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CLINICAL SERIES

Primary ciliary dyskinesia in children. Role of electron microscopy in countries with medium economic resources

Discinesia ciliar primaria en niños. Rol de la microscopia electrónica en países de medianos recursos económicos

Héctor Nuñez-Paucar[a,b], Carlos Valera-Moreno[a], Mariela Katherine Zamudio-Aquise[a], Alex Untiveros-Tello[a], Juan Carlos Torres-Salas[a], Roxana Lipa-Chancolla[c], Julia Fuentes-Torres[a], Noé Atamari-Anahui[a,b]

[a]Instituto Nacional de Salud del Niño-Breña. Lima, Perú.
[b]Universidad San Ignacio de Loyola, Vicerrectorado de Investigación, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud. Lima, Perú.
[c]Instituto Nacional de Salud del Niño-San Borja. Lima, Perú.

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What do we know about the subject matter of this study?

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive genetic disease, resulting in functional and structural defects in the cilia, with recurrent sinopulmonary infections. Diagnosis requires a combination of laboratory tests, some of which are not available in low- and middle-income countries.

What does this study contribute to what is already known?

We report the first 5 cases of primary ciliary dyskinesia in pediatrics in a middle-income country, describing the clinical, imaging, and ciliary ultrastructural features. In middle-income countries, electron microscopy associated with clinical and radiological features plays an important role in the early diagnosis of this disease.

Abstract

Primary ciliary dyskinesia (PCD) is a rare genetic disease that produces functional and structural defects in the cilia. In Peru, no cases of this disease have been reported in the pediatric population. **Objective:** To describe the clinical, radiological and ciliary ultrastructure characteristics in children with PCD, in a country with medium economic resources. **Clinical Case:** We report 5 patients with PCD treated at the Instituto Nacional de Salud del Niño-Breña (Peru). Age range 1 to 5 years (median 3 years). Three patients were male. The most frequent clinical manifestations were chronic wet cough, rhonchi, coarse crackles, recurrent bronchial obstructive syndrome, and recurrent pneumonia. All patients had atelectasis, three had bronchiectasis, and two had dextrocardia with situs inversus. Two patients had undergone lobectomy. Other causes of recurrent pneumonias were ruled out with immunodeficiency study, chlorine test and pulmonary aspiration The electron microscopy showed ab-

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Correspondence:
Noé Atamari-Anahui
noe.atamari@gmail.com

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Andrea Beckhaus Faccin

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sence of the inner arm of dynein as the most frequent pattern. All patients received treatment with antibiotics, nebulization with hypertonic saline, and respiratory physiotherapy with good adherence. **Conclusion:** In medium incomes countries, electron microscopy associated with clinical and radiological characteristics plays an important role in the early diagnosis of this disease. This is the first Peruvian report that contributes to the casuistry and epidemiology of this rare pathology.

Introduction

Primary ciliary dyskinesia (PCD) is an autosomal recessive genetic disease that causes functional and/or structural defects of the cilia[1-3]. It is estimated to have a prevalence of 1/10,000-20,000 live births, and it is increased in certain ethnic groups with high rates of consanguinity; however, the figures would be underestimated because many patients remain undiagnosed[1,2,4].

Impaired ciliary function results in chronic inflammation and infection of the upper and lower airways such as persistent rhinitis, sinusitis, otitis media, and suppurative lung disease, among others[5-7]. The onset of symptoms often occurs in the neonatal period characterized by neonatal respiratory distress, persistent nasal discharge, and wet cough. In childhood, these symptoms progress to recurrent sinopulmonary infections and eventually to bronchiectasis predominantly affecting the middle, lingular, and lower lobes[8]. Infertility may also occur in males and subfertility in females due to altered ciliary function of sperm flagella and fallopian tubes[9].

There is no gold standard for the diagnosis of PCD, however, it is necessary the combination of tests such as measurement of nasal nitric oxide (nNO) associated with highly suggestive tests such as cilia function analysis by high-speed video microscopy (HSVM), and, if available, some confirmatory tests such as ciliary ultrastructure defect visualization by transmission electron microscopy (TEM), genetic studies[10,11], and recently suggested for countries with limited economic resources, immunofluorescence (IF) analysis of protein expression[12]. However, about 30% of patients are not diagnosed by genetic studies and TEM, and the other tests are very necessary[4,5].

Since 2006, international focus groups have been formed that bring together physicians and experts interested in advancing research on this disease, establishing international PCD cohorts[1]. Since it is considered a rare or orphan disease due to the limited number of cases (prevalence lower than 5 cases/10,000 inhabitants) and because there is no follow-up or study program in the Peruvian health system[13], it can cause difficulties for timely diagnosis. The objective of this work is to describe the clinical, radiological, and ciliary ultrastructure characteristics in children with PCD, in a country with medium economic resources.

Clinical Case

We report five patients with a diagnosis of primary ciliary dyskinesia seen in the pulmonology service of the *Instituto Nacional de Salud del Niño-Breña* (Lima, Peru) between January 1, 2015, and December 31, 2019. The study was approved by the ethics committee of the *Instituto Nacional de Salud del Niño-Breña* (N°107-2021-CIEI-INSN); in addition, informed consent was obtained from family members.

The five cases were diagnosed while hospitalized, the median age at diagnosis was 3 years (range 1 to 5 years) and 3 patients were male. All patients came from different regions of Peru and are different families unrelated to each other. Cases 1 and 5 were misdiagnosed as asthma with poor therapeutic response; while cases 2, 3, and 4 were as chronic cough. None of the patients had a parental history of asthma. Cases 4 and 5 had a relative (father) with allergic rhinitis under treatment. Only case 1 had a sibling who died at 2 months of age from congenital heart disease at his home hospital. None of the patients had dysmorphism or recent surgeries at the time of diagnosis.

Among the clinical manifestations, all patients had a history of chronic respiratory infections (chronic wet cough, recurrent bronchial obstructive syndrome, recurrent pneumonia) with a median age at the onset of 4 months (range 1 to 10 months), and persistent rhonchi/coarse crackles in both hemithorax on clinical examination. Four had a history of neonatal respiratory distress and sinusitis characterized by persistent nasal discharge associated with sinus imaging abnormalities. Only two patients (cases 1 and 3) had recurrent otitis media; however, there was no hearing loss at follow-up (Table 1).

Bronchial secretion culture in case 1 and nasopharyngeal secretion culture in case 5 were positive for *Pseudomonas aeruginosa*, which were treated with antibiotics. None of the patients had positive blood culture results for any microorganism.

Among the radiological findings, four showed paranasal sinuses alterations such as mucoperiosteal thic-

kening or sinus opacity. All patients had chronic atelectasis and prominent pulmonary hilum (Figure 1). Two patients had dextrocardia with *situs inversus* and three patients had bronchiectasis (Figure 2).

Before the diagnosis of PCD, as part of the study of chronic wet cough, fibrobronchoscopy was performed in cases 1 and 3, observing a "mirror image" of the right and left bronchial tree and bilateral purulent bronchorrhea.

Due to the presence of cough with greenish yellowish phlegm predominantly at night lasting longer than three months, respiratory distress, and poor response to antibiotic therapy and airway clearance, associated with chronic bronchiectasis, it was decided to perform a right lower lobe lobectomy in case 1 and a left lower lobe lobectomy in case 5, both at 2 years of follow-up.

The diagnosis in all patients was made after ruling out cystic fibrosis, as all patients had negative sweat chloride tests (mean 20 mmol/L, pilocarpine iontophoresis method). In addition, cell count studies (flow cytometry) and immunoglobulins (IgM, IgG, IgE, IgA) were within normal ranges for their age in all patients, as well as echocardiography which was normal except for cases 1 and 3 which corroborated dextrocardia with *situs inversus*. Only in cases 1 and 5, specific IgE serological and Aspergillus immunodiffusion tests were performed, with undetectable results in both cases.

All patients underwent upper gastrointestinal endoscopy and pathological anatomy studies, resulting in reflux esophagitis in cases 2 and 4, treated with omeprazole, and in case 5 esophagitis and superficial chronic antral gastritis. Only in cases 2 and 5 it was possible to perform the pH-impedance test and fiberoptic endoscopic evaluation of swallowing (FEES) due to the possibility of chronic pulmonary aspiration, with no alterations in case 5, while, in case 2, an interarytenoid laryngeal cleft was found. The lipid-laden macrophage index in the bronchoalveolar lavage was positive in case 2 (238), so a radionuclide salivagram was performed with normal results. A lung perfusion scintigraphy study could only be performed in case 1, which showed a relative pulmonary function with right perfusion at 43% and left perfusion at 57%.

All patients underwent nasal brushing for collecting a sample that was fixed in glutaraldehyde. Subsequently, the sample was sent to the *Instituto Nacional de Salud del Niño de San Borja*, where it was evaluated by electron microscopy, showing in all cases images compatible with primary ciliary dyskinesia (Figure 3).

The study of ciliary ultrastructure by TEM (Tecnai G2 Spirit BioTwin) was performed on all patients. A minimum of 100 cilia were evaluated according to international recommendations in transversal sections and were considered within the normal range of up to 10% of defective cilia[14]. In addition, the quantitative criteria of Carlén et al. were considered to establish as PCD, which indicates a mean of < 1.6 outer arms of dynein/cilium (normal: 7.5 - 9.0) and a mean of < 0.6 inner arms of dynein/cilium (normal: 3.0 - 5.0)[15].

All patients evolved satisfactorily after the installation of therapeutic regimens such as azithromycin 10mg/kg/day 3 times a week due to its immunomodulatory role, nebulization with B2 agonists and 3% hypertonic saline, oral mucolytics (N-acetylcysteine), and respiratory physiotherapy 1 to 2 times a week, showing good adherence to treatment and no reports of adverse reactions (Table 2). Likewise, all of them achieved an adequate nutritional status, except for case 1 who, despite the established treatment, continued with acute undernutrition (Table 1). In addition, all of them strictly complied with the Peruvian vaccination schedule. During follow-up, all patients were stable with respiratory physiotherapy treatment and general care.

Discussion

In our series, the median age at diagnosis was 3 years which is lower than the median age (5.3 years) reported by PCD treatment centers in Europe, being 3.5 years in patients with *situs inversus* and 4.1 years in children diagnosed in centers with higher resolution capacity[16].

All patients had a history of recurrent respiratory infections similar to that found in reviews of patients with PCD. Recurrent otitis media was observed in two patients aged 3 and 5 years; of these, none developed hearing loss until follow-up, a result similar to that reported in an English study that found the 3- to 4-year-old age group to be the most affected[17]. In addition, of the five patients, two had *situs inversus*. This finding is proportional to what is estimated in these patients since this presentation has been reported in about 50% of patients with PCD[18]

Pseudomonas aeruginosa was found as pathogenic microorganisms in one patient, similar to that found in other studies where *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and mucoid-type *Pseudomonas aeruginosa* were reported as isolated agents in different culture media[4,19].

All patients had atelectasis and bronchiectasis, which, in two cases, required lobectomy due to chronic basal cystic bronchiectasis, being probable foci of recurrent infection. Surgical resection such as lobectomy or segmentectomy to reduce the risk of progression of infection to healthy lung tissue is controversial[20,21]; however, this therapeutic measure was considered due to the

Table 1. Clinical, morphological, and radiological characteristics of patients with Primary Ciliary Dyskinesia

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years) at diagnostic	5y 8m	3y 9m	3y 5m	1y 8m	4y 8m
Sex	Woman	Male	Male	Male	Woman
Gestation number	7, brother died at 2 months due to congenital heart disease	1 (Only-Child)	1 (Only-Child)	2	2
Place of origin	Piura	Lima	Ica	Lima	San Martín
Nutritional status at diagnosis (Z score)	IMC 12.2 (-3.36)	P/T -2.62 P/E -0.61 T/E 1.83	P/T -2.38 P/E 0.05 T/E 2.78	P/T 2.31 P/E 0.5 T/E -2.64	P/T -0.75 T/E -0.21 T/E 0.37
Onset of symptoms respiratory (months)	4	6	1	10	3
Clinical manifestations					
Chronic wet cough	+	+	+	+	+
Rhonchi and rales	+	+	+	+	+
Respiratory distress neonatal	+	-	+	+	+
Recurrent otitis media	+	-	+	-	-
Sinusitis	+	-	+	+	+
Recurrent bronchial obstructive syndrome	+	+	+	+	+
Recurrent pneumonia	+	+	+	+	+
Characteristics of ciliary ultrastructure	Absence of inner arms of dynein	Absence of inner arms of dynein	Absence of inner and outer arms of dynein	Absence of inner arms of dynein. Cilium with disposition "8+1"	Absence partial of inner arms of dynein
Radiological characteristics					
Paranasal sinuses	Mucoperiosteal thickening	Without alterations	Peripheral opacity of maxillary sinuses and ethmoid cells	Opacity of maxillary sinuses and ethmoid cells	Peripheral opacity of bilateral maxillary sinuses and ethmoid cells
Chronic atelectasis*	+	+	+	+	+
Pulmonary accentuation hiliobasal*	+	+	+	+	+
Dextrocardia with situs inversus*	+	-	+	-	-
Bronchiectasis**	+	-	+	-	+

*Chest x-ray. **Thorax tomography.

low socioeconomic condition of the patients since they lived in rural areas with difficult access to the health system, in addition to having localized bronchiectasis that did not respond to antibiotic therapy and airway clearance[22]. Likewise, some alterations in the ultrastructure of the cilia characteristic of this disease were found in all patients. However, it is important to consider that around 3 to 30% of patients with PCD show an uncertain or normal ultrastructure, therefore, a normal ultrastructure does not rule out PCD and, in these cases, when there is clinical suspicion, other complementary studies such as nasal nitric oxide test, ciliary motility studies, or genetic study are necessary[9,23].

There is no general consensus on the diagnosis of PCD. A European consensus classifies it into three diagnostic categories: positive, highly probable, and highly improbable[10]. In our patients, we could not perform the nasal nitric oxide test and video microscopy because it was not available in the country but we did obtain electron microscopy that found a defect in the cilia, which, associated with the patient's clinical history, would provide us with a positive diagnosis.

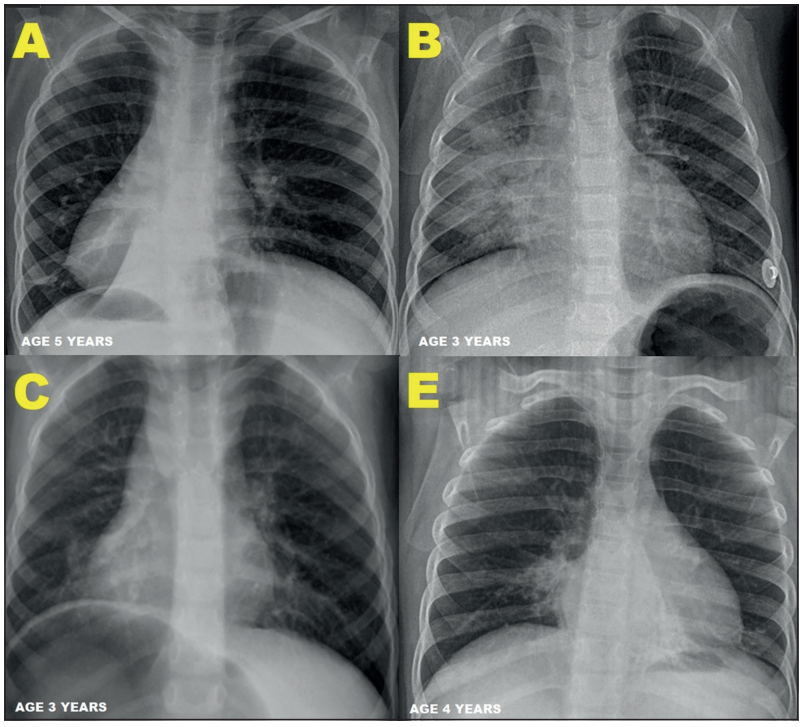

Figure 1. A (case 1, age 5 years): Chest X-ray shows situs inversus, accentuation of the right pulmonary hilum, with thickening of the right parahilar bronchial walls and right basal atelectasis. **B** (case 2, age 3 years): Chest X-ray shows consolidation opacities in the right hilar and parahilar region, with slight elevation of the right diaphragm. **C** (case 3, age 3 years): Chest X-ray shows situs inversus, faint right paracardiac consolidation, linear left paracardiac opacities. **E** (case 5, age 4 years): Chest X-ray shows right paracardiac consolidation, left basal retrocardiac atelectasis.

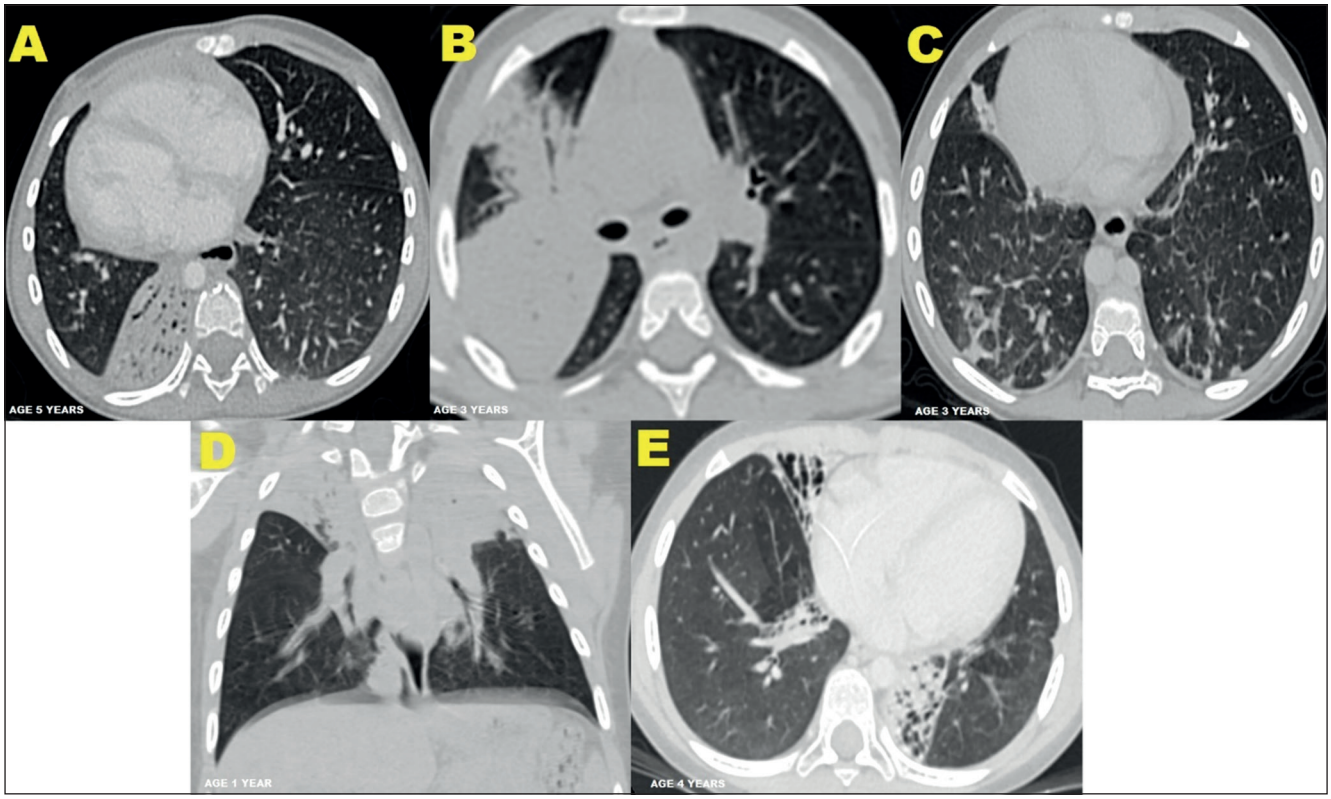

Figure 2. A (case 1, age 5 years): Chest tomography shows dextrocardia, segmental atelectasis of the lower lobe associated with cylindrical bronchiectasis in its interior and a ground glass pattern with a predominance of bilateral basal segments. **B** (case 2, age 3 years): The chest tomography shows an area of consolidation in the anterior upper lobe and atelectasis in the apical segment of the right lower lobe. **C** (case 3, age 3 years): Chest tomography shows subsegmental atelectasis of the right upper lobe and parenchymal fibrous bands in posterior segments, predominantly right. **D** (case 4, age 1 year): Chest tomography shows atelectasis of the right upper lobe and segmental atelectasis of the left upper lobe. **E** (case 5, age 4 years): Chest tomography shows bronchiectasis associated with atelectasis of the middle lobe, the right medial lower lobe and the left posterior lower lobe, and bilateral lung parenchyma with a mosaic pattern.

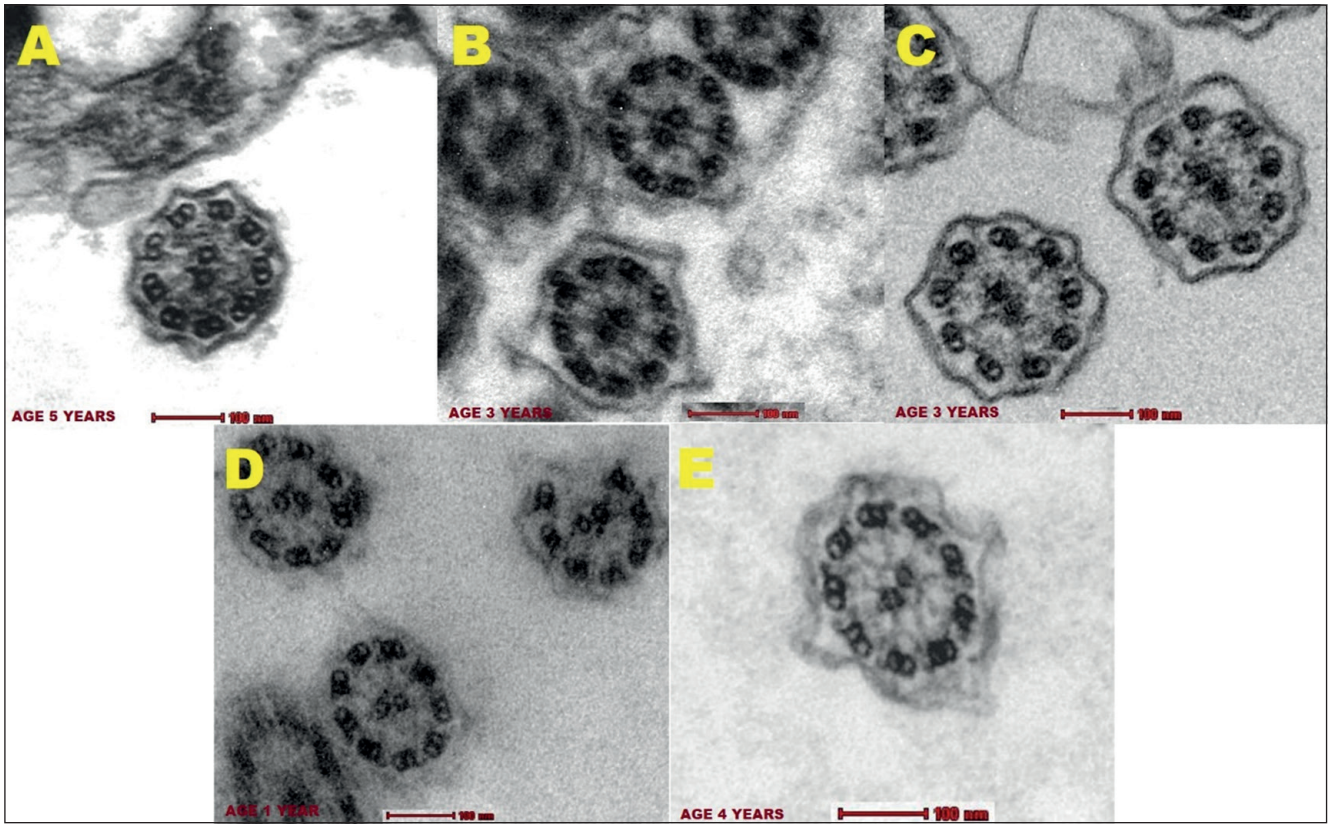

Figure 3. A (Case 1, age 5 years): Cross-section of the respiratory cilium with absence of inner arms of dynein (magnification x 85 000). **B** (Case 2, age 3 years): Cross-section of the respiratory cilium with absence of inner arms of dynein (magnification x 85 000). **C** (Case 3, age 3 years): Cross-section of the cilium with absence of inner and outer arms of dynein (magnification x 85 000). **D** (Case 4, age 1 year): Cross-section of the cilium with absence of inner arms of dynein, a cilium with an "8+1" arrangement is observed (magnification x 60 000). **E** (Case 5, age 4 years): Cross-section of cilia with ultrastructure with absence partial of inner arms of dynein (magnification x 85 000).

Table 2. Characteristics of treatment in patients with Primary Ciliary Dyskinesia

Treatment	Case 1	Case 2	Case 3	Case 4	Case 5
Antibiotics	Azithromycin 10mg/kg/day 3 times per week.	Azithromycin 10mg/kg/day 3 times per week.	Azithromycin 10mg/kg/day 3 times per week.	Azithromycin 10mg/kg/day 3 times per week.	Azithromycin 10mg/kg/day 3 times per week.
Mucolytics	N-acetylcysteine 100mg c/8hrs	N-acetylcysteine 100mg c/8hrs	N-acetylcysteine 100mg c/8hrs	N-acetylcysteine 100mg c/8hrs	N-acetylcysteine 200mg c/8hrs
Nebulizations	B2 agonist (salbutamol 0,5%) plus 3% hypertonic solution as needed	B2 agonist (salbutamol 0,5%) plus 3% hypertonic solution as needed	B2 agonist (salbutamol 0,5%) plus 3% hypertonic solution as needed	B2 agonist (salbutamol 0,5%) plus 3% hypertonic solution as needed	B2 agonist (salbutamol 0,5%) plus 3% hypertonic solution as needed

Note: Amoxicillin/clavulanic acid was also administered in acute respiratory episodes.

On the other hand, the North American consensus on PCD, proposes diagnostic criteria according to three age groups: a) zero to one month of age with *situs inversus totalis*, and unexplained respiratory distress at birth, plus at least one of the following: altered ciliary ultrastructure, biallelic mutations in PCD-associated genes, or abnormalities of ciliary function; b) 1 month to 5 years with two or more major clinical criteria (unexplained neonatal respiratory distress, laterality defects, chronic wet cough or bronchiectasis, chronic nasal congestion or pansinusitis), plus at least one of the following: altered ciliary ultrastructure, biallelic mutations in PCD-associated genes, or ciliary function abnormalities; and c) 5 to 18 years and

adults with two or more major clinical criteria plus at least one of the following: low nasal nitric oxide, altered ciliary ultrastructure, biallelic mutations in PCD-associated genes, or ciliary function abnormalities[11]. In our patients, in the age group 1 month to 5 years, two clinical criteria were met (wet cough and neonatal respiratory distress) associated with ciliary alteration on electron microscopy, which met the diagnosis criteria for PCD.

In all cases, an immunodeficiency study and sweat chlorine test were performed, with no alterations, in addition to studies to rule out other causes of recurrent pneumonia, such as pulmonary aspiration. Case 2 was included in this clinical series because of the altered result in electron microscopy. There is doubt whether the pulmonary involvement could be due to PCD or chronic pulmonary aspiration syndrome due to the high number of lipid-laden macrophages found; however, the FEES, pH- impedance, and salivagram studies showed no alterations. Despite this, treatment for PCD was started, which clinically favored the patient, and he is currently stable.

In Peru, only electron microscopy is available, which identifies the partial or complete absence of external and internal dynein arms, mixed defects, and microtubule disorganization defects. However, nexin binding defects, ciliary biogenesis defects, and defects caused by DNAH11 gene mutation are not identified by electron microscopy. Improving the performance of TEM in the study of PCD requires nasal or bronchial brushing for collecting good-quality samples to ensure the evaluation of an adequate number of ciliary cross-sections[24].

In all patients, we prescribe treatments based on consensus and expert opinion from European and North American centers, given the variability in clinical manifestations and the lack of clinical trial data, which makes a standardized management plan difficult. Mucociliary airway clearance by nebulization with 3% hypertonic saline is considered in the management of PCD, which is significantly less expensive than other mucolytic agents, however, controlled trials are required to estimate the benefit and safety of prolonged therapy.

It is unclear whether inhaled bronchodilators and corticosteroids would be useful during periods of pulmonary exacerbation of PCD, or whether they should be considered in patients who have PCD and asthma. In our series, inhaled corticosteroids used in the presence of suspected asthma were safely withdrawn once PCD was diagnosed. N-acetylcysteine with mucolytic and antioxidant properties is currently not universally recommended in PCD, however, current randomized clinical trials may provide new evidence for its use[25]. Likewise, the use of macrolides (azithromycin) in non-cystic fibrosis bronchiectasis has shown multiple benefits, including fewer pulmonary exacerbations, improved sputum volume, attenuation of FEV1 decline, and improved quality of life, so clinical trial evidence of the long-term utility of azithromycin in PCD is expected[10,11].

In follow-up, immunizations in patients with PCD are very important, so centers routinely vaccinate against *Bordetella pertussis*, *Streptococcus pneumoniae*, and influenza[26-28]. In our study, all patients strictly complied with the national vaccination schedule that includes vaccines for these microorganisms. Likewise, consensus guidelines recommend that patients be evaluated several times a year in PCD centers by a specialized multidisciplinary team[29]. In our institution, patients were evaluated every two to three months considering the economic and social context of each patient since they came from different places in Peru.

In countries with limited economic resources, the disease may be underdiagnosed, however, clinical characteristics or predictive scales can help to suspect this entity in association with some tests. In order to increase the possibilities of diagnosing PCD, centers with limited resources could request international collaboration and send samples for genetic study[12]. If electron microscopy is available, it could complement the studies and make a diagnosis of this disease as in the cases presented. Some countries such as Chile already have nasal nitric oxide tests and high-speed video microscopy[30], which would allow collaborative studies to help diagnose these patients early.

Conclusion

In this series of children, electron microscopy together with clinical (chronic cough, recurrent sinusitis, and recurrent pneumonia) and imaging (atelectasis and bronchiectasis) features play an important role in the diagnosis of PCD, because the other tests (nNO, HSVM, IF) are not available in low- and middle-income countries like ours.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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References

1. Goutaki M, Maurer E, Halbeisen FS, et al. The international primary ciliary dyskinesia cohort (iPCD Cohort): methods and first results. Eur Respir J. 2017;49(1):1601181.
2. Rubbo B, Lucas JS. Clinical care for primary ciliary dyskinesia: current challenges and future directions. Eur Respir Rev. 2017;26(145):170023.
3. Lucas JS, Alanin MC, Collins S, et al. Clinical care of children with primary ciliary dyskinesia. Expert Rev Respir Med. 2017;11(10):779-90.
4. Damseh N, Quercia N, Rumman N, et al. Primary ciliary dyskinesia: mechanisms and management. Appl Clin Genet. 2017;10:67-74.
5. Shoemark A, Burgoyne T, Kwan R, et al. Primary ciliary dyskinesia with normal ultrastructure: three-dimensional tomography detects absence of DNAH11. Eur Respir J. 2018;51(2):1701809.
6. Strippoli M-PF, Frischer T, Barbato A, et al. Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. Eur Respir J. 2012;39(6):1482-91.
7. Mirra V, Werner C, Santamaria F. Primary Ciliary Dyskinesia: An Update on Clinical Aspects, Genetics, Diagnosis, and Future Treatment Strategies. Front Pediatr. 2017;5:135.
8. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. Lancet Respir Med. 2018;6(9):715-26.
9. Lucas JS, Burgess A, Mitchison HM, et al. Diagnosis and management of primary ciliary dyskinesia. Arch Dis Child. 2014;99(9):850-6.
10. Lucas JS, Barbato A, Collins SA, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J. 2017;49(1):1601090.
11. Shapiro AJ, Zariwala MA, Ferkol T, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol. 2016;51(2):115-32.
12. Rumman N, Jackson C, Collins S, et al. Diagnosis of primary ciliary dyskinesia: potential options for resource-limited countries. Eur Respir Rev. 2017;26(143):160058.
13. Lizaraso Caparó F, Fujita R. Enfermedades Raras o Huérfanas, en Perú más huérfanas que raras. Horiz Méd. 2018;18(2):4-5.
14. Olm MAK, Caldini EG, Mauad T. Diagnosis of primary ciliary dyskinesia. J Bras Pneumol. 2015;41(3):251-63.
15. Carlén B, Stenram U. Primary ciliary dyskinesia: a review. Ultrastruct Pathol. 2005;29(3-4):217-20.
16. Kuehni CE, Frischer T, Strippoli M-PF, et al. Factors influencing age at diagnosis of primary ciliary dyskinesia in European children. Eur Respir J. 2010;36(6):1248-58.
17. Majithia A, Fong J, Hariri M, et al. Hearing outcomes in children with primary ciliary dyskinesia-a longitudinal study. Int J Pediatr Otorhinolaryngol. 2005;69(8):1061-4.
18. Afzelius BA, Stenram U. Prevalence and genetics of immotile-cilia syndrome and left-handedness. Int J Dev Biol. 2006;50(6):571-3.
19. Kobbernagel HE, Buchvald FF, Haarman EG, et al. Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia. BMC Pulm Med. 2016;16(1):104.
20. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primer. 2018;4(1):45.
21. Dettmer S, Ringshausen F, Vogel-Claussen J, et al. Computed tomography in adult patients with primary ciliary dyskinesia: Typical imaging findings. PLoS ONE. 2018;13(2):e0191457
22. Sendon CS, Cowles RA, Worhunsky DJ, et al. Pediatric unilobar resection in primary ciliary dyskinesia. Minerva Pediatr. 2020.
23. Armengot Carceller M, Carda Batalla C, Escribano A, et al. Study of mucociliary transport and nasal ciliary ultrastructure in patients with Kartagener's syndrome. Arch Bronconeumol. 2005;41(1):11-5.
24. Werner C, Kouis P. Should transmission electron microscopy and ultrastructural cilia evaluation remain part of the diagnostic work-up for primary ciliary dyskinesia? Ultrastruct Pathol. 2017;41(6):386-9.
25. Paff T, Omran H, Nielsen KG, et al. Current and Future Treatments in Primary Ciliary Dyskinesia. Int J Mol Sci. 2021;22(18):9834.
26. Dehlink E, Richardson C, Marsh G, et al. Are inhaled corticosteroids prescribed rationally in primary ciliary dyskinesia? Eur Respir J. 2018;51(3):1702221.
27. Andréjak C, Nielsen R, Thomsen VØ, et al. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013;68(3):256-62.
28. Levine H, Cohen-Cymberknoh M, Klein N, et al. Reversible airway obstruction in cystic fibrosis: Common, but not associated with characteristics of asthma. J Cyst Fibros. 2016;15(5):652-9.
29. Lucas JS, Davis SD, Omran H, et al. Primary ciliary dyskinesia in the genomics age. Lancet Respir Med. 2020;8(2):202-16.
30. Herrera Gana AM. Diagnóstico de la Discinecia Ciliar Primaria. Neumol Pediatr. 2019;14(2):76-80.