Clinical Outcomes at 9-10 Years of Age in Children Born with Cystic Fibrosis Transmembrane Conductance Regulator Related Metabolic Syndrome

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June 19, 2023

Abstract

Background and Objectives: There are limited data on cystic fibrosis (CF) transmembrane conductance regulator-related metabolic syndrome (CRMS) outcomes beyond infancy. The goal of this study was to analyze outcomes of infants with CRMS up to the age of 9-10 years using the CF Foundation Patient Registry (CFFPR). Methods: We analyzed data from the CFFPR for individuals with CF and CRMS born between 2010-2020. We classified all patients based on the clinical diagnosis reported by the CF care center and the diagnosis using CFF guideline definitions for CF and CRMS, classifying children into groups based on agreement between clinical report and guideline criteria. Descriptive statistics for the cohort were calculated for demographics, nutritional outcomes, and microbiology for the first year of life and lung function and growth outcomes were summarized for ages 6-10 years. Results: From 2010-2020, there were 8,765 children with diagnosis of CF or CRMS entered into the CFFPR with sufficient diagnostic data for classification, of which 7,591 children had a clinical diagnosis of CF and 1,174 had a clinical diagnosis of CRMS. CRMS patients exhibited normal nutritional indices and pulmonary function up to age 9-10 years. The presence of respiratory bacteria associated with CF, such as *Pseudomonas aeruginosa* from CRMS patients ranged from 2.1-9.1% after the first year of life. Conclusions: Children with CRMS demonstrate normal pulmonary and nutritional outcomes into school age. However, a small percentage of children continue to culture CF-associated respiratory pathogens after infancy.

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Short Title: CRMS Outcomes at 9-10 Years

Conflicts of Interest: The authors report no conflicts of interest related to this paper

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Results:

From 2010-2020, there were 8,765 children with diagnosis of CF or CRMS entered into the CFFPR with sufficient diagnostic data for classification, of which 7,591 children had a clinical diagnosis of CF and 1,174 had a clinical diagnosis of CRMS. CRMS patients exhibited normal nutritional indices and pulmonary function up to age 9-10 years. The presence of respiratory bacteria associated with CF, such as*Pseudomonas aeruginosa* from CRMS patients ranged from 2.1-9.1% after the first year of life.

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Word count: 246

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive condition caused by variants in the CF transmembrane conductance regulator (*CFTR)*gene [1]. Early diagnosis of CF through newborn screening (NBS) results in improved nutritional and pulmonary outcomes, and since late 2009 CF NBS has been offered in every state in the United States (US) [2-4]. An unintended consequence of CF NBS is the detection of infants with an abnormal NBS, but inconclusive diagnostic testing. In the US, this condition is termed CFTR-related metabolic syndrome (CRMS) [5]. The analogous term in Europe and Australia is CF screen positive, inconclusive diagnosis (CFSPID) [6].

There have been numerous studies of the clinical features and outcomes of CRMS/CFSPID over the last several years [7-9]. Although there are variations in study design and cohorts, some common themes are present. The vast majority (˜90%) of infants with CRMS/CFSPID do not convert to CF. However, a small percentage convert to CF, either because the variants identified through NBS or further testing are subsequently determined to be CF-causing or because the child's sweat Cl rises above the diagnostic threshold

of 60 mmol/L. In some cases children develop clinical features concerning for CF, such as a positive respiratory culture for Pseudomonas aeruginosa (Pa).

The majority of studies of CRMS have been limited to outcomes in the first three years of life, and there are limited data on outcomes in older children. The US CF Foundation Patient Registry (CFFPR) began collecting data on infants with CRMS in 2010, and contains one of the largest cohorts of infants with CRMS available. We previously reported on clinical outcomes in infants with CRMS in the CFFPR in the first 2 years of life, and found that nutritional status was normal in the majority of infants with CRMS [10]. However, a small percentage developed clinical features concerning for CF, such as a respiratory culture positive for Pa. We also found that a substantial proportion (41%) of infants who meet CFF guideline definition of CRMS were classified as CF by their CF Care Center.

The objective of this study was to describe the characteristics of children with CF and CRMS born 2010-2020, with a focus on nutritional, microbiologic, and pulmonary outcomes through age 10 years. Because our earlier analysis showed a high proportion of infants with CRMS were classified clinically as CF, we also aimed to quantify the extent to which diagnoses of CF or CRMS reported by CF care teams were consistent with CFF guidelines and characterize any differences in clinical characteristics among children reported as having CF but meet CFF guideline criteria for CRMS.

METHODS

The design of the CFFPR has previously been described [11]. In brief, individuals who obtain care at CFF accredited Care Centers in the United States are invited to participate in the CFFPR; data are available from 1986 to the present. Nutritional, microbiologic, pulmonary, and medication data from every outpatient encounter are reported, as well as demographic and diagnostic data and hospitalizations. Individuals with CF (parents or guardians in the case of those younger than 18 years of age) provide informed consent to participate. CRMS was added as a diagnostic category in 2010.

We included all individuals in the CFFPR born between 2010 to 2020 with a CF or CRMS diagnosis reported by a CF care center. We then reviewed reported sweat chloride and *CFTR* genotype data for these individuals to determine if the diagnosis reported by the CF care center agreed with CFF diagnosis guideline criteria [12]. In the event an individual reported multiple sweat chloride values, we used the highest lifetime sweat chloride value ever reported to the CFFPR. We utilized the Clinical and Functional Translation of CFTR Project (CFTR2) to determine the disease liability of CFTR variants [13]. Patients without adequate genetic or sweat chloride data to determine a CFF guideline diagnosis were excluded from the analysis. We previously reported that many infants assigned a clinical diagnosis of CF in the CFFPR by their CF Care Center did not meet diagnostic criteria for CF, but rather met criteria for CRMS [10]. We therefore classified children into four mutually exclusive categories: CF care center report CF and CFF guidelines diagnosis criteria indicate CF (CFc/CFg); CF care center report CRMS but CFF guideline diagnosis criteria indicate CF (CRMSc/CFg); and CF care center reported CF but CFF guideline diagnosis criteria indicate CRMS (CFc/CRMSg); and CF care center reported and CFF guidelines criteria both indicate CRMS (CRSMc/CRMSg). CRMSc/CFg were excluded from the descriptive analysis under the assumption those reported CRMS diagnoses may be data entry errors.

We then compared CFc/CFg children to children classified as CFc/CRMSg and CRMSc/CRMSg in terms of demographic characteristics and clinical characteristics including airway microbiology, anthropometrics, pulmonary function, and health care utilization in the first year of life using data reported 2010-2021. Pulmonary function outcomes were assessed in children [?]6 years using the percent predicted forced expiratory volume in one second ($ppFEV_1$) based on the Global Lung Function Initiative reference equations [14]. We calculated CFFPR participation through 2021 by group. We present the distribution of categorical variables as proportions and continuous variables using the mean and standard deviation. We calculated confidence intervals of the mean when presenting continuous variables by age. Significance testing was performed using chi-square tests of association or ANOVA to detect a difference across the three groups. Analysis was implemented in SAS version 9.4. This analysis was classified as exempt by North Star Institutional Review

Board.

RESULTS

A total of 9,793 children born between 2010-2020 contributed data to the CFFPR. We excluded 1,028 children missing sweat chloride or genotype data. Of the remaining 8,765 children, 7,591 had a CF diagnosis and 1,174 a CRMS diagnosis reported by a CF care team (Figure 1), leading to a CF:CRMS ratio of 6.5:1. Of those with a clinical diagnosis of CRMS, 65 had a guidelines-based diagnosis of CF and were excluded from comparison of summary statistics, leaving a total of 8,700 children**.** Only 42 infants who were initially diagnosed with CRMS had their diagnosis changed to CF in the CFFPR. Figure 1 illustrates how children were categorized based on CFF diagnosis guidelines. The agreement between CF care team-reported and CFF guidelines-based diagnosis was similar between children with CF (93%) and children with CRMS (94%). However, similar to our earlier analysis, a substantial number of infants (N=504) who met guideline criteria for CRMS were classified as CF by their CF Care Center (32% of all CRMSg). The distribution of sweat chloride data and number of CF causing variants for the entire study cohort is presented in Table S1 (available online). Among the children who met guideline criteria for CRMS, the proportion of children reported as having CFc by their care team (by birth cohort) has generally declined over time, with 38%-41% of children born in 2010-2012 to 18%-23% of children born 2018-2020 (Table S2).

Loss-to-follow-up among the CFc/CFg cohort was minimal, with only 4.2% of the overall CFc/CFg group not reporting data in 2021 compared to 17.3% of CFc/CFg and 43% of CRMSc/CRMSg children (p-value <0.0001). Figure 2 illustrates the proportion of each birth cohort that contributed data through 2021 and shows participation in the CFFPR is differential by age and diagnosis category. Participation rates by subgroup and birth year are presented in Tables S3-S5 and show much higher participation among the CFc/CFg group compared to children classified as CRMS by either a care team or CFF guidelines. Children classified as CRMSc/CRMSg born in 2010 had the lowest participation rates, as only 36.6% contributed data through 2021. A total of 41 deaths were reported in the entire cohort, with <5 deaths in the CFc/CRMSg or CRMSc/CRMSg subgroups.

We found differences in patient characteristics comparing CFc/CFg to the other two groups during the first year of life (Table 1). The proportion of Hispanic patients was higher in the CFc/CRMSg (20.0%) and CRMSc/CRMSg (16.8%) cohorts compared to CFc/CFg (13.9%) (p-value <0.0001). We found 35.2% of CFc/CFg reported any Medicaid/Medicare during the first year of life compared to 23.8% CFc/CRMSg and 15.0% CRMSc/CRMSg (p-value < 0.0001).

Differences in health care utilization and treatment were present between all three groups, with CFc/CRMSg and CRMSc/CRMSg children reporting fewer mean visits and few cultures in the first year of life. Very few CFc/CRMSg and CRMSc/CRMSg reported fecal elastase data (12.2% and 1.4%, respectively) but most children in those categories did report at least one throat culture (74.6% and 62.0%, respectively). CFc/CFg patients had a lower mean weight-for-age percentile (32.8$^{\text{th}}$ percentile) compared to CFc/CRMSg (44.1$^{\text{st}}$ percentile) or CRMSc/CRMSg (48.0$^{\text{th}}$ percentile) (p-value < 0.0001). Height percentile and weight-for-length percentiles were also higher among CFc/CRMSg and CRMSc/CRMSg children compared to CFc/CFg. The prevalence of airway microorganisms was highest in CFc/CFg children and lowest among CRMSc/CRMsg children. The prevalence of Pa among CFc/CRMSg children was 18% compared to 22% among CFc/CFg children; methicillin sensitive Staphylococcus aureus (MSSA) prevalence was also similar among those two groups. Infants with CFc/CFg were more likely to be prescribed CF therapies such as dornase alfa or bronchodilators. Pancreatic enzyme replacement therapy (PERT) was only reported in 24.0% of CFc/CRMSg and 3.8% of CRMSc/CRMSg children.

We next assessed the prevalence of airway bacteria among each diagnosis group at older ages among children for whom data are available (Table 2). The prevalence of positive Pa respiratory cultures in the first year of life in was higher in CF patients (22.8%) compared to CFc/CRMSg (18.1%) or CRMSc/CRMSg (7.0%) patients. A similar pattern was observed for *Stenotrophomonas maltophilia* , *Staphylococcus aureus* , and *Hemophilus influenzae* . Prevalence of Pa and other bacteria was higher in the CFc/CRMSg cohort compared

to the CRMSc/CRMSg cohort. In CFc/CFg patients, the annual prevalence of Pa was relatively unchanged by age (range 24%-28%)(Figure 3). However, in the CFc/CRMSg and CRMSc/CRMSg populations, the greatest prevalence of Pa occurred in infancy and was lower at age 2 and older (Figure 3).

Among children old enough for pulmonary function testing (>6 years of age), we compared the mean percent predicted forced expiratory volume in 1 second ($ppFEV_1$) between groups (Table 3) at integer ages. The mean $ppFEV_1$ in CFc/CFg children was lower compared to the other two groups from age six through age 10 years, with CRMSc/CRMSg children having the highest lung function at all ages. We also compared mean height and weight percentiles between groups (Table S4 and Table S5) at integer ages. Similar to $ppFEV_1$ results, mean height and weight percentiles in CFc/CFg children were lower compared to the other two groups from age 0 through age 10 years, with CRMSg/CRMSg children having the highest percentiles through age 1, then CFc/CRMSg having higher clinical measures.

Discussion:

In this study we performed a retrospective analysis of children reported to have CRMS in the CFFPR. Our results show that for the first 9-10 years of life, the large majority of infants with CRMS remain healthy and do not convert to CF. In contrast to children with CF, their ppFEV1 and nutritional indices are normal. However, a small percentage of children do develop clinical features concerning for CF, such as a respiratory culture positive for Pa.

Although several studies of prevalence and outcomes of CRMS/CFSPID, most studies have been limited to children [?]3 years old [7, 8]. Grove, et al performed a retrospective study of 29 infants with CRMS who were followed for 2-10 years and reported that 48% converted to CF [15]. However, many of these children were diagnosed on the basis of non-specific clinical signs, such as cough. More recently, Munck *et al* reported the results of a prospective matched cohort study of infants with CF and CFSPID [16]. Comparison of their results to ours is difficult because a large percentage (32%) of the CFSPID infants were later diagnosed with CF due to reclassification of their CFTR mutations as CF-causing. With that caveat in mind, their cohort also demonstrated normal nutritional and FEV_1 indices. However, chest computed tomography revealed the presence of bronchiectasis in 8% of the cohort, highlighting the potential for lung disease in CRMS/CFSPID infants. Terlizzi *et al* reported that 10% of CFSPID infants followed for up to 6 years converted to CF, based on an elevation of sweat chloride [?]60 mmol/L [17]. However, they did not report on any clinical features of these infants. Gonska, et al prospectively followed a cohort of infants with CRMS/CFSPID in Canada and Verona up to age 7 years [9]. Similar to our study, they found that nutritional indices and lung function were normal at age 7 years. Our study complements that of Gonska, et al and other by analyzing a larger, more diverse cohort of infants with CRMS/CFSPID followed at >100 CF Care Centers across the USA. We also analyzed microbiologic outcomes at different ages and showed that in contrast to infants/children with CF, Pa prevalence in CRMS/CFSPID declined with age. Taken together, the studies cited above and our results indicate that infants who meet a CFF guideline definition of CRMS may still present with clinical features concerning for CF even in childhood, and they support the need for continued close monitoring of this infants.

There are several limitations of our study, but also some strengths. Not all CRMS infants are entered into the CFFPR, either because their care teams or the families do not wish to enroll them. This may have resulted in underreporting of the true prevalence of CRMS. There were also many patients with incomplete genetic or sweat chloride data, which precluded us from being able to assign a guideline diagnosis of CF or CRMS. The CFFPR collects only limited clinical symptom and physical exam findings, such as cough or wheeze; having such data may have provided more insight into why some children were classified as CF despite not meeting sweat chloride or CFTR mutation criteria for this diagnosis. There is also variation in care amongst CF Centers, such as frequency of respiratory cultures and follow up sweat testing, which may have affected the consistency of some of our outcome measures. The loss to follow up rate was higher in the CRMSc/CRMSg compared to the other groups (Tables S3, S4, and S5). This may have resulted in selection bias towards retaining only those infants with more symptoms or concerns for CF. Thus we need to be circumspect in comparing clinical outcomes between the CRMSc/CRMSg and CFc/CRMSg groups.

Since follow up sweat testing was performed at the discretion of clinical care teams, we could not perform any analysis of serial sweat testing. Strengths of our study include the large number of patients in our study cohort followed at a large number of different CF Centers and the long follow up time.

In summary, this large registry-based analysis of CRMS infants up to ages 9-10 years shows that the large majority remain well, do not convert to a CF diagnosis, and have normal nutritional and pulmonary indices. However, a small proportion do develop clinical features concerning for CF. These results support continued close monitoring of these infants at least into early childhood. Future research should include longer follow up to ascertain the risk of CFTR-related disorder in these children and to identify any other risk factors for development of CF other than initial sweat chloride concentration.

Acknowledgements

The authors would like to thank the Cystic Fibrosis Foundation for the use of CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers, and clinic coordinators at CF centers throughout the United States for their contributions to the CF Foundation Patient Registry. We also thank Ase Sewall for her assistance with data preparation.

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