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Clinical Manifestations and Genotype of Primary Ciliary Dyskinesia Diagnosed in Korea: Multicenter Study

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ABSTRACT

Purpose: Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disorder that leads to secondary ciliary dysfunction. PCD is a rare disease, and data on it are limited in Korea. This study systematically evaluated the clinical symptoms, diagnostic characteristics, and treatment modalities of pediatric PCD in Korea.

Methods: This Korean nationwide, multicenter study, conducted between January 2000 and August 2022, reviewed the medical records of pediatric patients diagnosed with PCD. Prospective studies have been added to determine whether additional genetic testing is warranted in some patients.

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Results: Overall, 41 patients were diagnosed with PCD in 15 medical institutions. The mean age at diagnosis was 11.8 ± 5.4 years (range: 0.5 months-18.9 years). Most patients (40/41) were born full term, 15 (36.6%) had neonatal respiratory symptoms, and 12 (29.3%) had a history of admission to the neonatal intensive care unit. The most common complaint (58.5%) was chronic nasal symptoms. Thirty-three patients were diagnosed with transmission electron microscopy (TEM) and 12 patients by genetic studies. TEM mostly identified outer dynein arm defects (alone or combined with inner dynein arm defects, n = 17). The genes with the highest mutation rates were *DNAH5* (3 cases) and *DNAAF1* (3 cases). Rare genotypes (*RPGR*, *HYDIN*, *NME5*) were found as well. Chest computed tomography revealed bronchiectasis in 33 out of 41 patients. Among them, 15 patients had a PrImary CiliAry DyskinesiA Rule score of over 5 points.

Conclusions: To our knowledge, this is the first multicenter study to report the clinical characteristics, diagnostic methods, and genotypes of PCD in Korea. These results can be used as basic data for further PCD research.

Keywords: Primary ciliary dyskinesia; phenotype; genotype; signs and symptoms; diagnosis; therapeutics

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a genetic disorder characterized by predominantly autosomal recessive inheritance and biallelic mutations,[1] with an estimated prevalence of 1 in 10,000-40,000 people worldwide.[2] It is characterized by impaired mucociliary clearance with ciliary dysfunction, giving rise to heterogeneous clinical manifestations such as neonatal respiratory distress, recurrent and chronic oto-sino-pulmonary disease, laterality defects, and infertility.[3] Respiratory tract motile ciliary dysfunction is generally observed at an early age.[4] Patients typically present with frequent productive cough and recurrent upper or lower airway disorders during childhood. In patients with PCD, the lung function starts to decline during childhood and continues to deteriorate with age.[5] In addition, ear diseases are prevalent in PCD patients; therefore, misdiagnosis and inadequate treatment of patients during childhood can result in hearing impairment, speech delay, and learning disabilities in adulthood. Early diagnosis and proper management of pediatric PCD will help prevent damage to the respiratory and auditory systems and improve the quality of life at later stages.

However, there is currently no single gold standard diagnostic test for PCD.[6] The American Thoracic Society and European Respiratory Society guidelines recommend that for the diagnosis of PCD, a combination of technically demanding investigations is required, including the nasal nitric oxide (nNO) test, high-speed video microscopy analysis (HSVA) of ciliary beat frequency and pattern, transmission electron microscopy (TEM), ciliary protein immunofluorescence staining, and genetic testing.[1,7] Experienced pathologists should perform the histopathological analysis of TEM findings, and the test should be conducted in the absence of respiratory infection. However, approximately 30% of patients with PCD show normal ciliary structure and function.[8-10] Recently, genetic testing for diagnosing PCD have been developed for newborns, in whom mucosal biopsy may be challenging to undergo, or for patients whose histological results are unclear. More than 40 genes have been identified to be involved in PCD development; nevertheless, 20% to 30% of patients with a definite PCD diagnosis do not show a culprit genetic background.[11,12] Several studies have described a

direct correlation between genetic anomalies and disease phenotypes.[13] However, the genetic spectrum associated with PCD differs among patients and across nationalities.

There are limited data and treatment practices for PCD in Korea due to lack of awareness and available diagnostic approaches. The prevalence of PCD in Korea has not been reported, and most of the available evidence is documented in case reports.[14-16] In the present study, we analyzed the clinical characteristics, pulmonary function, diagnostic approach, and therapeutic options of PCD patients in Korea through a nationwide multicenter study.

MATERIALS AND METHODS

Study population

The medical records of pediatric and adolescent patients diagnosed with PCD between January 2000 and August 2022 at secondary and tertiary hospitals across Korea were retrospectively reviewed. A diagnosis of PCD was confirmed on the basis of suggestive clinical symptoms and positive results in TEM or genetic testing.[1,7] Data on demographics, clinical manifestations, pulmonary function testing, chest computed tomography (CT), and echocardiography, as well as those concerning any therapeutic options, were collected and documented. Patients who had previously been diagnosed with PCD were included in the study through a retrospective review of medical records. Newly diagnosed patients, with their own consent and that of their legal guardians, underwent additional genetic testing, even if the diagnosis had already been confirmed based on the clinical presentation and TEM results.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of the participating institutions (IRB No. CNUH-2017-12-029, 115288-202009-HR-043, AMC-2021-0139, SNUH-2008-192-1154, H-05-2020-218, CNUH-202-276, AJOUIRB-MDB-2017-116, KBSMC-2017-02-036, INHAUH-2020-10-011, DKU-2017-04-021, CR-2017-12-029, B-2103-672-403, DKUH-2018-08-012-005, BD-2018-08-012-005, YUMC 2021-09-024-004). Informed consent for the retrospective review of medical records was waived. Some patients were prospectively enrolled and genetically tested at the start of the study; written informed consent was obtained from all participants.

Clinical features

The European Respiratory Society recommends confirmation tests for PCD when patients show the following clinical features[1]: neonatal manifestations (neonatal chest symptoms, neonatal rhinitis, and/or admission to the neonatal intensive care unit), chronic respiratory symptoms (persistent wet cough, recurrent wheeze, bronchiectasis, and/or recurrent pneumonia), chronic ear symptoms (chronic serous otitis media, chronic ear perforation, and/or hearing loss), chronic nasal symptoms (chronic rhinitis and/or chronic sinusitis), situs anomalies, congenital heart defect, hydrocephalus, and/or subfertility.[1]

We examined clinical features such as typical symptoms, birth history, past medical history in the neonatal period, and age at diagnosis. Behan et al.[3] validated the PrImary CiliAry DyskinesiA Rule (PICADAR) score for predicting PCD, which is being used to describe the suspected clinical features of PCD. The PICADAR has seven predictive parameters (full-term birth, neonatal chest symptoms, admission to the neonatal intensive care unit, chronic ear symptoms, chronic rhinitis, situs inversus, and congenital cardiac defects).

TEM examination

All samples were obtained from nasal mucosal or bronchial biopsies. The main defects in the ciliary structure were investigated with TEM. PCD diagnosis requires the identification of an ultrastructural defect in the outer dynein arms (ODA), both ODA and inner dynein arms (IDA), IDA alone, IDA with microtubular disarrangement, central apparatus, or acilia.[17]

Genetic analysis

Genomic DNA (gDNA) was extracted from patient's whole blood samples, and genetic evaluation was performed using whole-exome sequencing. The gDNA extraction, library production, hybridization, and sequencing were performed by Macrogen (Macrogen Inc., Seoul, Korea) using an Agilent SureSelect Target Enrichment protocol for an Illumina paired-end sequencing library (version C2, December 2018) together with 1-μg input gDNA. The SureSelect Human All Exon V6 probe set was used in all cases. Sequencing was performed using the HiSeq™ 2500 platform (Illumina, San Diego, CA, USA). The raw sequence data were mapped to the hg19 reference genome. Variant analysis pipeline, annotation, and filtering processes were performed using the Burrows-Wheeler Alignment Tool (bwa-0.7.12), Picard (v1.130), GAKT (v3.4.0), and SnpEff (v4.1g). Genes known to be associated with PCD were analyzed more intensively for the analysis of whole-exome sequencing data. The clinical significance of variants was analyzed according to the 2015 American College of Medical Genetics (ACMG)/ Association for Molecular Pathology (AMP) guidelines.[18] When necessary to identify compound heterozygous variants, proband-parent trio whole-exome sequencing was performed.

Pulmonary function and imaging studies

Baseline spirometry was performed according to the American Thoracic Society guidelines.[19] Spirometric measurements were expressed as a percentage of the predicted value. Chest CT was performed to evaluate the lung parenchyma. The images were assessed for severity, distribution of bronchiectasis, peri-bronchial wall thickening, atelectasis, and other findings.

Statistical analysis

Results were expressed as numbers and percentages for categorical data and as a range for quantitative data with a non-normal distribution. The Kruskal–Wallis nonparametric test was used to compare quantitative data. A P value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In total, 41 patients, of which 21 (51.2%) were male, were diagnosed with PCD across 15 medical institutions (**Table 1**). Thirty-three patients were included through a retrospective review of medical records and eight patients were included through prospective studies. The age at diagnosis was 11.8 ± 5.4 years (range: 0.5 months-18.9 years). Most patients (n = 40, 97.6%) were born full term, 15 patients (36.6%) had respiratory symptoms (tachypnea, cough, and/or pneumonia) during the neonatal period, and 12 patients (29.3%) had a history of admission to the neonatal intensive care unit. The most common complaints were chronic nasal symptoms (n = 24, 58.5%). Nineteen patients (46.3%) had chronic ear symptoms such as glue ear and/or serous otitis media, and 7 (17.1%) hearing defects (hearing loss and/or ear perforation). Six patients (14.6%) had congenital heart abnormalities, and 6 patients (14.6%) had situs abnormalities. The PICADAR score was ≥ 10 in 3 patients (7.3%) and 6-9 in 12 (29.3%) patients (**Table 1**).

Table 1. Demographics and clinical characteristics in patients with primary ciliary dyskinesia in Korea (n = 41)

Characteristics	Value
Age at diagnosis (yr)	11.8 ± 5.4
Male	21 (51.2)
Full-term birth	40 (97.6)
Chest symptoms in the neonate	15 (36.6)
Admission to neonatal intensive care unit	12 (29.3)
Situs abnormality	6 (14.6)
Congenital heart disease	6 (14.6)
Chronic nasal symptoms	24 (58.5)
Chronic ear symptoms	19 (46.3)
Hearing symptoms	7 (17.1)
PICADAR score	
≤ 5	26 (63.4)
6–9	12 (29.3)
≥ 10	3 (7.3)

Data are presented as number (%) or mean ± standard deviation.
PICADAR, PrImary CiliAry DyskinesiA Rule.

Diagnosis

In total, 35 patients underwent nasal or bronchial mucosal biopsy for TEM analysis; 2 patients had either normal or inconclusive results (**Table 2**). Thirty-three patients were diagnosed with PCD based on the pathological findings. The TEM results showed that ODA defects (alone or combined with other defects = 17) were the most common. The defect of IDA was found to be isolated (n = 6) or associated with microtubular disarrangement (n = 2). Central pair defects were found in 7 patients. In 1 patient, acilia was present in the adenoid, nasal mucosa, and lung histology.

Seventeen patients underwent genetic studies, 13 of whom underwent mucosal biopsy as well. The genes with the highest incidence of mutations were *DNAH5* (3), followed by *DNAAF1* (3), *CCDC39* (1), *DNAH11* (1), *CFAP300* (1), *RPGR* (1), *DNAH8* (1), *NME5* (1), and *HYDIN* (1). Four patients did not show any mutations (**Table 3**). The genetic study and TEM results are shown in **Table 3**. *DNAH11* mutations were confirmed in those with normal TEM results. Among them, 4 patients who underwent mucosal biopsies but had normal or inconclusive results were diagnosed with genetic testing. Among patients with situs abnormalities, 4 underwent biopsy; 2 had ODA and IDA abnormalities, 1 a central pair defect, and 1 inconclusive result. Genetic testing was performed in 3 of these patients; a *DNAH5* mutation was found in 2 patients and a *DNAAF1* mutation in 1.

Table 2. Diagnostic tests for patients with primary ciliary dyskinesia in Korea (N = 41)

Variables	Values
TEM finding	33 (80.5)
ODA defect	3
ODA and other defect	14
IDA defect	6
Tubulous disorganization with IDA defect	2
Central pair defect	7
Acilia	1
Genetic test	12 (29.3)

Values are presented as numbers (%).
TEM, transmission electron microscopy; ODA, outer dynein arm; IDA, inner dynein arm.

Table 3. Results of genetic testing and TEM

Patient No.	Sex	Age at diagnosis	TEM	Gene	Variant	ACMG classification	Zygosity
1	F	0.5 months	Not done	*DNAH5*	c.5647C>T, (p.Arg1883Ter), c.10810dupA, (p.Ile3604AsnfsTer2)	Pathogenic; Likely pathogenic	Compound heterozygote
2	F	4.3 years	Normal	*DNAAF1*	c.376del, (p.Glu126LysfsTer35)	Pathogenic	Homozygote
3	F	10.9 years	Microtubular disarrangement	*CCDC39*	c.1228C>T, (p.Gln410*)	Likely pathogenic	Homozygote
4	M	14.6 years	Normal	*DNAH11*	c.2169+2T>C, c.3853-2A>G	Likely pathogenic; Likely pathogenic	Compound heterozygote
5	F	16.3 years	Not done	*DNAH5*	c.3066_3069dup, (p.Ala1024Hisfs*24), c.9365del, (p.Leu3122*)	Pathogenic; Pathogenic	Compound heterozygote
6	F	3.3 years	Tubular transposition defect	*CFAP300*	c.[309C>A];[361C>T] (p.[Cys103Ter];[Arg121Ter])	Pathogenic; Pathogenic	Compound heterozygote
7	M	3.8 years	Not determined	*DNAAF1*	c.376del, (p.Glu126LysfsTer35), c.1198_1199delinsG,(p.Pro400ValfsTer80)	Pathogenic; Pathogenic	Compound heterozygote
8	M	11.9 years	Central pair defect	*RPGR*	c.154G>A (p. Gly52Arg)	Likely pathogenic	Hemizygote
9	F	7.8 years	Acilia	*DNAH8*	c.2182A>G (p.Met728Val)	Uncertain significance	Heterozygote
10	M	5.4 years	Not done	NME5	c.572G>A, (p.Trp191Ter), c.479_480del (p.Tyr160PhefsTer11)	Pathogenic; Likely pathogenic	Compound heterozygote
11	M	18.6 years	Not done	DNAH5	c.[1089delC](;)[9365delT] (p.[Leu364TyrfsTer3];[Leu3122Ter]	Likely pathogenic/ Pathogenic	Compound heterozygote
12	M	14.5 years	IDA defect	Not detected			
13	M	10.3 years	Central pair defect	Not detected			
14	F	12.3 years	Microtubular disarrangement with IDA defect	Not detected			
15	M	5.6 years	ODA and IDA	HYDIN	c12121A>G (p.K4041E), c.5536G>A (p.E1846K)	Uncertain significance	Heterozygote
16	M	6.4 years	Central pair defect	Not detected			
17	M	11.4 years	Not determined	DNAAF1	c.[1172C>T](;)[1462C>T] (p.[Pro391Leu];[Arg488Ter])	Likely pathogenic/Likely pathogenic	Likely pathogenic/Likely pathogenic

TEM, transmission electron microscopy; ODA, outer dynein arm; IDA, inner dynein arm.

Imaging studies and pulmonary function testing

All patients (mean age at evaluation: 11.3 ± 6.0 years, range: 0.5 months-24.2 years) underwent chest CT. As a result, bronchiectasis and atelectasis were found in 33 and 15 patients, respectively. The most common areas affected by bronchiectasis were the right middle lobe (n = 21), right lower lobe (n = 19), and left lower lobe (n = 16).

Initial lung function tests were performed at the age of 12.4 ± 4.3 years (range: 5.5-19.9 years). The lung function test findings were compared with the TEM results. The pulmonary function was preserved in patients with isolated ODA defects (n = 2, forced vital capacity [FVC], %predicted: 85.0 ± 11.0, forced expiratory volume in the first second [FEV1], %predicted: 94.0 ± 9.8, FEF_{25-75}, %predicted: 98.0 ± 30.9). However, patients with both ODA and IDA defects demonstrated decreased lung function (n = 2, FVC, %predicted: 71.1 ± 23.8, FEV1, %predicted: 66.3 ± 18.6, FEF_{25-75}, %predicted: 55.5 ± 47.5). In addition, patients with IDA defects associated with microtubular disarrangement showed decreased lung function (n = 2, FVC, %predicted: 81.0 ± 15.6, FEV1, %predicted: 74.0 ± 13.1, FEF_{25-75}, %predicted: 65.7 ± 14.5). The pulmonary function of patients with central pair defects or IDA defects alone was quantified as well (n = 4, FVC, %predicted: 86.0 ± 12.2, FEV1, %predicted: 80.0 ± 13.6, FEF_{25-75}, %predicted: 67.0 ± 23.6). However, the difference was not statistically significant ($P > 1.0$).

Therapeutic options

At each medical center, there was a different treatment practice. N-acetylcysteine (n = 10, 24.4%) was the most commonly used inhalation therapy agent, followed by 7% hypertonic saline nebulizer (n = 8, 19.5%) and 3% hypertonic saline nebulizer (n = 7, 17.1%). Inhaled short-acting beta-agonists, inhaled corticosteroid, inhaled long-acting beta-agonists, and macrolides were administered to 26.8% (n = 11), 26.8% (n = 11), 4.9% (n = 2), and 2.4% (n = 1) of patients, respectively.

DISCUSSION

To our knowledge, this is the first study to describe the diagnosis and treatment of PCD using Korean multicenter clinical data. The age at diagnosis of PCD ranged from 0.5 months to 18.9 years, with a mean age of 11.8 years. The most commonly used diagnostic techniques were biopsy with TEM, and the most common abnormality in PCD was ODA defects (isolated or combined with IDA defects). At the time of writing this report, the majority of patients were still being followed up according to the corresponding protocol at each center.

The European Respiratory Society reported high validity of the PICADAR score, which includes various predictive factors.[1,3] The sensitivity and specificity of a cut-off PICADAR score of 5 were reported to be 0.90 and 0.75, respectively.[1] However, only 42.9% of patients met these criteria in the present study. Therefore, PICADAR scoring may help identify clinical features of PCD; however, in this study, it was not helpful in diagnosis of PCD since it was low in many patients with confirmed PCD. In the future, it will be necessary to develop a scoring system suitable for Korean patients with more clinical data from patients with PCD.

PCD diagnosis is known to be delayed, with a median age at diagnosis of 5.5 years in Europe and 2-22 years in the United States.[20,21] The mean age at diagnosis of PCD in our study was 11.8 years, suggesting a delayed diagnosis. This may be related to the fact that the most common complaints of patients with PCD were nonspecific respiratory symptoms, such as nasal congestion and/or prolonged cough. These nonspecific symptoms often occur in children and adolescents because of recurrent upper respiratory tract infections, making it challenging to establish a differential diagnosis without obtaining a detailed history. To prevent delays in PCD diagnosis, awareness of rare lung diseases among clinicians, generalization of diagnostic methods, and development of management strategies for rare diseases are necessary. Therefore, it is important to educate neonatologists, pediatricians, otolaryngologists, and primary care physicians about the clinical features of PCD. The primary symptoms of PCD include neonatal respiratory distress, even in term babies, chronic persistent lower respiratory tract symptoms, chronic persistent upper respiratory symptoms, and/or lateral defects. If 2 or more of these clinical manifestations are present, the patients should be strongly suspected of having PCD.

Abnormal pulmonary function begins at an early age, and as a result, many children show abnormal airflow function.[22,23] There is disagreement regarding the correlation between TEM results and lung function findings in patients with PCD.[13,24] One study reported that patients with PCD with specific phenotypes such as IDA defects, central pair defects, or microtubular disorganization showed severely impaired pulmonary function.[13] In the present study, most patients showed decreased lung function, except those with isolated ODA defects; however, statistical significance could not be achieved given the small number of patients analyzed. A longitudinal study reported that lung function can be preserved with aggressive treatment.[25]

National registry management and regular follow-up of lung function to monitor disease progression should thus be employed.[17]

The most widely used PCD diagnostic method is the detection of ciliary abnormalities in clinically suspected patients using TEM. It is known that approximately 70% of cases can be diagnosed by histological examination.[9,10] However, this examination is dependent on adequate sample collection by skilled and experienced clinicians. Moreover, 30% of patients did not exhibit ciliary defects and showed normal axonemal ultrastructure.[21] Mutations in *DNAH11* are known to be associated with normal cilia and beat frequencies; our study results are in line with these findings.[26]

PCD is a genetically heterogeneous disease that does not have a clear racial or sexual preference. Known genetic abnormalities in PCD reportedly differ among countries.[27] In Eastern Asia, the most common pathogenic or likely pathogenic PCD genes are *DNAH11*, *DNAH5*, and *DNAAF3*. *DNAH11*, *DNAH5*, and *DNAI1* are the most common in Europe, while *DNAH11*, *DNAI1*, and *CCDC39* are the most common in African or African American patients. Mutations in any protein involved in ciliary assembly, structure, or function can cause this condition. Gene discovery has relied on a combination of experimental models and targeted screening of candidate genes encoding proteins of the ciliome. However, whole-exome and massive parallel sequencing have led to the identification of new genes through international collaboration in Europe and North America.[28,29] In the present study, one patient was diagnosed with PCD by TEM, but an *RPGR* mutation was identified later through a genetic study.[21] Since this mutation is known to be associated with retinitis pigmentosa, the patient underwent additional ophthalmologic examinations. Almost all genes associated with PCD are autosomal recessive, except for X-linked syndromic genes (*RPGR* and *OFD1*).[17] Additionally, genetic counseling should be planned following disease confirmation in all patients.

As it is difficult to diagnose PCD using a single test, the diagnostic methods should be selected according to the clinical characteristics of the patient. Ciliary biopsy with TEM, PCD genetic panels, functional ciliary movement analysis with HSVA, nNO testing, and immunofluorescence testing are the different diagnostic tools available. Nasal fractional exhaled nitric oxide testing is not invasive and can be easily performed, but it is not commonly standardized, and the functional ciliary movement analysis with HSVA is only possible in centers that have a high level of experience with this technology.

This study has several limitations. First, because medical records were retrospectively reviewed for some patients and genetic testing was prospectively performed for some, it was not possible to compare electron microscopy results and genotypes in all patients. Secondly, PCD diagnostic methods in Korea are limited to TEM and genetic tests in patients with clinical symptoms, as nNO testing and HVMA are not available. Therefore, since cases confirmed only by EM and genetic studies are reported, the number of patients is limited. Finally, as management systems for rare lung diseases are not nationally implemented in Korea, patient information could not be collected using the same test protocol. Consequently, pulmonary function tests or CT scans were not performed with a consistent protocol in Korean patients with PCD, and a small number of patients reported the results at different ages.

To our knowledge, this is the first multicenter study to report the clinical characteristics, diagnosis, and genotypes of PCD in Korea. We expect the results of this study to serve as the basis for the management of rare lung diseases in Korea.

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