Rhinosinusitis in Pediatric Primary Ciliary Dyskinesia: Impact of Disease

Jay M. Bhatt, MD¹, Ethan G. Muhonen, MD², Maxene Meier, MS³, Scott D. Sagel, MD, PhD⁴,⁵, and Kenny H. Chan, MD⁴,⁶

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Abstract

Objectives. Primary ciliary dyskinesia (PCD) is a genetic disorder characterized by abnormal respiratory cilia ultrastructure and/or function causing defective mucociliary clearance. We investigated the extent and severity of rhinosinusitis in a large cohort of children with PCD and explored associations among risk factors, including genotype and sinus disease.

Study Design. Retrospective chart review.

Setting. Tertiary academic children’s hospital.

Subjects and Methods. A review was conducted with a patient registry at the PCD Foundation Center at our institution. Demographic, imaging, clinical, and operative data were reviewed through the institutional electronic health record system.

Results. Fifty-four subjects were identified with mean and median age at diagnosis of 5.2 and 4.0 years. The male:female ratio was 35%:65%. Sinus symptoms were present in 46 (85%) subjects, 22 of whom had chronic rhinosinusitis. Nineteen (35%) subjects underwent operative intervention, consisting of endoscopic sinus surgery (ESS; 16 patients) and maxillary lavage (3 patients). Nineteen subjects underwent adenoidectomy for PCD-related indications. Five sinus-related admissions in 3 subjects were noted during the study period, and no complication of rhinosinusitis occurred in the cohort. Genetic test results were available in 27 subjects, in whom 23 (85%) had biallelic mutations in a PCD gene. Demographic factors, Lund-Mackay score, and PCD genotype were not found to be predictors for ESS or hospitalization in our cohort.

Conclusion. While rhinosinusitis was common in our PCD cohort, most patients did not require ESS. Since complications of rhinosinusitis were uncommon, we recommend judicious surgical management tailored to the patient’s symptoms.

Keywords
rhinosinusitis, sinus disease, sinus surgery, primary ciliary dyskinesia

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Primary ciliary dyskinesia (PCD) is a disorder of cilia function, whether autosomal recessive (majority of cases) or X-linked (rare), that affects 1 in 15,000 to 40,000 people.¹,² As a result of dysfunctional ciliated epithelia in the respiratory tract, some of the most common upper respiratory manifestations of PCD are sinonasal symptoms, including chronic rhinosinusitis (CRS) in >50% of patients.³ Sinus disease in children with PCD is often worsened by abnormal sinus development, as noted by frontal and sphenoid sinus aplasia or hypoplasia observed in up to 73% of patients.⁴ A recent survey completed by 44 patients or caregivers from a German PCD cohort found that 59% experienced recurring sinonasal problems. Of these, 86% underwent diagnostic imaging studies, and 69% underwent at least 1 sinus surgical procedure.⁵ Additionally, nasal polyposis has been reported to occur in 15% of children with PCD.⁶

However, published PCD clinical reports have been limited by their scope and cohort size. Regardless of the isolated organism, PCD patients receive a mean 25 individual courses of antibiotics by 10 years of age, which is much higher than that of the normal population.⁵ There have been 3 small studies (range, 1-35 subjects) describing endoscopic sinus surgery (ESS) outcomes, and ESS has been shown to decrease CRS symptoms at 30-month follow up.⁷⁻⁹
have been no published studies on complications and hospitalization for CRS in this population. Similarly, there have been no studies exploring the relationships of PCD genotypes with clinical sinus disease.10

Because of the paucity of clinical information on how severely CRS affects the PCD population and our access to a relatively large pediatric PCD population, we investigated the extent and severity of CRS in our PCD population and examined associations among risk factors, including PCD genotype and sinus disease.

Methods

Following Colorado Multiple Institutional Review Board approval, the electronic health record (EHR; Epic, Verona, Wisconsin) and a database maintained by the PCD Foundation Center at Children’s Hospital Colorado, Aurora, Colorado, were reviewed. Subjects with a known diagnosis of PCD who were registered in the database were cross-referenced with the EHR, and all subjects with an adequate clinical history available for review in the EHR were included. The cohort for the current analysis comprised those with confirmed PCD based on abnormal ciliary ultrastructure by transmission electron microscopy and/or identification of biallelic mutations in a known PCD-causing gene with compatible clinical features.11

PCD genetic testing with multigene panels available in commercial genetic laboratories was performed in a subset of our subjects. A confirmed genetic diagnosis of PCD was based on identifying 2 disease-causing mutations in a single PCD gene. Individuals who had variants of uncertain significance or who were found to only have 1 mutation identified in a single PCD gene were deemed as having a negative test. In addition to demographic data, information pertaining to sinus computed tomography (CT) findings, surgical interventions, and sinus-related hospitalizations was collected. Lund-Mackay (LM) scores were calculated for each CT scan.12 A 1-way analysis of variance was used to test the association between groups (ESS, maxillary lavage, and no procedure) and LM scores. All statistical tests were considered significant at an alpha level of 0.05. All analyses were conducted with R 3.4.1 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). REDCap (Research Electronic Data Capture) was utilized to enter all survey results. Hosted at the University of Colorado School of Public Health and HIPAA compliant (Health Insurance Portability and Accountability Act), REDCap is a secure web-based application designed to support data capture for research studies.

Results

A total of 55 subjects with PCD from 2004 to 2017 were identified, and 54 were included in the final analysis as sufficient clinical information was present in their EHR. The demographic characteristics of the study cohort are summarized in Table 1. PCD was diagnosed at a mean age of 5.2 years. Our cohort consisted of twice as many girls (n = 35, 65%) as boys (n = 19, 35%). The majority (70%) of the cohort was Caucasian, followed by Hispanic (22%). Genetic testing was performed in 27 subjects, in whom 23 (85%) had biallelic mutations in these PCD genes: CCDC40 (n = 9), DNAH5 (n = 5), DNAH11 (n = 4), CCDC39 (n = 3), PIH1D3 (n = 1), and RSPH4A (n = 1).

Forty-six (85%) patients exhibited sinus symptoms, and 22 (45%) carried a formal clinical diagnosis of CRS based on clinical history and examination. Sixteen subjects (13 of 19 from the surgical group and 3 of 35 from the nonsurgical group) had CT data in addition to imaging reports, allowing us to calculate LM scores. While all imaging reports showed severe sinusitis, the mean ± SD LM score for the subgroup was 15.8 ± 2.6. The highest disease burden was noted in the ostiomeatal complex, followed by the anterior ethmoid sinuses (Table 2).

Among our 54 patients, 19 (35.2%) underwent sinus-related procedures. Surgical intervention included ESS (n = 16) and maxillary lavage (n = 3). The paranasal sinuses requiring surgical intervention, in decreasing frequency, were the maxillary, ethmoid, sphenoid, and frontal sinuses. The mean number of sinus procedures was 1.93 per patient when surgery was needed or 1.86 among the entire cohort. Among these patients, 16 (ESS, n = 10; maxillary lavage,
n = 3; nonsurgical, n = 3) had CT scans available for LM scoring. The mean LM score for the ESS group was 16.6 ± 2.76; for the maxillary lavage group, 16.7 ± 2.31; and for the nonintervention group, 15.0 ± 2. There was no difference in LM scores among the groups (P = .652). A total of 20 subjects underwent an adenoidectomy: 1 had an adenotonsillectomy for sleep-disordered breathing, and 19 underwent an adenoidectomy for PCD-related indications. Of these 19 subjects, 8 underwent adenoidectomy with or without tubes; 7 underwent adenoidectomy with or without tubes with a subsequent sinus-related procedure; and 4 underwent adenoidectomy in conjunction with a sinus-related procedure.

Assessment of outpatient medical therapy related to CRS in the cohort was deemed to be inaccurate, since the EHR would not have captured ambulatory activities rendered by primary care physicians outside our health care system. Five sinus-specific hospitalizations for 3 subjects were recorded in the cohort with the following discharge diagnoses: chronic sinusitis (n = 1), pneumonia and sinusitis (n = 1), and acute exacerbation of chronic sinusitis (n = 3). No complications resulting from rhinosinusitis were noted in this cohort. More male patients were hospitalized (26%) than female patients (14%).

The significance of having a known PCD mutation and the likelihood of an altered clinical course (ESS and hospitalization) were explored. No statistical significance was found in any of these factors when the positive and negative mutation subgroups were compared. LM scores were also compared between those with DNAH5 or DNAH11 mutations (associated with outer dynein arms abnormalities) and those with mutations in CCDC39 or CCDC40 (associated with central microtubular disorganization and absence of inner dynein arms). Two of the 3 patients who were hospitalized also had a history of functional ESS.

Discussion

With the standard definition of CRS (≥12 weeks of symptoms), our pediatric PCD cohort experienced a much higher CRS burden than that of the general pediatric population. Within our cohort, all but 8 patients (85%) reported clinically significant sinus symptoms, and 22 (45%) carried a formal diagnosis of CRS. By comparison, previous work has shown that CRS may occur in only 9% of the 1- to 5-year-old population, and one recent study utilizing data from the National Center for Health Statistics showed that a CRS diagnosis was associated with only 2% of visits to ambulatory care settings in patients aged 0 to 20 years from 2005 to 2012.13,14 The ethnic makeup of the cohort likely represented the regional geographic composition and does not denote a racial predilection for the disease. Findings from our study add to the limited knowledge in this area by quantifying the extent and severity of CRS in a relatively large referral pediatric PCD population.

When imaging is available, the LM score can be used to increase the positive predictive value of imaging and help guide treatment options.15 In children, a score >5 is helpful in predicting sinus disease, which was the cutoff used in our study to indicate the presence of sinus disease in the imaging reviewed.16 In our cohort, we noted that mean CT disease burden was 15.8 ± 4.0, well above the cutoff for sinus disease. When subgroup analyses were performed, we failed to show correlations of higher LM for a corresponding need for ESS and hospital admissions as well as likelihood for PCD mutations. Clearly, the determinants for surgical intervention and hospitalization lay more in the clinical picture than LM score alone.

Failure to correlate sinus disease severity and need for ESS with PCD genotype likely reflects our small sample size with genetic information. As we are learning about genotype-phenotype relationships in PCD, particularly in terms of lung disease,17,18 the same may be true for upper airway disease.

CRS is highly prevalent in pediatric cystic fibrosis (CF), and there are some similarities but unique differences as compared with PCD. Naturally, with a prevalence rate of 1:3000, CF is a more thoroughly studied disease. Hamilos19 recently published a useful review on CF. While mucostasis is seen in both diseases, it is caused by dysfunctional chloride channels in CF. The distinctive physical finding in CF is nasal polyps, which is present in 18% of children aged <6 years and 45% in adolescents. Distinctive pathogens of Staphylococcus aureus and Pseudomonas aeruginosa are commonly found in children. Despite nasal polyposis, underdeveloped paranasal sinuses are commonly found in cases of CF. Limited surgical data exist in children, but adults with CF and polyposis have been found to need more frequent repeat ESS.

The most significant limitation of this study lies in the size of our cohort. Although 54 subjects represent a relatively large sample size as compared with other published single-center cohorts, we failed to identify any disease risk factors as the result. The other limitation is the lack of a prospective symptom-based quality-of-life instrument such as the SN-5 (Sinus and Nasal Quality of Life Survey) to evaluate pre- and post-ESS disease burden to confer efficacy. Finally, the retrospective nature of this investigation precludes prospective collection of microbiologic data, definition of surgical indications, as well as follow-up of treatments and outcomes in these patients.

Conclusion

Pediatric subjects with PCD are afflicted greatly by rhinosinusitis when compared with the general pediatric population. Even though the disease burden is higher in our PCD population, most did not require ESS, develop complications, or require hospitalization. Thus, we recommend judicial use of surgical management tailored to the patient’s symptoms and disease course. We agree with the need for a multicenter and possibly multinational database or disease registry to prospectively track data pertaining to diagnosis, treatment, and outcomes of CRS in children with PCD.20
Author Contributions

Jay M. Bhatt, designed study and helped with analysis interpretation; critically reviewed and revised the article; helped to draft the article and approved final manuscript, and agrees to be accountable for the work; Ethan G. Muhonen, designed study and helped with analysis interpretation; critically reviewed and revised the article; reviewed edits by other authors and approved final manuscript, and agrees to be accountable for the work; Maxene Meier, reviewed and analyzed data; critically reviewed and revised the article; reviewed edits by other authors and approved final manuscript, and agrees to be accountable for the work; Scott D. Sagel, designed study and helped with analysis interpretation; critically reviewed and revised the article; reviewed edits by other authors and approved final manuscript, and agrees to be accountable for the work; Kenny H. Chan, designed study, designed analysis plan, helped with participant recruitment and data collection; drafted the article and critically reviewed edits by other authors; approved final version and agrees to be accountable for the work.

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