RETROSPECTIVE CHART REVIEW OF HOSPITALIZATIONS AND HEALTH PROBLEMS OF CHILDREN WITH VELOCARDIOFACIAL SYNDROME

A thesis submitted to the

Division of Research and Advanced Studies
of the University of Cincinnati

in partial fulfillment of the
requirements for the degree of

MASTER OF SCIENCE

in the Department of Analytical and Diagnostic Sciences
of the College of Allied Health

2002

by

Michelle Wojtasiak

B.S., University of Wisconsin – Madison, 1998

Committee Chair: Robert Hopkin, M.D.

ABSTRACT

Velocardiofacial syndrome (VCFS) is a genetic condition caused by the deletion of chromosome region 22q11.2-22q11.2. The majority of VCFS majority of research has focused on recognition of VCFS and the effects of heart and palate defects on individuals with this condition. Few studies have examined the contribution of VCFS to pediatric hospitalization. Therefore, the purpose of this retrospective chart review was to: 1) describe and quantify the hospitalizations and health problems of children with VCFS during the first five years of life, and 2) compare the medical needs of children with VCFS to children with isolated heart defects, isolated palate defects, and typical healthy children. Data on hospitalizations, birth defects, and health concerns for all cohorts were collected. When heart- and palate-related surgical hospitalizations were excluded, children with VCFS required a significantly greater number of hospitalizations in the first year ($p=0.0015$) and second through fifth years ($p=0.0066$) of life. A greater percentage of children with VCFS were hospitalized for respiratory illness than were children in other cohorts ($p=0.0100$). Individuals with VCFS were more likely to be diagnosed with a feeding problem ($p<0.0001$), failure to thrive (FTT) ($p=0.0059$), and hypotonia ($p<0.0001$) than individuals in other cohorts. Because of the high risk for feeding problems and FTT, all individuals with VCFS should undergo a multidisciplinary feeding team evaluation. Care must be taken not to falsely attribute failure to thrive to congenital heart disease or to poor parenting skills. Because VCFS is a risk factor for respiratory illness, parents should be educated on methods to reduce environmental risk factors for respiratory illness, including smoke, from the child's environment. Future prospective

studies should expand upon this knowledge and examine the hospitalizations and medical needs of children with VCFS beyond age five years.

ACKNOWLEDGEMENTS

Financial support for Michelle Wojtasiak was provided by the University of Cincinnati Summer Graduate Student Research Fellowship.

I would like to acknowledge the many individuals who made this study possible. First and foremost, I would like to acknowledge the many children and families affected by VCFS who have received care at Cincinnati Children's Hospital Medical Center. May their triumphs be many and their trials few. Dr. Robert Hopkin, my thesis advisory committee chairperson, spent countless hours discussing methodology, sharing his expertise, and offering guidance. Dr. Judy Bean offered invaluable assistance with data analysis and manuscript preparation. Judith Johnson assisted with the study development and offered excellent advice on manuscript preparation. Dr. Howard Saal offered creative input and offered use of his database for ascertainment of the cleft palate and VCFS cohorts. Dr. Anita Cavallo offered use of the Pediatric Primary Care Clinic (PPCC) database for ascertainment of the normal cohort. Dr. Robert Beekman offered use of the Division of Cardiology database for ascertainment of the isolated congenital heart defect cohort. All the faculty and staff in Cardiology and PPCC generously offered their hospitality and assistance as I reviewed charts in their divisions. Stacey Poe offered assistance with statistical analysis. I would also like to thank my family, friends, and classmates for their advice and encouragement. Finally, I would like to thank Errick Coughlin, to whom I may very well owe my sanity.

TABLE OF CONTENTS

LIST OF TABLES

BACKGROUND

In the early 1990s, researchers discovered that Velocardiofacial syndrome (VCFS) is caused by the deletion of chromosomal region 22q11.2-22q11.2. [1-3] This finding has led some scientists to refer to the condition as "Deletion 22q11 syndrome". [4] Although the features of VCFS are variable, the word "velocardiofacial" calls attention to three of the most common clinical features: anatomic and functional defects of the palate (velum), congenital heart defects (cardio), and a characteristic pattern of minor anomalies of the face (facial).

Because heart defects are a serious anomaly occurring in a majority of this population, much of the research performed to this date has had a cardiac focus. The association of congenital heart disease (CHD), especially conotruncal anomalies [5-8], with VCFS is well documented. Approximately 80% of individuals diagnosed with VCFS have heart defects [8-13], which often require surgical repair and prolonged hospitalizations in infancy and early childhood. [11]

Cleft palate (CP) and velopharyngeal insufficiency (VPI) are also common in individuals with VCFS. Overt or submucosal clefts occur in 25-30% of reported cases. VPI has been reported in an additional 27-73% of cases. [10, 12, 14] These children often require surgery and speech therapy to improve speech and language development. [15]

Individuals with VCFS have an increased risk for feeding disorders. Published reports place the incidence of feeding disorders at 30%-96% in the VCFS population. [10, 15]

Although the presence of feeding difficulties did not correlate to the presence of CHD or palate defects in one study [10], another found that feeding disorders generally occurred secondary to palate defects. [11] Nasal regurgitation and poor suck were reported to be the most common feeding disorders in infants with VCFS. [15]

Immune dysfunction remains an area of current research in VCFS. Seventy-seven percent of individuals with VCFS have immunodeficiency of varying degrees of severity, most commonly impaired T cell production and impaired immunolgic function. [16] Immunodeficiency in individuals with VCFS appears to be most significant in infancy, with some individuals showing improvement with age. [10]

Published reports have varied greatly in the number of children with VCFS affected by frequent respiratory illnesses. While it may seem intuitive that frequent respiratory illnesses may be related to immunodeficiency in children with VCFS, this hypothesis has not been strongly supported by published data. One large study reported that nine percent of individuals with documented immune system abnormalities and four percent of individuals with normal immune studies had a history of infection. [11] Another study reported that 23% of the VCFS cohort had been hospitalized at least twice for treatment of an infection; 43% of these individuals had documented immunodeficiency. [16] A third study reported that 47% of a cohort of 50 individuals had been hospitalized for at least one respiratory problem [15], but the immune status of these children was not reported.

Airway disorders and malformations represent an additional potential risk factor for respiratory illness in children with VCFS. A study of children with VCFS and tetrology of Fallot (TOF) found 14% of individuals had brochomalacia and experienced periodic respiratory distress and illness. [6]

Published descriptions of the clinical features of VCFS indicate that patients can be affected by any of over 100 different congenital anomalies. [17] These clinical reports and the availability of reliable diagnostic testing allow physicians to recognize and diagnose VCFS with increasing efficiency. However, while it is understood how palate and heart defects affect individuals with VCFS, limited data exist on the overall health care needs of these children. It is likely that a genetic defect that causes so many physical manifestations also affects the human body in less visible ways that influence health.

A previous study published by Hopkin *et al.* examined the need for medical interventions and hospitalizations during the first year of life in a cohort of twelve patients with VCFS. The cohort required a total of 26 hospitalizations before age one year. After controlling for cardiac surgery, infants with and without heart defects were equally likely to be hospitalized. [18] This finding suggests that hospitalization of children with VCFS may not be strongly associated with heart defects and warrants investigation in a larger cohort of children.

Increased understanding of total childhood morbidity caused by VCFS will increase awareness of the importance of presymptomatic screening for specific medical problems.

Greater awareness of potential health concerns may lead to an improved consensus on VCFS health care management guidelines. Increased understanding of the medical care needs of and morbidity in children with VCFS will also allow health care providers to give better anticipatory guidance to families and caretakers of these children.

PURPOSE AND HYPOTHESIS

The purpose of this study was to determine if additional morbidity occurs in children with VCFS with greater frequency than in children in the general population and children with comparable major birth defects. Comparison of children with VCFS to children with isolated heart defects and cleft palate can determine the contribution of these anomalies to hospitalizations and interventions required by children with VCFS. Additional hospitalizations and procedures can be attributed to the chromosomal deletion that causes VCFS.

Hypothesis: After controlling for heart- and palate-related hospitalizations, children with VCFS have significantly increased numbers and lengths of hospitalizations compared to children with isolated heart defects, isolated palate defects, and children with no known birth defects or genetic conditions.

METHODS

This study is a retrospective chart review of four independent cohorts of pediatric patients who received health care services during the period spanning birth to age five years at Cincinnati Children's Hospital Medical Center (CCHMC). The four cohorts include: 60

children with VCFS (VCFS cohort), 20 children with isolated CP (CP cohort), 26 children with isolated CHD (CHD cohort), and 20 children with no known birth defects, chronic illnesses, or genetic conditions (normal cohort). The CHD cohort was comprised of 15 children with TOF and 11 children with ventricular septal defect (VSD). TOF and VSD were chosen because these were the most frequent heart defects in the VCFS cohort. Individuals with VCFS and isolated CP were identified through a database maintained by CCHMC Division of Human Genetics. Individuals with TOF and VSD were identified using a database maintained within CCHMC Division of Cardiology Echocardiography Lab. Healthy children were identified using a database maintained by CCHMC Pediatric Primary Care Center. The study was reviewed and approved by the CCHMC institutional review board.

For all cohorts, individuals were excluded if complete medical records spanning the period birth to age five years were not available. For individuals who died prior to age five years, record availability for the period from birth to time of death was required. To be included, all individuals with VCFS were required to have 22q11.2 deletions confirmed by fluorescence *in situ* hybridization (FISH) and to have been evaluated by a medical geneticist. In order to determine morbidity directly associated with CHD and CP, individuals with documented genetic disorders, additional birth defects, or chronic medical conditions unrelated to the heart or palate defects were excluded from the control cohorts. The CP cohort was comprised of individuals who were examined by a medical geneticist to rule out syndromic cleft palate (with the exception of possible Stickler syndrome, which is not known to be associated with hospitalization in the first five years

of life). Individuals requiring tracheostomies due to Pierre Robin-related airway compromise were excluded from the CP cohort, as most individuals with VCFS with and without cleft palate do not require tracheostomy. The medical records of individuals with VSD and TOF were screened beyond age five years for additional risk factors for VCFS, including oral motor apraxia, velopharyngeal insufficiency, and chronic illness not known to be associated with isolated heart defects. Individuals with risk factors specific to VCFS were excluded from the CHD cohort. Individuals with conditions not specific to VCFS, such as speech delay or failure to thrive (FTT), were included. Individuals in the CHD cohort were selected to match individuals in the VCFS cohort on type and severity of heart defect.

Complete medical records, both divisional and institutional, of all individuals for the period birth to age five years were reviewed. Data were abstracted and entered into the study database. Abstracted data included demographic information; age, length of stay, admitting and discharge diagnoses and procedures performed for each hospitalization; and presence of birth defects and medical conditions, such as feeding problems. A hospitalization was defined as any hospital admission or outpatient visit that required a minimum of one overnight stay. Hospitalization at birth was included for each individual. Up to three feeding problems were recorded for each child as described in the medical record. For children with multiple feeding problems, the three most specific findings were recorded. CP was considered a feeding problem, because it necessitates special feeding techniques.

Statistical analyses were performed using SAS ®, Version 8.1. Categorical data were analyzed using Chi-square and Fisher's Exact tests. Continuous data were analyzed using analysis of variance methods. All results were considered significant at the 0.05 level. If differences were seen, Bonferroni's multiple comparison procedure was used to control for the level of significance in determining where differences existed.

RESULTS

The complete study population consisted of 126 individuals. Data on study participant characteristics are summarized in Table 1. The normal cohort differed significantly from other cohorts for Medicaid use. No other differences were observed among the four cohorts.

Table 1. Study participant demographics by cohort

	VCFS	CHD	CP	Normal	p value
n	60	26	20	20	N/A
Gender (% male)	50.00	46.15	50.00	65.00	0.6087
Ethnicity (% Caucasian)	95.00	80.10	95.00	85.00	0.1093
Medicaid (% ever used)	38.33	23.08	36.84	80.00	0.0010
Range of birth years	1983-2001	1993-1997	1993-1997	1996-1997	N/A

N/A = Not applicable.

Hospitalizations were categorized by primary admitting and discharge diagnoses. The study population required 450 hospitalizations during the period of birth to age five years, including 126 birth hospitalizations. The recorded hospitalizations included 82 heart surgeries (including heart catheterizations), 55 respiratory illnesses, 44 palate repairs

(including correction of CP and VPI), 18 febrile illnesses, ten FTT, ten suspected apnea, and seven congestive heart failure. The remaining 98 hospitalizations were for other reasons.

The duration of hospitalization was documented for 396 recorded hospitalizations (88.0%), including 109 birth hospitalizations (86.5%). Data on hospitalization durations are summarized in Table 2. Exclusion of the individual hospitalized for 145 days at birth decreased the birth hospitalization duration average to 14.68 ± 19.41 days and the first year of life hospitalization duration average to 11.58 ± 14.46 days but did not alter the statistical significance. No significant differences were found among the four cohorts for hospitalization duration per individual for the second through fifth years of life when examined by individual year (data not included).

Table 2. Average duration of hospitalization in days by cohort

	Cohort			
	VCFS	**CHD**	**CP**	**Normal**
All hospitalizations	8.10 ± 7.02	4.70 ± 3.04	3.48 ± 3.13*	2.36 ± 1.34*
Birth only	17.09 ± 26.15	4.67 ± 5.18	5.94 ± 6.47	2.35 ± 1.34*
1st year of life	12.51 ± 18.25	6.39 ± 4.15	4.62 ± 4.60*	3.33 ± 1.27*
1st year of life excluding birth	9.16 ± 9.87	7.11 ± 2.74	3.04 ± 1.34*	3.25 ± 0.96

*Denotes cohorts that are significantly different from the VCFS cohort for that row

The percentage of individuals hospitalized per cohort during discrete time intervals and for respiratory illness was analyzed. Data are summarized in Table 3. The VCFS cohort had a significantly greater percentage of individuals hospitalized during the first year of

life and the second through fifth years of life when heart and palate surgery-related hospitalizations were excluded. Birth hospitalizations were excluded from first year of life analyses.

Table 3. Percentages of individuals hospitalized per cohort for time intervals

	Cohort				
	VCFS	**CHD**	**CP**	**Normal**	**p value**
1st year of life	70.00%	61.54%	100.00%	25.00%	<0.0001
1st year excluding heart and CP repair surgeries	51.67%	11.54%	25.00%	25.00%	0.0015
2nd year of life	33.33%	26.92%	20.00%	10.00%	0.1952
3rd year of life	21.67%	11.54%	0.00%	0.00%	0.0116
4th year of life	25.00%	7.69%	0.00%	5.00%	0.0103
5th year of life	21.67%	7.69%	30.00%	5.00%	0.0829
2nd-5th years of life	66.67%	38.46%	45.00%	15.00%	0.0004
2nd-5th years of life excluding heart and CP repair surgeries	46.67%	23.08%	15.00%	15.00%	0.0066

Hospitalization for respiratory illness and a history of frequent respiratory illnesses specifically noted in the medical record were examined as two independent variables. Data on respiratory illnesses in recorded in Table 4. When children with VCFS without CHD were independently examined, one of sixteen (6.25%) individuals had a history of frequent respiratory illness recorded in the chart, which was statistically similar to the other cohorts. Likewise, one of sixteen individuals with VCFS and without CHD had at least one hospitalization for a respiratory illness, statistically similar to the other cohorts.

Table 4. Percentages of individuals with respiratory illnesses by cohort

	Cohort				
	VCFS	**CHD**	**CP**	**Normal**	**p value**
Hospitalized for respiratory illness	38.33%	19.23%	15.00%	5.00%	0.0100
Hospitalized for respiratory illness excluding individuals with laryngeal malformations	38.00%	19.23%	15.00%	5.00%	0.0160
History of frequent respiratory illnesses	35%	0%	0%	0%	$p<0.0001$

Seven individuals with VCFS and low T cell counts or thymic hypoplasia were hospitalized for respiratory illness. Sixteen individuals with normal immune studies or no suspected immune dysfunction were admitted for respiratory illness. The seven individuals with immune dysfunction averaged 2.0 respiratory hospitalizations per person; the sixteen individuals with no immune dysfunction averaged 1.8 hospitalizations. The range of respiratory hospitalizations per individual was one to four hospitalizations for both groups. Four individuals in the VCF cohort underwent tracheostomy; one of these individuals had one hospitalization due to respiratory illness.

The average number of hospitalizations per individual was analyzed by cohort for discrete time intervals. These analyses included only individuals who had been hospitalized during the specified time intervals. Data on average number of hospitalizations per individual are summarized in Table 5. No significant differences were found among the four cohorts for average number of hospitalizations per individual for the second through fifth years of life when examined by individual year (data not

included). No significant differences were found among the CHD, CP, and normal cohorts for any analyses performed on average number of hospitalizations per individual.

Table 5. Average number of hospitalizations per individual by cohort

	Cohort			
	VCFS	**CHD**	**CP**	**Normal**
Hospitalizations (n)	288	71	61	30
Birth-5th year of life	4.80 ± 4.07	2.73 ± 2.42*	3.05 ± 131	1.50 ± 0.95*
1st year of life	2.78 ± 1.85	1.81 ± 0.90*	2.5 ± 1.00	1.30 ± 0.57*
2nd-5th years of life	2.02 ± 3.341	0.92 ± 2.02	0.55 ± 0.69	0.20 ± 0.52*

*Denotes cohorts that are significantly different from the VCFS cohort for that row

Specific feeding problems were analyzed by cohort. The results are summarized in Table 6. When CP was excluded as a feeding problem, the VCFS cohort had significantly more feeding problems than the other cohorts. The VCFS cohort also had a higher incidence of FTT and hypotonia than did the other cohorts.

Table 6. Percentages of individuals per cohort with diagnoses related to feeding problems

	Cohort				
	VCFS	**CHD**	**CP**	**Normal**	**p value**
Feeding problem	78.33%	15.38%	100%	10%	<0.0001
Feeding problem excluding CP	78.33%	15.38%	25%	10%	<0.0001
FTT	35%	11.54%	10%	5%	0.0059
Hypotonia	30%	0%	5%	0%	<0.0001

*Denotes cohorts that are significantly different from the VCFS cohort for that row.

The subcohort of 26 individuals with VCFS and VSD or TOF was independently compared to the CHD cohort. This VCFS subcohort had an average of 4.65 ± 3.37

hospitalizations per individual, significantly higher than the 2.73 ± 2.43 hospitalizations per individual for the CHD cohort (p=0.0221). When heart surgery-related hospitalizations were excluded, individuals in the VCFS subcohort continued to have a significantly higher average number of hospitalizations per person (3.46 ± 2.82 hospitalizations) than did the CHD cohort (1.54 ± 1.24 hospitalizations) (p=0.0031). Additional comparisons between the VCFS subcohort and CHD cohort are available in Table 7.

Table 7. Comparisons between CHD cohort and subcohort of individuals with VCFS and CHD

	Cohort		
	VCFS with CHD	**CHD alone**	**p value**
History of frequent of respiratory illness	38.46%	0%	0.0004
Feeding problem	69.23%	15.38%	p<0.0001
Hypotonia	30.77%	0%	0.0021
FTT	38.47%	11.54%	0.0250

DISCUSSION

It was hypothesized that children with VCFS have significantly increased numbers and lengths of hospitalizations after controlling for heart- and CP-related hospitalizations. During the first year of life, over half the VCFS cohort was hospitalized for reasons unrelated to the surgical repair of CHD and CP (Table 1). Less than half as many children in the CHD and CP cohorts were hospitalized during the first year of life; after accounting for hospitalizations for surgical repair of birth defects, the percentage of children in these cohorts hospitalized in this period was similar to normal children. Infants with VCFS therefore have significant health problems requiring hospitalization in

addition to those caused by heart and palate defects. Correction of additional birth defects accounts for a percentage of these hospitalizations. The morbidity caused by congenital birth defects, however, is compounded by additional health concerns that affect infants with VCFS.

Feeding disorders are a major contribution to hospitalization and morbidity in infants with VCFS (Table 6). The effects of CHD and CP are compounded by additional risk factors for feeding disorders in this population, causing the majority of children to have at least one diagnosed feeding disorder. Hypotonia is likely a contributing risk factor for feeding disorders in some children with VCFS. Oral motor apraxia has been associated with VCFS [15], this was likely another major contributing factor. Because of the high incidence of feeding disorders in children with VCFS, a thorough evaluation by a multidisciplinary feeding team should become standard of care for all young children diagnosed with VCFS. The feeding team may include health professionals from gastroenterology, nutrition, behavioral psychology, speech pathology, occupational therapy, and nursing. The evaluation should include complete medical, feeding, and dietary histories; weight and height measurements; physical examination; assessment of the child's nutritional and caloric needs; and observation of the child's eating and drinking behaviors. A thorough multidisciplinary feeding evaluation allows care providers to develop a comprehensive individualized feeding program that meets the needs of both the child and parents. [19-21]

The feeding difficulties experienced by infants with VCFS contribute to the high incidence of FTT in this population (Table 6). Further more, feeding problems with CHD increase the incidence of FTT in children with VCFS over that observed in children with isolated CHD. In individuals with CHD, a feeding disorder may be less aggressively managed or go unrecognized if the heart defect is assumed to be the cause of FTT. This could lead to earlier surgical repair of a heart defect and supports the need for feeding team evaluation in this population. Feeding problems in individuals with VCFS who are not diagnosed in infancy may be even more likely to be overlooked. Late diagnosis of VCFS is especially common in individuals without conotruncal defects or major malformations. These growth-related issues have implications for health care management of children with VCFS. If CHD is assumed to be the cause of FTT, surgical repair of the heart lesion may be expected to resolve the growth delay. Continued failure of the child to gain weight, or the presence of FTT in a child without CHD, may be erroneously attributed to poor parenting skills rather than an intrinsic aspect of the underlying condition. Parenting skills are especially likely to be questioned in cases of familial VCFS, when the parent may exhibit learning delay or mental illness. In the author's experience, parental blame has been placed before adequate investigation of the cause of FTT in more than once instance. A complete diagnostic evaluation of the FTT, including caloric counts, must be performed before a cause can be attributed. In cases where removing the child from parental care is necessary, the situation may be handled more sensitively when parents, social workers, and health care providers understand the difficulties intrinsic to feeding infants with VCFS. Parents must also be educated on the

high incidence of FTT in infants with VCFS to help alleviate parental anxiety and self-blame.

As demonstrated in Table 5, the percentage of children with VCFS requiring hospitalization continues to be significant in the second through fifth years of life, after controlling for surgical correction of heart defects and VPI (common in children with CP and VCFS) [22]. This indicates that children with VCFS continue to experience significant morbidity throughout infancy and early childhood. Parents of children with VCFS need to be made aware of this increased risk of hospitalization throughout the first five years of life, including the potential for VCFS-related morbidity beyond that caused by their child's specific birth defects. In the future, targeted studies should be performed to examine how the health care needs of children with VCFS change as children get older. Because the percentage of children with VCFS requiring hospitalization remained steady at 20-25% during the third to fifth years of life, it is possible that the morbidity and hospitalizations experienced by individuals with VCFS remains significant throughout childhood. Future studies should extend the investigation beyond the fifth year to determine the hospitalization and health care needs of these children throughout childhood.

Respiratory illness is a greater source of morbidity and hospitalization in the VCFS population than in normal children and children with isolated CP or CHD. Compared to the CHD cohort, individuals with VCFS were twice as likely to require hospitalization for at least one respiratory illness. Additionally, 35% of individuals with VCFS had a history

of respiratory infections noted in the medical record. (Table 4) While total respiratory illnesses were not specifically counted, this documentation in the records of children with zero or one respiratory hospitalization suggests additional respiratory illnesses managed at home or on an outpatient basis. Tracheostomy was not a significant risk factor for respiratory hospitalization in the VCFS cohort. The percentage of individuals in the cohort with VCFS who required respiratory-related hospitalizations remained significant when individuals with laryngeal and tracheal disorders were excluded, indicating that VCFS was a risk factor for respiratory illness hospitalization in the absence of diagnosed airway malformations. The majority of these hospitalizations occurred in individuals with VCFS who had CHD, suggesting an association between hospitalization for respiratory illness and heart defects in children with VCFS. Because a history of CHD is a risk factor for severe respiratory illness [23], a history of CHD may increase the likelihood of hospital admission for a child presenting with respiratory symptoms.[24] However, the increased number of individuals hospitalized for respiratory illness in the VCFS cohort compared to the CHD cohort suggests that respiratory infections occurred more frequently or caused increased morbidity in individuals with VCFS. Future research should be performed to identify reasons for the increased morbidity due to respiratory illnesses. If specific risk factors for respiratory illness can be identified in the VCFS population, targeted screening for these risk factors and preventive interventions may be possible. Parents and health care providers should be advised that children with VCFS, especially those with heart defects, have an increased risk of morbidity and hospitalization due to respiratory illness. Parents may also be advised to remove additional risk factors for respiratory infection, such as cigarette smoke and contact with

infected individuals, from the child's environment. [25, 26] Parental education on reduction of environmental risk factors for respiratory illness in the home can be an effective means of decreasing the incidence of respiratory illness in children. [27]

Individuals with VCFS and thymic hypoplasia or low T cell counts who require hospitalization for respiratory illness do not appear to differ from children with VCFS and no known immune dysfunction who require respiratory hospitalization. The average number of hospitalizations and range of hospitalizations per individual were the same for the two groups. This suggests that immune abnormalities may not account for the increased risk of respiratory illnesses and hospitalizations observed in children with VCFS.

The comparisons of hospitalization duration among the four cohorts in Table 2 are striking, despite that many of the analyses did not achieve statistical significance. For all duration of hospitalization analyses, the average duration for the hospitalizations of children with VCFS was greater than those required by the other three cohorts. The lack of statistical significance in some comparisons appears to be caused by the extreme variability in the duration of hospitalizations required by the VCFS cohort. For example, the average birth duration for the VCFS cohort was greater than three and one-half times that of the CHD cohort, but this finding did not achieve statistical significance. The birth hospitalizations for the VCFS cohort ranged from one to 145 days in length. This extreme variability makes offering anticipatory guidance to parents difficult. With the exception of the child hospitalized for 145 days at birth, there were not significant

outliners that could be responsible for this variability. The presence of feeding difficulties or FTT will likely increase the length of recovery time after surgeries and procedures and result in an increased length of hospitalization. Caution should be used when advising parents of the length of hospitalization required for children with VCFS, as there appears to be extreme variability in recovery time among these children.

The source of children for the normal cohort may also have inflated the background rate of hospitalization. Because CCHMC is a regional referral center for children with birth defects and chronic illness, individuals in the VCFS, CP, and CHD cohorts may not reside in the immediate vicinity of the hospital. These children may have received additional inpatient care at their neighborhood institutions. The normal cohort was ascertained through a primary care center that manages local children. These local children would have received all their inpatient and outpatient care at CCHMC. Therefore, the hospitalizations of the normal cohort will likely be more completely represented in the CCHMC medical record than those of the other cohorts. Additionally, CCHMC is located in a socioeconomically-disadvantaged city neighborhood. The significantly increased use of Medicaid in the normal cohort compared to all other cohorts reflects this bias (Table 1). Because socioeconomic disadvantage is a risk factor for pediatric hospitalization [28, 29], the inclusion of this population of children as a normal control may inflate the background rate of hospitalization over that of healthy children in the general population. If inflation of hospitalization rates among normal controls occurred, it would have served to minimize differences seen among the cohorts.

Because sufficient numbers of five-year-old children with isolated VSD and TOF who had tested negative for VCFS using FISH were not available, children who had not been tested for VCFS were included in the CHD cohort. Screening of the medical records for additional birth defects, oral motor apraxia, and VPI was performed for each child in order to minimize the chance that a child with VCFS was incorrectly included in the CHD cohort. Because approximately 15% of children with TOF are believed to have VCFS [6], one would have expected two of the children in the CHD cohort to have VCF if children with heart defects were selected randomly. Due to screening of the medical record for VPI and other features of VCFS in the children with CHD, it is unlikely that children with VCFS were included in the CHD cohort. However, if one or more children with VCFS were incorrectly assigned to the CHD cohort, this would only minimize the differences between the CHD and VCFS cohorts.

The incomplete understanding of VCFS has implications beyond health care management. Current data limit the amount of anticipatory guidance that can be offered to parents of children with VCFS. The lack of information on the number of surgical procedures, hospitalizations, and health problems that can be expected may leave parents unprepared to cope with their children's medical needs. Because parental attitudes are key factors in child coping and development, negative parental experiences and/or attitudes can adversely affect both child and family. [30]

Children with VCFS have more frequent and longer hospitalizations than do children with isolated CHD, isolated CP, and typical healthy children. Respiratory illnesses and

feeding disorders appear to contribute substantially to morbidity and hospitalization in children with VCFS. Children with VCFS should undergo a multidisciplinary feeding team evaluation. All children should be considered at high risk for respiratory illnesses, including those in whom immune dysfunction is not suspected. Parents should be advised of the incidence of hospitalization, feeding disorders, and respiratory illnesses in children with VCFS. Future studies should attempt to determine the reasons for increased respiratory illness in children with VCFS and should extend these findings by examining the hospitalizations of older children with VCFS.

BIBLIOGRAPHY

1. Driscoll, D.A., M.L. Budarf, and B.S. Emanuel, *A genetic etiology for DiGeorge syndrome: consistent deletions and microdeletions of 22q11.* Am J Hum Genet, 1992. **50**(5): p. 924-33.

2. Scambler, P.J., et al., *Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome.* Genomics, 1991. **10**(1): p. 201-6.

3. Scambler, P.J., et al., *Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus.* Lancet, 1992. **339**(8802): p. 1138-9.

4. Wulfsberg EA, L.-C., J Neri G, *What's in a name? Chromosome 22q abonrmalities and the DiGeorge, Velocardiofacial, and Conotruncal Anomalies Face syndromes.* Am J Med Genet, 1996. **65**: p. 317-319.

5. Goldmuntz, E., et al., *Frequency of 22q11 deletions in patients with conotruncal defects.* J Am Coll Cardiol, 1998. **32**(2): p. 492-8.

6. Maeda, J., et al., *Frequent association of 22q11.2 deletion with tetralogy of Fallot.* Am J Med Genet, 2000. **92**(4): p. 269-72.

7. Frohn-Mulder, I.M., et al., *Chromosome 22q11 deletions in patients with selected outflow tract malformations.* Genet Couns, 1999. **10**(1): p. 35-41.

8. Marino, B., et al., *Congenital heart defects in patients with DiGeorge/velocardiofacial syndrome and del22q11.* Genet Couns, 1999. **10**(1): p. 25-33.

9. Goldberg R, M.B., Marion, R, Scambler PJ, Shprintzen RJ, *Velo-cardio-facial syndrome: A review of 120 patients.* Am J Med Genet, 1993. **45**: p. 313-319.

10. McDonald-McGinn, D.M., et al., *The Philadelphia story: the 22q11.2 deletion: report on 250 patients.* Genet Couns, 1999. **10**(1): p. 11-24.

11. Ryan, A.K., et al., *Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study.* J Med Genet, 1997. **34**: p. 798-804.

12. Motzkin, B., et al., *Variable phenotypes in Velocardiofacial syndrome with chromosomal deletion.* J Pediatr, 1993. **123**(3): p. 406-410.

13. Yamagishi, H., et al., *Ventricular septal defect associated with microdeletions of chromosome 22q11.2.* Clin Genet, 2000. **58**(6): p. 493-6.

14. Goldberg, R., et al., *Velo-cardio-facial syndrome: A review of 120 patients.* Am J Med Genet, 1993. **45**: p. 313-319.

15. Rommel, N., et al., *Retrospective analysis of feeding and speech disorders in 50 patients with velo-cardio-facial syndrome.* Genet Couns, 1999. **10**(1): p. 71-78.

16. Sullivan, K.E., et al., *Lack of correlation between impaired T cell production, immunodeficiency, and other phenotypic features in chromosome 22q11.2 deletion syndromes.* Clin Immunol Immunopathol, 1998. **86**(2): p. 141-6.

17. Lipson, A.H., et al., *Velocardiofacial (Shprintzen) syndrome: an important syndrome for the dysmorphologist to recognize.* J Med Genet, 1991. **28**: p. 596-604.

18. Hopkin, R.J., et al., *Increased need for medical interventions in infants with velocardiofacial (deletion 22q11) syndrome.* J Pediatr, 2000. **137**(2): p. 247-9.

19. LIfschitz, C.H., *Feeding problems in infants and children.* Curr Treat Options Gastroenterol, 2001. **4**(5): p. 451-457.

20. Siktberg, L.L. and D.L. Bantz, *Management of children with swalling disorders.* J Pediatr Health Care, 1999. **13**(5): p. 223-229.

21. Lefton-Greif, M.A. and J.C. Arvedson, *Pediatric feeding/swallowing teams.* Semin Speech Lang, 1997. **18**(1): p. 5-11.

22. Perkins, J.A., K. Sie, and S. Gray, *Presence of 22q11 deletion in postadenoidectomy velopharyngeal insufficiency.* Arch Otolaryngol Head Neck Surg, 2000. **126**(5): p. 645-8.

23. Kaneko, M., et al., *Risk factors for severe respiratory syncytial virus-associated lower respiratory tract infection in children.* Pediatr Int, 2001. **43**(5): p. 489-492.

24. *RSV infection and bronchiolitis: who qualifies for prevention?* Prescrire Int, 2000. **9**(50): p. 173.

25. Wright, A.L., et al., *Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illness in infancy.* J Pediatr, 1991. **118**(2): p. 207-214.

26. Holberg, C.J., et al., *Child day care, smoking by caregivers, and lower respiratory tract illness in the first 3 years of life.* Pediatrics, 1993. **91**(5): p. 885-892.

27. Greenberg, R.A., et al., *Evaluation of a home-based intervention program to reduce infant passive smokin and lower respiratory illness.* J Behav Med, 1994. **17**(3): p. 273-290.

28. Naclerio, A.L., J.W. Gardner, and M.M. Pollack, *Socioeconomic factors and emergency pediatric ICU addmissions.* Ann N Y Acad Sci, 1999. **896**: p. 379-382.

29. McConnochie, K.M., K.L. Roghmann, and G.S. Liptak, *Socioeconomic variation in discretionary and mandatory hospitalization of infants: an ecologic analysis.* Pediatrics, 1997. **99**(6): p. 744-784.

30. Weil, J., *Psychosocial Genetic Counseling*. 2000, New York: Oxford University Press.

UNIVERSITY OF CINCINNATI

August 16, 2002

I, Michelle Lea Wojtasiak,

hereby submit this as part of the requirements for the degree of:

Master of Science

in Medical Genetics

It is entitled Retrospective Chart Review of Hospitalizations Required by Children with Velocardiofacial Syndrome

Approved by:

Robert Hopkin

Judy D. Bean

Judith A. Johns