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Primary ciliary dyskinesia in six patients with bronchiectasis

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Abstract

Introduction: Primary ciliary dyskinesia [PCD] is generally considered as a rare autosomal recessive disorder. Previous studies reported various prevalence of PCD among patients with bronchiectasis.

Material and methods: Six PCD patients who were diagnosed during the investigation of 40 patients with bronchiectasis were enrolled in this study. Ultra structural studies for both epithelium and cilia were performed, and the deformities in detailed electron microscopic images confirmed the diagnosis of PCD.

Results: Four patients experienced the first symptoms shortly after the birth, 1 by the age of 1 and 1 by the age of 4 years. Except of 1 case that was diagnosed 2 months after the onset of disease, diagnosis delay was longer than 5 years in all patients. Consanguineous marriage was observed in the parents of all patients. Upper respiratory tract infections were documented for all patients.

Conclusions: PCD should be considered as a probable underlying disorder in patients with bronchiectasis. Past medical history of otitis media and history of similar clinical findings in family members should raise suspicion toward PCD.

Key words: bronchiectasis, diagnosis, primary ciliary dyskinesia

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Introduction

Primary ciliary dyskinesia (PCD) is an autosomal recessive genetic disorder caused by the impaired function of cilia of the respiratory tract epithelial cells which may also involve other ciliated cells in the reproductive system of the male or female [1]. PCD is considered to be a rare disease with a probably underestimated incidence rate of 1:15000 to 1:20000 per year [1]. The main clinical feature of PCD is chronic recurrent infections of respiratory tract as a result of the failure in the clearance of respiratory airways [1]. These patients may also experience additional features of PCD including situs inversus [mirror image laterality of circulatory system and visceral organs in 50% of patients], dyspnea, rhinosinusitis, bronchitis and otitis media from early childhood, which may be followed by bronchiectasis and respiratory failure later during the course of disease [1, 2].

Nowadays, bronchiectasis is not commonly observed in healthy population mainly due to the routine utilization of vaccination and antibiotic therapy. However, there are some underlying risk factors taking part in the development of bronchiectasis during the childhood. PCD, alongside with other more common causes such as cystic fibrosis and primary immunodeficiency disorders, are the predisposing conditions for bronchiectasis [2]. During the investigation of cases with recurrent respiratory infections, primary suspi-

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cion toward PCD is often made by the classical presentation of situs inversus, followed by otitis media, and male infertility. In some cases with neonatal onset, variable symptoms of icterus, hydrocephaly and gastroesophageal reflux are also reported [2]. In the absences of the major clinical features, the diagnosis of PCD may be postponed until other probable causes of bronchiectasis have been ruled out [2].

Transmission Electron Microscopy [TEM] is the gold standard for the diagnosis of PCD which is expensive, time consuming and available only in a few reference centers with experienced specialists [3]. As a result, many physicians miss to include PCD assessments in their early work ups for bronchiectasis, which causes diagnostic delay and undervaluation of PCD prevalence in the society. Increased awareness of physicians regarding the probability of PCD in bronchiectasis patients helps in considering this disorder at early stages resulting in the better management of patients and decreased morbidity and mortality [2].

The reported prevalence of PCD among patients with bronchiectasis is widely varied from 4.3% to 19.1% in the literature [2, 4]. Here we report 6 patients with PCD who were known cases of bronchiectasis from childhood and early adolescence and were diagnosed during the investigation of 40 patients with bronchiectasis (15%) in our center. The diagnosis of PCD was confirmed by pathologic findings of electron microscopy. Clinical history and manifestations, radiologic findings, pulmonary function tests and complications of the disease are presented here.

Material and methods

In this study we included six PCD patients who were diagnosed in our previous study on the evaluation of humoral immunity in patients with bronchiectasis [5]. In our investigated 40 bronchiectasis cases, six (15%) were diagnosed cases of PCD. One patient was a known case of situs inversus prior to the suspicion toward PCD. Other differential diagnosis such as asthma, cystic fibrosis (CF), immunodeficiencies, anatomic defects and aquired ciliary dysknesia due to smoking, allergens and pollutants were excluded in all 6 patients. Electron microscopic evaluations were performed in all cases. Ultra structural studies for both epithelium and cilia were done, and the deformities in detailed electron microscopic images confirmed the diagnosis of PCD.

Patients fulfilled a specific questionnaire containing the clinical manifestations, medical and familial history of disease, and therapeutic interventions of PCD. The questionnaire provided data regarding the medical history, clinical signs and symptoms, delay diagnosis, number of medical attending and care qualities, long term complications of disease and medical and surgical treatments. Serial pulmonary function tests and sputum cultures were performed and lung radiographic images were also reviewed.

Results

The median age of the patients at the time of the study was 18 years [ranged from 9 to 25 years]. In 4 patients the symptoms of the disease began at birth, while in 2 patients [P3 and P6] the age at the onset of disease was 4 and 1 years, respectively. One patient was diagnosed 2 months after the onset of disease. The remaining 5 patients experienced a diagnosis delay from 5 to 16 years. Patients' demographic data are summarized in Table 1.

First or second degree consanguinity was reported in the parents of all patients. Two patients also mentioned the symptoms of immotile cilia disease in their family members. In P3, patient's 6 years old sister had experienced recurrent episodes of upper respiratory tract infections and her radiographic images showed situs inversus, with evidences of lobar bronchiectasis and pan-sinusitis. In another patient, P2, his two brothers with current ages of 31 and 32 years, experienced recurrent pulmonary infections and chronic cough from the early childhood. Moreover, to treat infertility one of them needed microinjection techniques as a result of probable sperm immobility. In this brother, one of his twin children experienced icterus and hydrocephaly in the neonatal period.

There were some common clinical manifestations among the study population. Upper respiratory tract infections with chronic cough, dyspnea, sputum production, wheezing, rhinosinusitis, nasal and sinus mucopurulent secretions were observed in all patients. Otitis media were also reported, except in patients P1 and P2. In PCD cases with otitis media, 3 cases (P3, P5 and P6) had experienced persistent and recurrent episodes of infections till the end of follow-up period, unlike P4 in whom otitis media was managed effectively.

Situs inversus, as the most reported specific presentation of PCD, was noted in only one patient (P6). Clinical findings during the early childhood had no difference before and after the definite diagnose of PCD, and involvements of lungs, sinuses, nasal cavity and ears were newly added by the process of PCD at further years

Table 1. Demographic data of 6 patients with PCD

ID	Gender	Consanguinity of parents	Age (y)	Age at onset (y)	Age at the diagnosis (y)	Diagnostic delay (y)	Structural defect
P1	M	+	22	At birth	16	16	Inner dynein arms defect
P2	M	+	25	At birth	15	15	Inner and outer dynein arms defect
P3	F	+	17	4	11	7	Inner and outer dynein arms defect
P4	M	+	19	At birth	13	13	Inner dynein arms defect
P5	F	+	11	At birth	2 months	2 months	Inner dynein arms defect
P6	M	+	9	1	6	5	outer dynein arms defect

Table 2. Major clinical manifestations of PCD patients

ID	Clinical manifestations				
	Rhinitis & sinusitis	Supportive respiratory drainages	Recurrent pneumonia	Recurrent otitis media	Situs inversus
P1	+	+	+	–	–
P2	+	+	+	–	–
P3	+	+	+	+	–
P4	+	+	+	-	–
P5	+	+	+	+	+
P6	+	+	+	+	–

Table 3. The results of first and last spirometry tests performed during the follow-up period

ID	Time	FEV_1 (act/pred.)		FVC (act/pred.)		FEV_1/FVC		MEF 25–75 (act/pred.)	
	First/last (y)	First	Last	First	Last	First	Last	First	Last
P1	2004/2011	84%	72%	95%	102%	73%	61%	65%	33%
P2	2004/2011	104%	78%	97%	76%	88%	87%	62%	77%
P3	2008/2011	60%	79%	75%	81%	71%	87%	59%	72%
P4	2004/2011	85%	84%	84%	74%	84%	83%	106%	97%
P5	2008/2011	88%	74%	97%	87%	81%	69%	67%	56%
P6	2008/2011	65%	64%	61%	73%	84%	86%	31%	35%

of managements. In patients with the onset of disease at birth, neonatal respiratory distress was the most significant first presentation of the disease, and no patient experienced other probable symptoms such as icterus, hydrocephaly and gastroesophageal reflux during this period. Table 2 shows the major clinical manifestations of the study population.

All patients underwent serial spirometeries during the follow-up period. For each patient, the results of FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 st second), MEF25–75 (mid-expiratory flow) and FEV_1/FVC in the first and last spirometery are presented in Table 3. In P3 and P4, chronic respiratory damages did not develop obstructive lung disease, while in other cases the changes showed progressive decline in FEV_1. In P2, P4 and P5, decline in the respiratory function showed a mixed (both obstructive and restrictive) pattern, while in others it only showed obstructive pattern (Table 3).

Regarding the patients' radiographic studies, spiral chest HRCT and sinuses CT scans were performed in all cases. In HRCT of P1, P2 and

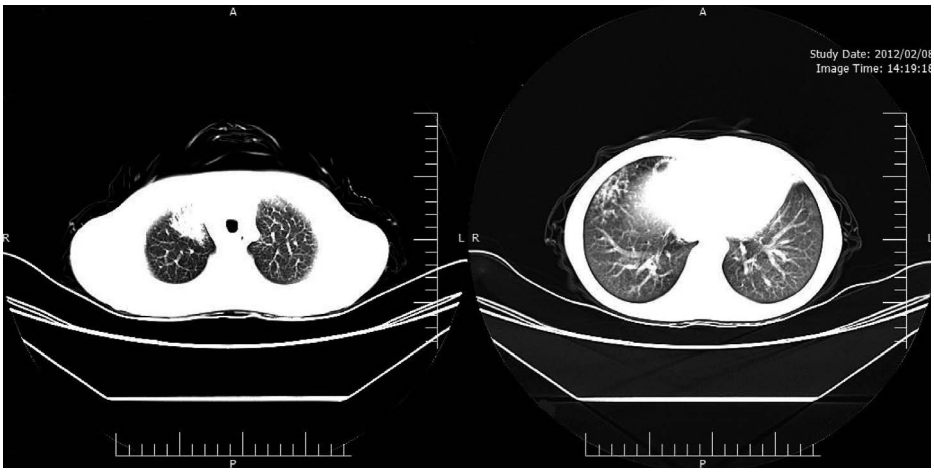

Figure 1. Chest HRCT of P6. **A** — evidences of right upper lobe segmental collapse which presents the early stage of bronchiectasis; **B** — the same HRCT series shows narrow collapse of right middle lobe

Table 4. Long term complications and surgical interventions

Patients	Long term complications				Surgical interventions
	Bronchiectasis	Sinus obstruction	Tympanic membrane perforation	Infertility	
P1	+	–	–	+	
P2	+	–	–	+	
P3	+	+	+	–	Tympanoplasty, FESS, tonsillectomy
P4	+	+	–	–	FESS
P5	+	–	+	–	Ventilation tube implantation, tonsillectomy
P6	+	–	+	–	Tonsillectomy

P4, obvious evidences of bronchiectasis such as bronchial dilations, bronchial walls thickening and mucus-filled bronchi were noted in right middle lobe, left lower lobe and lingula. Mucosal thickening and opacity were also suggesting for chronic sinusitis in coronal CT scans of sinuses in these patients. In patients P1 and P2, nasal septal deviation was found, and in P3 and P4, all the openings of the sinuses were obliterated. P3 had chronic sinusitis with obstruction of sinusal openings, and her sister had situs inversus, bilateral lobar bronchiectasis and pansinusitis in HRCT. Patient P5 had situs inversus, and the HRCT of P6, showed early stages of bronchiectasis by generalized peribronchial thickenings and partial segmental collapses in right upper and middle lobes (Fig. 1).

Long term complications of PCD were widely different between patients. In subjects P1, P2 and P4, bronchiectasis was the main complication which was accompanied by sperms immotility in P1 and P2 and obstruction of sinuses in P4. In patients P3, P5 and P6, the main complication was tympanic membrane perforation, and bronchiectasis less significant. In P4, recurrent otitis media had been managed while in P3, P5 and P6, chronic recurrent otitis media led to hearing loss due to supportive accumulations in the middle ear and tympanic membrane perforations. Some surgical interventions were performed because of the disabling complications. In P3, tympanic membrane defects were concomitant with obstruction of sinuses. Functional endoscopic sinus surgery (FESS) was done in P3 and P4, and tympanoplasty and ventilatory tube implantation were the major interventions for P3 and P5, respectively. No patient underwent lobar pneumonectomy as a result of complicated bronchiectasis.

The most important management measures included prophylactic antibiotic therapy, annual vaccinations against influenza, indicated Pneumovax administration, and physiotherapy. Data regarding the long term complications and surgical interventions are shown in Table 4.

Discussion

The current study presents 6 PCD patients in whom the diagnosis was made during the investigation of 40 cases with bronchiectasis. Five out of these 6 patients were incomplete cases of Kartagener syndrome without dextrocardia, and one was complete Kartagener syndrome with situs inversus. Various reports regarding the prevalence of situs inversus, or dextrocardia in PCD patients estimated a proximate prevalence of 50% [6, 7]. In contrast to our findings, in a study on 6 cases with primary ciliary dyskinesia in Brazil, 5 were cases of Kartagener syndrome with *situs inversus totalis* or situs ambiguous [8]. The diagnosis of PCD is less likely to be overlooked in the presence of situs inversus or dextrocardia.

In a study of 55 children with PCD by Coren et al, consanguinity was positive in 5 of 55 patients (9%) [7]. High rate of parental consanguinity of in our study may be somewhat due to the high rate of consanguinity of marriages in Iran which is estimated to be around 38.6% [9] which may also affect the clinical features of our cases.

Currently, various tests can be used to support the diagnosis of PCD. Screening tests include saccharin testing, radioaerosol testing, and nasal nitric oxide testing, while diagnostic testing includes electron microscopy analysis of ciliary structure, ciliary beat pattern and frequency analysis, and genetic testing. Any positive screening results warrants confirmatory diagnostic tests [3, 10].

In this study based on medical history of patients, evidences of PCD were found in the history of patients' family members. However, we failed to investigate those subjects for the probability of PCD mainly due to the limitation of subjects in accessing electron microscopy, Hierarchical Feature Vector Matching (HFVM) and nasal nitric oxide measurements as well as genetics evaluations. More comprehensive studies may reveal the importance of PCD assessment in patient family members such as the history of recurrent respiratory infections during early childhood. A diagnostic delay is expectable because in absence of situs inversus, positive family history, and before the later presenting infertility most noticeably in male patients, there is no specific feature in respiratory tract symptoms at the early years of the disease [7].

Many physicians missdiagnose PCD or eliminate PCD from their differential diagnosis due to inexperience with diagnostic testing methods. Also there are overlaps in the clinical presentations of the main differential diagnosis of PCD, including immunodeficiency disorders, CF, asthma and anatomic defects [11]. Presenting symptoms at early stages such as rhinitis, otitis media, cough and dyspnea, sinusitis and bronchitis are also common in healthy children without underlying medical problems [12]. In adolescence, the upper respiratory tract symptoms continue with the same organs involvements, but male infertility is revealed by investigations in 50% of cases [13], as in 2 adults in this report. Some practical symptomatic aspects to differentiate PCD from CF are otologic features. Almost all patients with PCD will experience at least 1 episode of otitis media by the age of 5 years with reoccurrences by the age of 17 years. Without findings of otitis media, the physician should doubt the diagnosis of CF rather than PCD [14]. Variable manifestations of auditory tract infections with chronic secretory otitis media, middle ear fluid, tympanic membrane perforation and otorrhea which may persist in PCD are not found in CF patients. Herein this report, the 4 younger patients had chronic recurrent otitis media from the beginning of the disease. Recurrent otitis media could be a leading point to prompt the diagnosis of PCD in these, compared with two older patients with more diagnostic delay. Other less common clinical features of PCD at neonatal stage such as GERD, cardiac abnormalities, hydrocephalus and polycystic kidney diseases [5] were absent in our patients.

In all PCD patients, spirometery should be requested and considered as routine follow-up investigations [15]. Lung involvement included obstructive, restrictive and mixed patterns in function, which is compatible with other studies on respiratory outcomes of PCD [7]. While the lung damages at the time of the diagnosis of PCD are partially reversible, lack of routine follow-up and proper management can result in a poor prognosis [16].

In our patients, findings of HRCT scan from lungs showed bronchial wall thickening and dilation, lobar atelectasia and collapse in adult patients with developed bronchiectasis. In patients with recent diagnosis at early childhood, the opacities of affected middle and lower segments with atelectasia and mild dilations of bronchi implicated early stages of bronchiectasis [13, 17]. Radiologic evidences for bronchiectasis are almost always found in all adults with PCD, and are correlated with the severity and chronicity of the disease and a delayed diagnosis in adults [18]. There are recent limited reports about the prevalence of PCD in bronchiectasis populations. In one retrospective study on children with

bronchiectasis in Korea, primary PCD were documented in 4.3% of patients as an underlying etiology [2]. In our report, cases were selected from a community of 40 bronchiectasis patients [adult and children], which indicates a prevalence of 15%. Further studies on larger populations of bronchiectasis patients are necessary to estimate the accurate prevalence of PCD in bronchiectasis which may be variable at the worldwide level.

In our report, 3 younger patients with earlier diagnosis of PCD, had lungs less affected by bronchiectasis lesions in HRCT. In these patients, radiographies may not be predictive for severe obstructive lung disease with decreased FEV_1 [7]. The findings of bronchiectasis in PCD are most notable in right middle lobe and lingula, as that in our report. Pathologic findings in HRCT of CF patients have different distributions, in which the upper lobes are predominantly affected [7]. CT imaging of sinuses revealed nasal septal deviation in 2 of our patients, and obstructed sinusal openings in other 2 cases undergoing FESS. Paranasal CT scan is often requested along with HRCT during follow-ups [2]. In a study by Noone et al., 100% of PCD cases who had paranasal CT scan for sinuses had evidence of chronic sinusitis [19].

Routine medical follow-ups are indicated for all PCD patients. In the management of PCD patients, the assessments contain pulmonary function tests, sputum culture and radiological imaging. Otoscopy must be performed, and audiometery is also requested as needed. The treatment approach during supervision is aggressive antibiotic therapy, regular clearance of airways with physiotherapy and regular washing of nasopharynx with saline, immunizations against pneumococcal polysaccharide vaccine and annual influenza vaccinations [12].

There is no documented schedule for routine medical follow-up. It is suggested that respiratory investigations should be performed twice year for adults, and every 2–3 months for children with PCD [12].

Long term complications in PCD include bronchiectasis, obstructed sinus openings, tympanic membrane perforation and infertility, as seen in our patients. Surgical interventions in PCD should be avoided unless inevitable [12]. Patients with sinunasal involvements were unresponsive to symptomatic treatments so that surgery was indicated. Surgical tympanostomy tubes were inserted because of hearing loss due to effusions in middle ear. Tympanostomy in PCD patients should be performed according to a cost beneficial assessment on the degree of hearing loss and the outcomes such as otorrhea and tympanic membrane perforation [14]. Infertility, as a complication of PCD due to flagella defects and immotility of sperms is more prominent in males. However, many patients have fathered children with no medical intervention [13]. There are reports about male patients who had retrieved the ability to bear children after intra cytoplasmic sperm injection (ICSI) [20].

In conclusion, PCD should be considered as a probable underlying disorder in patients with bronchiectasis even without specific manifestations such as situs inversus. Some positive features in patient's medical history such as otitis media and history of similar clinical findings in family members should raise suspicion toward PCD.

Conflict of interest

The authors declare no conflict of interest.

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