AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2025, Vol. 9(1):e70079

DOI: 10.1002/oto2.70079
http://oto-open.org
WILEY

Progression of Otologic and Nasal Symptoms in Primary Ciliary Dyskinesia Throughout Childhood

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Abstract

Objective. Primary ciliary dyskinesia (PCD) is characterized by upper and lower airway disease. Multiple studies have demonstrated the progression of pulmonary disease; however, longitudinal changes in the otologic and nasal symptoms have not been well described in patients. This study defines age-related prevalence, age of onset, and age-related trends in self-reported otologic and sinonasal comorbidities in individuals with PCD.

Study Design. A prospective, longitudinal, multicenter, observational study spanning up to 12 years.

Setting. Six PCD centers in North America.

Methods. Inclusion criteria were <19 years of age and a confirmed diagnosis of PCD based on electron microscopy and/or genetics. A standardized medical history questionnaire and physical exam were completed during each study visit. Descriptive statistics were performed for the entire cohort as well as for subgroups based on ciliary ultrastructure.

Results. A total of 147 participants were followed for an average of 7.6 ± 3.2 years. Pressure equalization tubes (PETs) were placed in 80%, transient hearing loss was reported in 68%, and persistent hearing loss was reported in 30%. Hearing aids and speech therapy were utilized by 8% and 27%, respectively. PETs were placed earlier in those with inner dynein arm/microtubular disorganization defects than those with outer dynein arm defects. Participants reported chronic nasal congestion in 97%, sinusitis in 87%, and 35% underwent >1 sinus surgery.

Conclusion. There is a high prevalence of reported otologic and sinonasal morbidity among people with PCD that begins during early childhood and persists. Further analysis is indicated to evaluate differences over time among participants with varying ultrastructural defects.

Level of Evidence. Level 2.

Keywords

hearing loss, immotile cilia syndrome, Kartagener's syndrome, sinusitis

Received September 23, 2024; accepted January 11, 2025.

Primary ciliary dyskinesia (PCD) is a genetic disorder, predominantly autosomal recessive, that leads to impaired mucociliary clearance in the upper and lower airways. Over 50 genes have been implicated in PCD.[1]

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Clinical manifestations include recurrent sinus infections and otologic comorbidities in addition to lung disease. Recent research has focused on defining the lower airway morbidities and progression of lung disease.[2–4] However, our understanding of the otologic and sinonasal comorbidities of PCD is poorly characterized, especially over time.

Several retrospective and cross-sectional studies have evaluated otologic and sinonasal comorbidities in children and adults with PCD.[5–15] These studies generally demonstrate high rates of hearing loss, nasal congestion, and sinusitis. However, several limitations exist in existing literature including the following: (1) the studies are retrospective in nature and performed at otolaryngology clinics; (2) accurate diagnosis of PCD is questionable in older studies; (3) existing studies generally have low sample size and represent a single time point. We present a unique data set that was collected using contemporary diagnostic criteria adopted by the American Thoracic Society in 2018. We described symptoms of 147 patients with 933 visits that were evaluated without referral to otolaryngology or audiology. Overall, it is unknown if otologic and nasal symptoms continually worsen over time or if people with PCD with these comorbidities improve over time.

Defects in the ultrastructure and function of motile cilia cause PCD. Approximately 70% of genetic defects can be characterized using transmission electron microscopy (TEM); however, some patients with PCD have normal TEM. Additionally, the motility of cilia varies across PCD genetic variants with subsets having motile cilia that cannot effectively coordinate to transport mucus. Contemporary diagnostic criteria involve the assessment of the clinical presentation, TEM, genotyping, high-speed video microscopy analysis, fluorescent antibody testing, and/or nasal nitric oxide testing.[1,5]

Recent studies have reported that certain ultrastructural defects, associated with specific genetic variants, can lead to worse lower airway disease.[2,6] Specifically, inner dynein arm coupled with microtubular disorganization (IDA/MTD) defects are associated with worse lung function compared to outer dynein arm (ODA) defects.[2,6,7] The timeline of disease progression, as well as genotype–phenotype relationships, has not yet been established with respect to the otologic and rhinologic symptoms of PCD.

We hypothesized that both nasal and otologic symptoms would improve over time as the sinonasal cavity and Eustachian tube develop during childhood. The main objectives of this study are to define (1) age-related prevalence, age of onset, and age-related trends of upper airway comorbidities in PCD; and (2) differences in comorbidities based on ultrastructural defects and/or genotypes.

Methods

Participants

Participants were enrolled at 6 sites—University of North Carolina, Chapel Hill, NC; Washington University, St. Louis, MO; Children's Hospital Colorado, Aurora, CO; Seattle Children's Hospital, Seattle, WA; The Hospital for Sick Children, Toronto, Canada; and Lucile Packard Children's Hospital-Stanford, Palo Alto, CA—through the Genetic Disorders of Mucociliary Clearance Consortium. Institutional Review Boards approved the protocols at each individual site. Inclusion criteria included an age of less than 19 years at enrollment and a confirmed diagnosis of PCD.

PCD diagnosis was defined as a compatible clinical phenotype (key clinical features of the chronic sinopulmonary disease and/or neonatal respiratory distress and situs inversus) plus a defect in ciliary ultrastructure (inner or outer dynein arm, MTD, radial spoke, and central complex), and/or identification of 2 known disease-causing gene mutations, as described previously by Shapiro et al.[5] Exclusion criteria were lung transplantation, pregnant or lactating females and those with co-existing malignancy, end-stage renal disease, or severe diseases that may have significant impact on lung function (eg, cystic fibrosis, primary immune deficiency, severe congenital heart disease, and severe scoliosis). Institutional Review Board approval was obtained at each site, along with informed consent from the participant's parent/legal guardian and/or assent as appropriate based on age.

Study visits were held annually with a goal of 10 years per participant. At each visit, a medical history (complete history at the initial visit and interval history during subsequent visits) and physical examination were completed. Medical history included the following:

1. Birth history: gestational age, days in the hospital, days on oxygen, presence or absence of meconium aspiration, presence or absence of neonatal respiratory distress syndrome, and presence or absence of a laterality defect.
2. Otitis media: history of otitis media including age of first infection, number of infections within first 2 years of life, presence or absence of ear tubes, age at the first set of ear tubes, number of sets of ear tubes, presence or absence of transient hearing loss, permanent hearing loss, need for speech therapy, and need for hearing aids.
3. Sinusitis: history of sinusitis, number of episodes per year, number of sinus surgeries, presence or absence of radiographic evidence of sinus disease. A physician reviewed radiographic studies if available.
4. Chronic nasal congestion: history of chronic nasal congestion and whether this occurred based on the season or throughout the year.

At subsequent visits, interval medical history questionnaires included the following:

1. Otitis media: number of infections since the last visit, presence or absence of ear tubes and if placed

since the last visit, presence or absence of transient hearing loss, permanent hearing loss, need for speech therapy, and need for hearing aids.
2. Sinusitis: number of episodes since the last visit, number of surgeries since the last visit, and presence or absence of radiographic evidence of sinus disease. Radiographic studies were reviewed if available.
3. Chronic nasal congestion: presence since the last visit. A physical examination was performed by a physician at each study visit.

Nasal biopsies for electron microscopy were performed using a standardized nasal curettage technique of the inferior turbinate using a Rhino-Pro™ (Arlington Scientific, Inc.) from the surface of the inferior turbinate as described previously.[15,16] The methods used for examining ciliary ultrastructure have been described previously.[8–11] Electron photomicrographs were reviewed and scored by 3 independent investigators for the presence of Class 1 ultrastructural defects associated with PCD,[12] including the absence of ODA, absence of ODA and IDA, and absence of IDA with MTD (IDA/MTD).

Statistical Analysis

Participants were grouped based on these ultrastructural defects and/or genetic variants associated with specific ultrastructural defects, plus normal/near normal/other ultrastructural defects. The 5 groupings were as follows: (1) ODA defects, (2) IDA/MTD defects, (3) ODA/IDA defects, (4) normal/near normal/other ultrastructural defects, and (5) *DNAH11* gene mutation. Those with *DNAH11* mutations are grouped and analyzed separately because although they appear to have normal axonemal ultrastructure on TEM, this gene encodes a component of the ODA.

Descriptive statistics are presented for the entire cohort and for the 5 ciliary ultrastructure/genetic defect groups. Generalized linear mixed models were used to assess the trend of upper airway comorbidities. Adjusted odds ratios (OR), 95% confidence intervals (CI), and *P* values are reported. The analysis was conducted using SAS 9.4 software (SAS Institute).

Results

A total of 147 participants were enrolled. Demographics are described in **Table 1**. These participants completed 933 study visits, with a median of 6 visits per participant (range 1-9). The average ages of participants' first and last visits were 7.9 and 15.5 years, respectively. Participants were followed for an average of 7.6 ± 3.2 years. The majority of our cohort had ODA defects (40.1%) and IDA/MTD defects represented 27.9% of the participants studied.

Overall Prevalence of Otologic and Nasal Comorbidities

The prevalence of chronic/recurrent otitis media and chronic sinonasal congestion is >97% across all groupings (**Table 2**). At least 1 set of pressure equalizer tubes (PETs) was placed in 80% of participants, 68% reported transient hearing loss, and 30% reported persistent hearing loss. Sinusitis was reported in 88% of participants. Notably, 35% of participants had at least 1 sinus surgery. The breakdown of prevalence by ultrastructural group/genetics is also noted in **Table 2**. There were no significant differences in the prevalence of upper airway disease manifestations based on ultrastructural grouping or genetics.

Table 1. Demographics and Ultrastructural Defects of Enrolled Participants

	Total (n = 147)	ODA (n = 59)	IDA/MTD (n = 41)	ODA/IDA (n = 21)	Normal ultrastructure (n = 14)	*DNAH11* (n = 12)
Gender						
Male	75 (51.0%)	31 (52.5%)	21 (51.2%)	13 (61.9%)	7 (50.0%)	3 (25.0%)
Race						
White	118 (80.3%)	51 (86.4%)	32 (78.0%)	13 (61.9%)	13 (92.9%)	9 (75.0%)
Black	5 (3.4%)	1 (1.4%)	2 (4.9%)	2 (9.5%)	0	0
Asian	17 (11.6%)	4 (6.8%)	4 (9.8%)	6 (28.6%)	1 (7.1%)	2 (16.7%)
American Indian/ Alaskan	4 (2.7%)	2 (3.4%)	1 (2.4%)	0	0	1 (8.3%)
Pacific Islander/ Hawaiian	1 (0.7%)	1 (1.4%)	0	0	0	0
Unknown	2 (1.4%)	0	2 (4.9%)	0	0	0
Ethnicity						
Non-Hispanic	133 (90.5%)	56 (94.9%)	36 (87.8%)	20 (95.2%)	11 (78.6%)	10 (83.3%)
Hispanic or Latino	14 (9.5%)	3 (5.1%)	5 (12.2%)	1 (4.8%)	3 (21.4%)	2 (16.7%)

Abbreviations: IDA/MTD, inner dynein arm/microtubular disorganization; ODA, outer dynein arm; ODA/IDA, outer dynein arm/inner dynein arm.

Table 2. Prevalence of Upper Airway Comorbidities

		Total (n = 147)	ODA (n = 59)	IDA + MTD (n = 41)	ODA/ IDA (n = 21)	Normal EM (n = 14)	*DNAH11* (n = 12)
Otologic	Chronic/recurrent otitis media	144 (98%)	59 (100%)	40 (98%)	20 (95%)	14 (100%)	11 (92%)
	PETs	117 (80%)	46 (78%)	33 (80%)	15 (71%)	13 (93%)	10 (83%)
	Transient hearing loss	100 (68%)	45 (76%)	24 (59%)	13 (62%)	10 (71%)	8 (67%)
	Permanent hearing loss	44 (30%)	13 (22%)	17 (41%)	5 (24%)	4 (29%)	5 (42%)
	Hearing aids	12 (8%)	5 (8%)	6 (15%)	0 (0%)	1 (7%)	0 (0%)
	Speech therapy	39 (27%)	17 (29%)	9 (22%)	6 (29%)	5 (36%)	2 (17%)
Nasal	Chronic nasal congestion	142 (97%)	58 (98%)	40 (98%)	19 (90%)	14 (100%)	11 (92%)
	Sinusitis	13 (88%)	54 (92%)	33 (80%)	17 (81%)	14 (100%)	12 (100%)
	Nasal polyps	31 (21%)	16 (27%)	6 (15%)	4 (19%)	5 (36%)	0 (0%)
	Sinus surgery	52 (35%)	23 (39%)	13 (32%)	3 (14%)	9 (64%)	4 (33%)

Abbreviations: IDA/MTD, inner dynein arm/microtubular disorganization; ODA, outer dynein arm; ODA/IDA, outer dynein arm/inner dynein arm; PETs, pressure equalizing tubes.

Table 3. Age of the First Occurrence of Upper Airway Comorbidities

Average age (AA)	ODA (n = 59)	IDA + MTD (n = 41)	ODA/IDA (n = 21)	Normal (n = 14)	*DNAH11* (n = 12)
First OM (mo)	15.4 ± 43.2	8.7 ± 15.4	10.3 ± 12.8	5.3 ± 3.4	9.2 ± 9.8
50% OM (mo)	4	4	6	6	6
First PETs (mo)	24.2 ± 21	15.8 ± 12.5	31.1 ± 27.5	24.9 ± 25.7	26.6 ± 17.7
50% PETs (mo)	18	12	24	15	24
First sinus surgery (y)	7.7 ± 4.3	7.2 ± 5.7	3.5 ± 0.7	7.3 ± 3.8	11.3 ± 5.0

Abbreviations: IDA/MTD, inner dynein arm/microtubular disorganization; ODA, outer dynein arm; ODA/IDA, outer dynein arm/inner dynein arm; OM, otitis media; PETs, pressure equalizing tubes.

Age-Related Trends

By 24 months of age, 50% of participants had PETs (**Table 3**). By the age of 4 months, 50% had developed OM in the ODA and IDA/MTD ultrastructure groups. In the ODA/IDA, normal ultrastructure group, and *DNAH11* group, 50% had developed OM by 6 months of age. The average age of the first set of PETs was significantly different in the IDA/MTD group (15.8 ± 12.5 months) compared to the ODA group (24.2 ± 21 months), $P < .04$. There were no other significant differences between groups.

As the cohort aged most comorbidities including nasal congestion remained stable, but sinusitis increased (Supplemental Figure S1, available online). The prevalence of otitis media remains high (>80% of the population), and ear tubes remain present in >75% of participants across the age spectrum.

For every 1-year increase in age: (1) there was an increase in the odds of experiencing sinusitis by 29% (95% CI 1.20-1.39, $P < .0001$); (2) there was a significant decrease in the odds of experiencing transient hearing loss by 6% (95% CI 0.90-0.97, $P < .001$); and (3) there was a significant decrease in the odds of needing speech therapy by 13% (95% CI 0.82-0.93, $P < .0001$) (Supplemental Figure S2, available online).

Discussion

This large, prospective, longitudinal, North American multicenter, observational study of children with PCD highlights the significant otologic and nasal morbidity associated with this disorder. This cohort provides novel data on age-related prevalence, age of onset, and age-related trends of otologic and nasal morbidities. Across all ultrastructural/genotype groups, there was a high prevalence of morbidity.

Otologic complaints are widely reported in studies of individuals with PCD.[10,13–15] In our longitudinal study, chronic or recurrent otitis media was nearly universal (98%). It was present in 100% of those with ODA defects, 98% with IDA/MTD defects, 95% with ODA/IDA defects, 100% with normal ciliary ultrastructure, and 92% with *DNAH11* mutations. Diagnosis of the first otitis media infection occurred on average at 15.4 ± 43.2 months in the ODA group, 8.7 ± 15.4 months in the IDA/MTD group, 10.3 ± 12.8 months in the ODA/IDA group, 5.3 ± 3.4 months in the normal ultrastructural group, and 9.2 ± 9.8 months in the *DNAH11* group. While there was an age range among groups regarding the development of the first episode of otitis media (5.3-15.4 months), half of the participants in each group developed otitis media much earlier, ranging from 4 to 6 months of age.

International trends in PET placement for PCD vary widely, with European groups tending to favor amplification (ie, hearing aids) and avoidance of PETs and North American groups tending to favor PETs. Our cohort received no specific guidance regarding otologic evaluation or placement of ear tubes and was frequently treated by local clinicians not associated with academic centers. In our cohort, at least 1 set of tubes was placed in 80% of participants, consistent with previous studies.[15,17] PETs were placed in 78% of participants with ODA defects, 80% with IDA/MTD defects, 71% with ODA/IDA defects, 93% with normal ultrastructure, and 83% with *DNAH11* mutations. In comparison, in the United States, ~8% of children undergo PET placement.[18] The average age of the first set of PETs placement was 24 months in the ODA group, 16 months in the IDA + MTD group, 31 months in the ODA/IDA group, 25 months in the normal ultrastructure group, and 27 months in the *DNAH11* group. Unlike the prevalence of PETs, the age at the first tube is consistent with individuals without PCD whose average age of PET insertion is ~1.4 years.[19] The placement of the first set of PETs differed significantly between the ODA group and the IDA + MTD group with the IDA/MTD group having PETs placed earlier (15.8 ± 12.5 months vs 24.2 ± 21 months). The IDA/MTD cohort requiring earlier intervention for an otologic comorbidity is consistent with previous studies demonstrating that the IDA + MTD group were diagnosed earlier, have worse lung function, and worse growth curves compared to those with ODA defects.[2] Again, while there was an age range of placement of first PETs (15.8-31.1 months), the age at which half of the participants had their first set placed was much earlier, ranging from 12 to 24 months.

Previous cross-sectional studies with smaller cohorts report varied findings regarding hearing loss, through both subjective and measured tools.[17,20–22] We expected high rates of transient conductive hearing loss that would improve as children grew. Transient hearing loss was reported by 68% of individuals but improved with age. However, the high rate of permanent hearing loss (30%) warrants more attention to determine if this is due to unresolved effusions, tympanosclerosis, or ototoxic complications of medical treatment. As hearing loss was a patient-reported outcome in this study, we do not have data on whether this was a conductive versus sensorineural hearing loss; therefore, the problem is likely underestimated.

The prevalence of hearing aid use (8%) and speech therapy (27%) among children with PCD has not been previously reported in the literature. The prevalence of these therapies is notable as they incur high monetary costs and significant time commitments from patients and their families. Given that initial hearing loss is expected to result from conductive hearing loss related to chronic effusions, early ear tube placement or amplification may prevent the need for speech therapy.

Consistent with previous non-longitudinal cohort studies,[17,23] self-reported chronic nasal congestion (97%) and self-reported sinusitis (88%) were common. Sinus surgery for the recalcitrant disease was reported in 35% of participants, with an average age of first surgery ranging from 3.5 ± 0.7 years to 11.3 ± 5.0 years depending on the ultrastructural group. More research is needed regarding the efficacy of sinus surgery, optimal extent of surgery, and long-term outcomes, such as how surgery affects quality of life and respiratory disease.

While this is a large study of a rare disease, there are limitations. Prominently, no evaluation was performed by an otolaryngologist to confirm reported symptoms and/or reported interventions (ie, sinus surgery). Physical examination did not include formal nasal endoscopy. Hearing loss was also self-reported based on history, and we were unable to determine whether it was sensorineural, conductive, or mixed. While these limitations are significant, unlike many current studies and even futures studies, there is limited selection bias for patients with more severe otologic and nasal symptoms, diagnosis of PCD was made using well-established criteria, and data from 147 individuals and nearly 1000 patient visits were reported. Additionally, subjective patient reports directly reflect the morbidity experience by the patients.

Conclusion

This study defined the prevalence and age-related trends of upper airway morbidities experienced by those with PCD. We report that otitis media and nasal congestion are present in nearly every participant and that prevalence remains persistently high throughout childhood. PETs were placed at a significantly earlier age in the IDA/MTD group, which is an ultrastructural defect associated with poorer lung function. This study provides a broad, longitudinal description of the upper airway morbidities in a large cohort of patients with PCD throughout childhood and emphasizes the need for additional study of the otolaryngologic complications of PCD. Toward this, the Genetics Disorders of Mucociliary Clearance Consortium is actively conducting an international, multicenter study that involves obtaining audiograms, tympanograms, radiographic data, nasal endoscopy evaluation, mucus analysis, and olfactory testing at a single visit for ~100 individuals with PCD.

Author Contributions

Isabelle Dagher, drafting the manuscript, analysis, interpretation; **Adam J. Kimple**, drafting the manuscript, analysis, interpretation, final approval of the manuscript; **Thomas W. Ferkol**, design of the work, data acquisition, revising the manuscript; **Scott D. Sagel**, design of the work, data acquisition, revising the manuscript; **Sharon D. Dell**, design of the work, data acquisition, revising the manuscript; **Carlos E. Milla**, design of the work, data acquisition, revising the manuscript; **Lang Li**, analysis, analysis, revising the manuscript; **Feng-Chang Lin**, analysis, analysis, revising the manuscript; **Kelli M. Sullivan**, design of the work, data acquisition, revising the manuscript; **Maimoona A. Zariwala**, design of the

work, data acquisition, revising the manuscript; **Michael R. Knowles**, design of the work, data acquisition, revising the manuscript; **Margaret Rosenfeld**, design of the work, data acquisition, revising the manuscript; **Margaret W. Leigh**, design of the work, data acquisition, revising the manuscript; **Stephanie D. Davis**, design of the work, data acquisition, revising the manuscript.

Disclosures

Competing interests: S.D.D.: PI of clinical study for ReCode Therapeutics. T.W.F.: Co-investigator of clinical study for ReCode Therapeutics and lead-investigator for clinical trial for Parion Sciences. S.D.D., A.J.K., T.W.F., M.R.K., M.W.L., M.R., and M.A.Z. are members of the Medical and Scientific Advisory Council of the Primary Ciliary Dyskinesia Foundation. Remaining authors have no conflicts of interest to disclose regarding this submission.

Funding source: The Genetic Disorders of Mucociliary Clearance Consortium (U54HL096458) is part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR) funded through a collaboration between NCATS and the National Heart, Lung, and Blood Institute (NHLBI). Other support includes NIH/NHLBI R01HL071798, NIH/NCATS Colorado CTSA UMI TR004399, and the UNC Children's Research Institute Carolina for the Kids Grant Program. The study was also supported in part (KNO) by the intramural research program of the NHLBI and NIH.

Supplemental Material

Additional supporting information is available in the online version of the article.

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