares the number and proportion of children requiring at least one intervention for the subdivided cohort of those with VCFS and a palate defect compared to the CP cohort. Overall, the 33 individuals in the VCFS cohort who had both a heart defect and a palate defect accounted for approximately half (52.7%) of the surgical procedures and nearly two-thirds (67.1%) of the hospitalizations among the total VCFS cohort. Individuals with VCFS who also had a CHD and a palate defect required an average of 2.67 surgical procedures and 1.48 hospitalizations between the ages of 5 and 10.

**Table 4. Number and percentage of children requiring at least one intervention by type for those with VCFS and a heart defect compared to the CHD cohort.**

| | VCFS and heart defect<br><br>n=52<br>n(%) | VCFS, palate and heart defect<br><br>n=33<br>n(%) | VCFS and heart defect, no palate defect<br>n=19<br>n(%) | CHD<br><br>n=35<br>n(%) |
|---|---|---|---|---|
| Cardiac procedure | 10 (19) | 6 (18) | 4 (21) | 7 (20) |
| Palate procedure | 17 (33) | 17 (52) | 0 | 0 |
| Any surgical procedure | 43 (83) | 30 (91) | 13(68) | 12 (34) |
| Any hospitalization | 32 (62) | 24 (73) | 8(42) | 9 (26) |

**Table 5. Number and percentage of children requiring at least one intervention by type for those with VCFS and a palate defect compared to the CP cohort.**

| | VCFS and palate defect<br><br>n=53<br>n(%) | VCFS, palate and heart defect<br><br>n=33<br>n(%) | VCFS and palate defect, no heart defect<br>n=20<br>n(%) | CP<br><br>n=30<br>n(%) |
|---|---|---|---|---|
| Cardiac procedure | 6 (11) | 6 (18) | 0 | 0 |
| Palate procedure | 24 (45) | 17 (52) | 7(35) | 5 (17) |
| Any surgical procedure | 48 (91) | 30 (91) | 18(90) | 13 (43) |
| Any hospitalization | 33 (62) | 24 (73) | 9(45) | 5 (17) |

**Discussion**

Children with VCFS had significantly increased numbers of medical interventions between the ages of 5 and 10 compared to children with CHD, CP, and children in the general population. Most interventions required were for abnormal structure or function of the palate, problems involving the ear canal, airway complications, and cardiac procedures.

Children with CHD had a higher proportion of those requiring at least one cardiac procedure between the ages of 5-10 (20%) than children with VCFS (13%) (Table 2). The increased incidence of cardiac surgery among children with CHD was expected, as only 67.5% of children with VCFS had a heart defect compared to all children in the CHD cohort. After subdividing the cohorts, children with VCFS and a heart defect had approximately the same proportion of those experiencing at least one cardiac surgery (19%) as those with isolated CHD (20%) (Table 4). Studies have shown that those with a 22q11.2 deletion have a more complicated postoperative course and a higher risk for surgical morbidity and mortality after cardiac surgery.[7-8] This study found that individuals with VCFS did not require more surgical cardiac procedures and did not experience significantly longer hospitalization times compared to the CHD cohort. It is possible that as children with VCFS get older, their risk for complicated postoperative cardiac course approaches that of those who do not have VCFS. This may also be explained by the age of the study population, as most cardiac repairs are done before the age of five, and children with VCFS who passed away before this age would not have been included in this study.

Although only 69% of the VCFS cohort had a palate defect, there were twice as many children requiring surgical correction of the palate in the VCFS cohort than the CP cohort. The increased incidence of palatal correction among children with VCFS may be explained by a

palate that differs neurologically from those with non-syndromic CP. Children with VCFS are at risk for a speech delay and VPI, and this risk continues into school age[9-10]. Speech problems were a common finding for children with VCFS, and 83% of children with VCFS had speech delay or VPI recorded in their medical record. Many of the features of VCFS contribute to delays in speech and language in children with VCFS including palatal and velopharyngeal abnormalities, learning delays, and an increased risk for frequent otitis media and hearing loss. Speech and language problems create difficulties with social interaction, and severe speech problems have been shown to negatively influence overall quality of life[11]. Parents of school aged children with VCFS report that the main problems for their children are social behavior, concentration deficit, learning disabilities, and speech problems[9]. Because of the high incidence of palatal dysfunction in 5-10 year olds with VCFS even in the absence of overt cleft palate, a thorough speech and language evaluation in conjunction with a plastic surgeon or otolaryngologist should be standard of care for all children with VCFS. Additionally, children with VPI may benefit from a genetic evaluation for VCFS.

Over half of the surgical procedures performed on children with VCFS were for ear canal dysfunction or airway evaluations. Nearly half of the children in the VCFS cohort (47%) required at least one non-palate related ENT surgical procedure between the ages of 5 and 10 compared to 27% of children with CP (Table 2). Chronic otitis media and middle ear effusion were common reasons for surgical intervention among the VCFS cohort. The increased incidence of otitis media in children with VCFS is due to a combination of factors including abnormal anatomy and function of the ear, immune dysfunction, and palatal dysfunction. These factors put children with VCFS at increased risk for hearing loss, which is usually mild to moderate conductive loss[5]. Frequent chronic otitis media increases the risk for hearing loss, so

school age children with VCFS should have hearing evaluated and appropriate interventions should occur to manage ear canal dysfunction.

Children with VCFS were hospitalized significantly more often than children in the other cohorts. Between the ages of 5 and 10, 44% of the VCFS cohort was hospitalized. Most hospitalizations were for surgical repair of the palate or cardiac surgery including cardiac catheterization; however 23% of inpatient hospitalizations among children with VCFS were unrelated to a heart condition or palate dysfunction. The results of this study indicate children with VCFS require medical interventions for reasons beyond heart and palate abnormalities.

One child in VCFS cohort was hospitalized with psychiatry at the age of 8 because of behavioral concerns, as the child was refusing oral feeds. Behavioral problems severe enough to require inpatient care are uncommon at this age, but may be more common among children with VCFS. Significant mental illness is well documented in association with VCFS[12], however the onset of mental illness is typically seen in adolescence or early adulthood. In children with VCFS, behavioral or psychiatric concerns can present in childhood and monitoring for psychiatric issues is essential, even among school-age children.

This study was a retrospective medical record review, and it is possible that not all surgical procedures and hospitalizations were included in the records. To ensure the records were as complete as possible, individuals whose last known address was over 40 miles from the hospital were excluded. An additional limitation is ascertainment bias among the CHD, CP, and community cohorts. Children in these cohorts could possibly have an underlying genetic syndrome, as most children in those cohorts did not have FISH testing for a 22q11.2 deletion or any other genetic testing. In the CP group, 27 of the 30 individuals had been evaluated by a geneticist at least once for the presence of syndromic cleft palate, however none had genetic

testing. Among the CHD group, none had been evaluated by a geneticist. All cohorts were screened for features suggestive of VCFS such as VPI and learning disabilities.

Children in the community cohort had a higher proportion of those using Medicaid (Table 1), indicating a lower socioeconomic status among this cohort. The community cohort was made up of children who received primary care at a hospital located in a socioeconomically-disadvantaged city neighborhood. Socioeconomic status has been shown to be a risk factor for pediatric hospitalization[13], thus, we would expect the community cohort to have an inflated number of hospitalizations. However, the community cohort did not have any inpatient hospitalizations.

Late diagnosis of VCFS is especially common in individuals without heart defects or major malformations, but it is important to recognize this disorder as early as possible so that children with VCFS can receive the appropriate management. Features such as VPI and conotruncal heart defects in addition to less specific problems like chronic otitis media and frequent respiratory infections may be indicators that a child should be evaluated for VCFS. School age children who have a diagnosis of VCFS should be monitored for VPI, speech problems, and ENT complications.

The results of this study indicate that children with VCFS experience significant morbidity throughout childhood. This study can be used by health care providers to create management recommendations for children with VCFS and to provide anticipatory guidance to parents of children with VCFS. Future studies are needed to evaluate medical interventions required among adolescent and adult patient populations. In addition, children with VCFS have health problems not involving surgical procedures and hospitalizations, and further research could examine which health problems cause kids with VCFS the most morbidity. This study was

retrospective in nature, but prospective studies could be done to evaluate management protocols that can be used to improve patient outcomes.

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