Case Report

Primary Ciliary Dyskinesia : A Case Presentation and A Current Review†

Weerachai Tantinikorn, M.D.*
Kitirat Ungkanont, M.D.*
Vanneet Khawcharoenporn, M.D.**

Abstract : **We present a 14 year-old girl with a history of chronic rhinorrhoea, nasal obstruction and recurrent epistaxia. Physical findings showed huge nasal polyp with broadening of nasal bridge, perforation of left ear drum and a right middle ear effusion. Despite a strict program of nasal saline toilet, broad-spectrum antibiotics covering beta-lactamase producing organisms, and meticulous technique of endoscopic sinus surgery, the patient's symptoms and nasal polyp reappeared very quickly. A set of investigations was done in order to confirm and rule out suspected diseases. The electron microscopic study of the patient's nasal mucosa revealed partial absence of inner dynein arms and extra singlet at the center in some axoneme compatible with primary ciliary dyskinesia.**

เรื่องย่อ : **Primary Ciliary Dyskinesia : A Case Presentation and A Current Review**
วีระชัย ตันตินิกร พ.บ.,* กิติรัตน์ อังกานนท์ พ.บ.,* วรรณีต ขอเจริญพร ภ.บ.**
**ภาควิชาโสต นาสิก ลาริงซ์วิทยา, **ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.*
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รายงานผู้ป่วยเด็กหญิงไทย อายุ 14 ปี มาพบแพทย์ด้วยปัญหาคัดจมูก น้ำมูกไหลเรื้อรัง และเลือดกำเดาออกเป็น ๆ หาย ๆ ตรวจร่างกายพบบริเวณสันจมูกมีการโป่งนูนขึ้นอย่างชัดเจนจากการที่มีริดสีดวงจมูกขนาดใหญ่อุดตันภายในช่องจมูกเป็นเวลานาน เยื่อแก้วหูซ้ายมีรอยทะลุเล็ก ๆ และมีน้ำมูกใส ๆ ไหลจากหูชั้นกลาง หูขวาตรวจพบสารน้ำขังในหูชั้นกลาง (middle ear effusion) ผู้ป่วยได้รับการรักษาด้วยยาต้านจุลชีพที่ครอบคลุมเชื้อที่สร้าง β-lactamase และการผ่าตัดไซนัสโดยใช้กล้อง (endoscopic sinus surgery) รวมทั้งการล้างจมูกด้วยน้ำเกลืออย่างเต็มที่ หลังการรักษาผู้ป่วยมีริดสีดวงโตขึ้นใหม่อย่างรวดเร็ว ร่วมกับอาการน้ำมูกเหนียวข้นไหลอย่างต่อเนื่อง

**Department of Otolaryngology, **Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*
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คณะผู้รักษาจึงได้ทำการตรวจทางห้องปฏิบัติการเพิ่มเติมอีกหลายอย่าง เพื่อให้ได้การวินิจฉัยปัญหาของผู้ป่วย จากการตรวจทางพยาธิวิทยาของชิ้นเนื้อจากเยื่อบุจมูกด้วยกล้องจุลทรรศน์อิเล็กตรอน พบว่ามีการขาดหายไปบางส่วนของ inner dynein arms และมี extra singlet บริเวณ center ในบาง axoneme เข้าได้กับการวินิจฉัยเป็น primary ciliary dyskinesia

INTRODUCTION

The ciliated epithelium of respiratory tract has the principal function of keeping the respiratory tract clean. An ultrastructural defect with ineffective beating of the cilia can impair both nasal and pulmonary mucociliary transport. This results in stagnation of the secretions and infection which may penetrate to the deeper tissue. On the other hand, infection and external noxious stimuli to the respiratory mucosa can alter both the physiology and ultrastructural anatomy of the cilia. Cilia and spermatozoa have the same ultrastructure with the typical 9+2 arrangement of the microtubules. Immotility or abnormal beating of the sperm flagella leads to infertility in male patients. The following case report typifies some of the clinical problems incurred by affected patients. Electron microscopic study of the patient's nasal mucosa specimen identified the major ultrastructural defect of the ciliary axoneme compatible with primary ciliary dyskinesia.

CASE REPORT

A 14-year old girl was referred to our department with a history of recurrent epistaxis. She had had symptoms of nasal obstruction with a foul smelling mucopurulent discharge, which was sometimes painful, and had had pus draining from her left ear for 3 years. Her parents and siblings had no history of chronic respiratory diseases or any other hereditary disease. On physical examination, huge nasal polyps protruded beyond the nostrils causing the dorsum of her nose to bow out (Figure 1). A tenacious mucopurulent discharge was found covering the polyps. Inflamed and enlarged adenoids occupied more than 80% of the nasopharyngeal space. Her right ear showed a retracted and amber color tympanic membrane with fluid collection in the middle ear and the left ear showed a small perforation with a purulent discharge. Other systems were examined and found to be within normal limits.

A pure tone audiogram demonstrated bilateral conductive hearing loss with a 25 dB air-bone gap. A paranasal sinus film showed total opacification of all sinuses with mucosal thickening in both nasal cavities. Chest x-ray was normal. A complete blood count and urine analysis were unremarkable. Allergic skin prick test was positive for Bermuda and Timothy grass, cat, Alternaria, mixed fish and beef.

After a full course of antibiotics with 4 weeks of oral amoxicillin and saline nasal irrigation, paranasal sinus computer tomographic study revealed a soft tissue mass fully filled the nasal cavity, both maxillary, ethmoidal and frontal sinuses (Figure 2). There was also enlargement of the adenoid which nearly obliterated the nasopharyngeal space. In addition to adenoidectomy, we performed endoscopic sinus surgery and found that multiple polyps came from uncinate processes, bulla ethmoidalis, and middle turbinates. Maxillary antrums and ethmoid air cells were also filled with polyps and thickened mucosa with mucopurulent discharge. We removed all polyps, enlarged the natural ostium and performed bilateral anterior ethmoidectomy, trying to preserve normal mucosa as much as possible. Pus culture showed no growth. After a few weeks, she was able to breathe comfortably through her nose and her left ear became dry. One month later, at the second follow up visit, despite vigorous nasal toilet, high dose intranasal steroids and antibiotic administration with amoxicillin-clavulanic acid, nasal polyps had regrown very quickly with a tenacious discharge and her left otorhoea resumed.

Immunoglobulin studies were within the normal range. A saccharin test was done and despite waiting for 60 minutes, the patient still could not taste the sweetness of saccharin. Second endoscopic

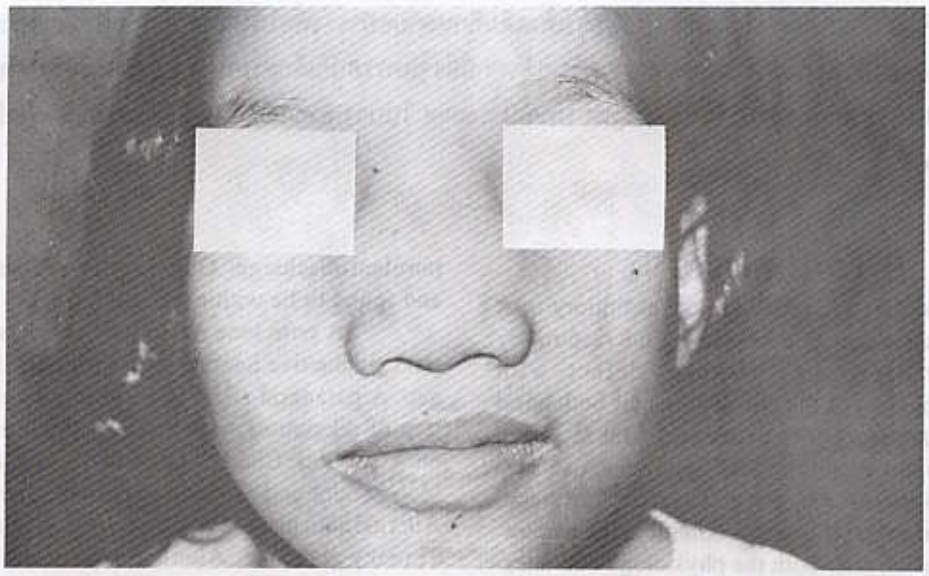


Figure 1. Portrait of the patient showing ballooning of the dorsum of her nose.

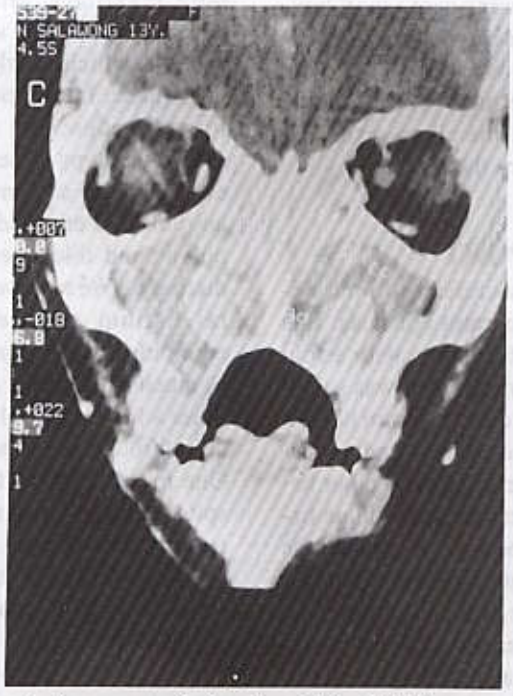


Figure 2. CT scan of the paranasal sinuses revealed polyps fully filled in nasal cavity, maxillary and ethmoid sinuses.

sinus surgery and right myringotomy tube placement were performed 4 months later due to huge obstructed nasal polyps and a persistent right middle ear effusion. Mucopurulent discharge culture still showed no growth. A mucosal specimen from an inferior turbinate was sent for electron microscopic study. The ultrastructure of the cilia showed partial absence of inner dynein arms (Figure 3a) and extra singlet of the center in some axoneme. The orientation of the ciliary axoneme was also random at more than 30 degrees. Compound cilia and an extra singlet were also observed in some axonemes (Figure 3b). The diagnosis of primary ciliary dyskinesia was made.

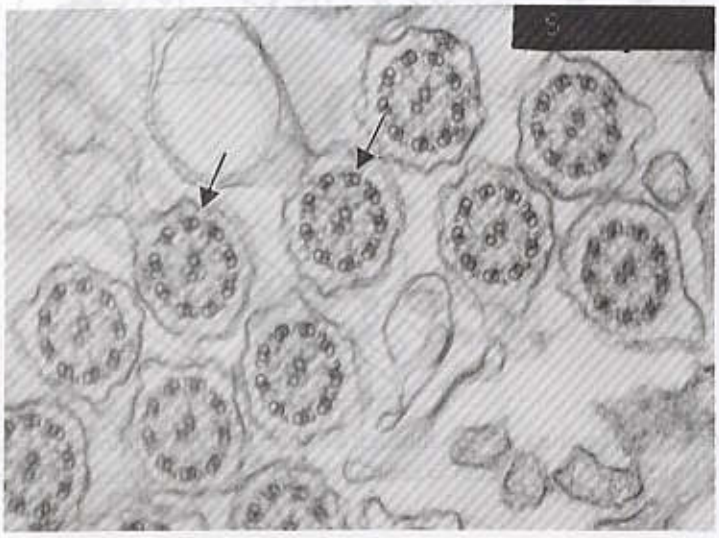


Figure 3a. Electron micrograph showing partial absence of inner dynein arms (arrow).

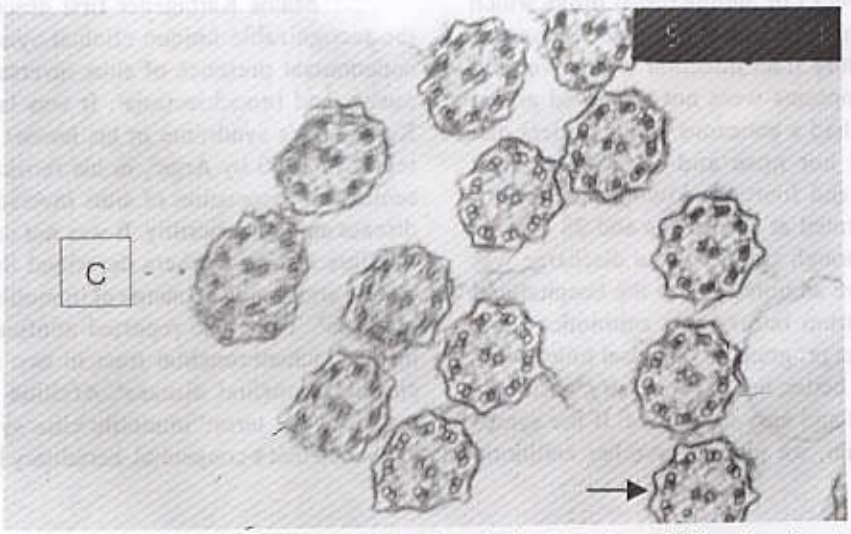
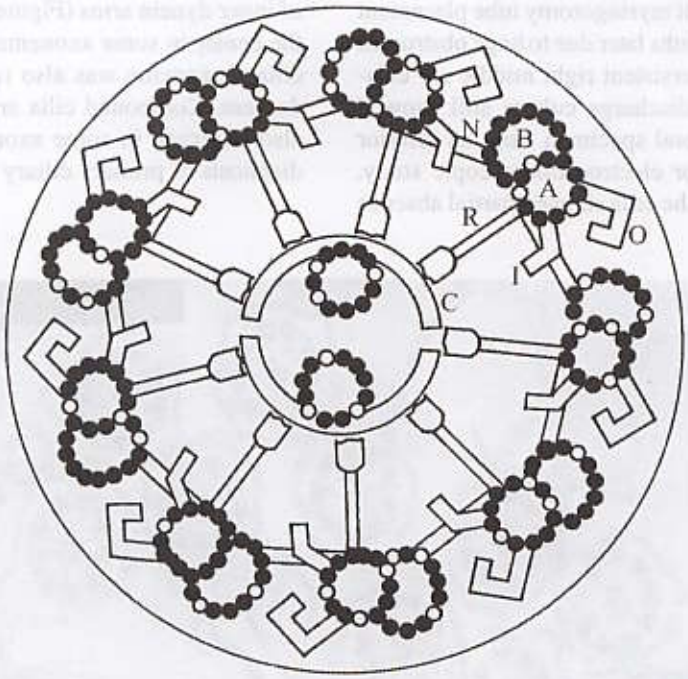


Figure 3b. Cross sectioned cilia, supernumerary singlet tubule (arrow), multidirectional orientation and compound cilia (c) are demonstrated.



Schematic diagram of a cross section through a cilium at mid-shaft level. A= subunit A, B= subunit B, N= nexin link, R= radial spoke, C= central sheath, O= outer dynein arm, I= inner dynein arm.

A vigorous nasal toilet program and many courses of 2-4 weeks of antimicrobial drugs which cover beta- lactamase producing common pathogens of upper respiratory tract infection were given but the patient's symptoms were not improved as expected. She still had a tenacious mucopurulent discharge through her nose and intermittent left otorhoea. Third and fourth endoscopic polypectomies were performed at 13 months and 28 months respectively. Although culture of the discharge was never positive, we admitted her to the hospital and gave broad-spectrum intravenous antibiotics for 2 weeks with a strict program of sinunasal toilet. Now she seems to feel better, her left ear is dry, nasal discharge is mucoid and easy to remove. If her symptoms worsen again, we plan to give her antibiotic prophylaxis.

DISCUSSION

Mains Kartagener first described in 1933 the recognizable unique clinical syndrome with a concomitant presence of situs inversus, chronic sinusitis and bronchiectasis[1]. It was later named as Kartagener's syndrome in his honors. There was a report in 1960 by Arge[2], in his fertility clinic, presenting an association of situs inversus, respiratory disease and male sterility. It was not until 1975, that Afzilius and co-workers described the absence of dynein arms in the axoneme of immotile human spermatozoa[3]. They also reported nonfunctioning cilia in the tracheobronchial tract in two subjects with chronic bronchial disease[4]. Afzilius subsequently proposed the term "immotile cilia syndrome" and explained that a congenital, hereditary lack of dynein

arms in respiratory cilia and sperm flagella was the cause of chronic respiratory disease and male infertility in the patients[5]. Many reports later demonstrated that the cilia and sperm flagella beat ineffectively in uncoordinated fashion, not totally immotile, resulting in impairment of mucociliary clearance. As a result, the terms "primary ciliary dyskinesia" (PCD) and "dyskinetic cilia syndrome" appeared in the literature to give a more correct explanation of the abnormality. The former seems to be more frequently used. With defective cilia, viscera will take up the normal or the reversed position during embryogenesis by chance resulting in a similar number of cases with and without situs inversus. Kartagener's syndrome could therefore be regarded as a subgroup of the PCD.

Ultrastructurally, cilia and flagella are similar. They are composed of the characteristic "9+2" arrangement of microtubules (Figure 4). The peripheral doublets are connected to another by the nexin links and connected to the central sheath by the radial spokes. Both nexin links and radial spokes may have a function to provide structural rigidity and maintain the integrity of the axoneme. The dynein arms extend from A subunit toward the adjacent doublet in a clockwise direction. It contains ATPase which is essential in providing energy for ciliary motion.

PCD is an autosomal recessively inherited disease with a heterogeneous group of conditions characterized by specific ultrastructural defects of cilia and spermatozoa. The incidence of PCD has been calculated to be 1 in 16,000[6]. Fifty percent of affected individuals have situs inversus known as Kartagener's syndrome, 1 in 32,000[6]. PCD has been reported 5.6% in the patients who suffer from recurrent respiratory disease[7].

The characteristic clinical presentation of PCD is a history of chronic repeated upper and lower respiratory tract infection. Situs inversus, which is present in 50% of the patients in association with sinubronchial diseases, is a very helpful clue to make a diagnosis of PCD. The severity of the symptoms varies in each patient. A newborn baby may have neonatal respiratory distress without evidence of conventional risk factors. Persistent mucopurulent rhinorrhoea associated with chronic sinusitis and otitis media is present in nearly all patients.[8,9] The sinunasal disease is difficult to manage because the mucopurulent discharge collects in the sinus cavities and physical therapy and postural drainage can not be performed successfully. Typically, symptoms abate with the administration of antibiotics and reappear very quickly after discontinuation of such therapy[6]. Nasal polyps are found in about 30% of the patients with PCD.[8,9] Otitis media with chronic middle ear effusion is commonly present and it always requires the replacement of tympanostomy tube[6,10,11]. In severe cases, hyponasal speech, anosmia and halitosis are common. Stagnation and impaction of secretions in the lower respiratory tract results in chronic bronchitis, recurrent pneumonia, atelectasis and reactive airway disease which eventually causes erosion and distention of the bronchial wall leading to bronchiectasis.

Most of the male patients with PCD are infertile. However, it has been found that an ultrastructural abnormality of the ciliary axoneme is not always accompanied by a similar abnormality of the sperm axoneme. There are reports of normal motile spermatozoa with intact dynein arms in a patient who had immotile respiratory cilia lacking dynein arms, on the other hand, normal dynein arms motile respiratory cilia was found in a man who had immotile spermatozoa lacking dynein arms.[12,13] It seems that cilia and spermatozoa are sufficiently different to have at least some proteins that are not genetically shared.[25] The follopian tube is surrounded by functional smooth muscle and also lined with ciliated epithelium. Theoretically, female infertility and ectopic pregnancy can occur more frequently in the PCD patients, however, there is no available data to make a firm conclusion on this subject.

There are some reports regarding abnormal chemotaxis of neutrophil but the clinical significance of this finding is unknown. Abnormal function of ependymal cilia may affect the circulation of cerebrospinal fluid and increase the risk of intracranial hypertension resulting in hydrocephalus.[15] There is a report of significant association between PCD and severe esophageal and major cardiac diseases.[16]

The clinical presentation of PCD is not unique or pathognomonic for making the diagnosis. So a set of investigations should be considered in

order to confirm and rule out the other suspected diseases. It should be based on the availability of the tests and the prevalence of the underlying conditions. Immunoglobulin studies, flexible or rigid endoscopy and esophageal pH monitoring should be considered, depending on the clinical presentation, before going on to the more expensive, sophisticated and time consuming investigations of PCD. Literatures from the USA and Europe suggest to perform sweat test to rule out cystic fibrosis. In fact, cystic fibrosis is a very rare disease in Thailand. Up to the present time, there have been no reports of cystic fibrosis in Thailand from the medline search. This makes cystic fibrosis in Thailand rank the last in differential diagnosis.

Beside clinical evaluation, there are two components to the thorough evaluation of PCD. They are functional and ultrastructural studies. Functional studies consist of mucociliary transport studies and ciliary motion analysis. The interaction between cilia in coordinated metachronal fashion leads to the effective movement of the overlying mucosal blanket. If the cilia have abnormal structure and function, the movement of the mucosal blanket will be compromised. The saccharin test is a simple method for the mucociliary transport studies. It measures the time it takes for the perception of sweetness after placement of a saccharin particle on the anterior end of inferior turbinate. This test is cheap and easily to perform but it can not be usually used in small children or infants, and its reliability has been questioned. With a gamma camera, we can measure the removal of inhaled radiolabelled (99mTc) aerosol of human serum albumin from the lung or a droplet of labelled albumin from the nose[11]. Various methods have been developed to measure the ciliary beat frequency (CBF) and to analyze ciliary wave form. Ciliary movement should be metachronal and coordinated in the same direction, with a beating frequency of 8-22 Hz.[6,10,17] It needs well-trained personnel and highly sophisticated instruments such as high speed cinematography and stroboscopic, photoelectric and laser light scattering spectroscopy.[6,11,17,18]

A standard light microscopic study at 400× magnification can be used to observe the ciliary movement pattern, even intraoperatively[7,19]. It is suggested to be is used as a screening test before transmission electron microscopic studies[19]. However, this technique may be unreliable and does not correlate with the ciliary motion analysis by high speed cinematography[11].

A transmission electron microscopic study is always used to reach a final diagnosis of PCD. Many reports have described the ultrastructural abnormalities of the ciliary axoneme and sperm flagella. These are absence or lack of dynein arms, radial spokes and nexin links, ciliary aplasia, abnormal length of cilia, abnormal arrangement of microtubules, compound cilia, loss of ciliary membrane, and disorientation of cilia[6,10,11,20-23]. Since all ciliated cells of the respiratory tract express the same congenital defect, the diagnosis of PCD can be performed on nasal cilia, bronchial cilia, or both. It seems more convenient to start by studying nasal cilia before deciding to get a bronchial specimen. Nasal sampling can be taken adequately by blushing, scraping or excisional biopsy.

The abnormalities found in both functional and ultrastructural studies could be primary congenital hereditary disease or secondary to chronic infection of the upper and lower airway. The question is whether the ciliary abnormalities are primary, secondary, or mixture of both. The qualitative and quantitative assessment have been summarized to indicate the cause of the ciliary abnormality[7,17,22,23]. In healthy persons, 3-9% of cilia can exhibit ultrastructural and functional defects. A percentage of abnormal cilia higher than 10% is considered to be clearly abnormal[7,10,23,24]. PCD is found to have a high percentage of abnormal cilia with the same uniform ultrastructural defects, while secondary ciliary dyskinesia (SCD) has a lower percentage of abnormal cilia with heterogeneous defects. However, the exact difference in the percentage of abnormal cilia in PCD and SCD has not been clarified and standardized. It may depend on the varying degree of inflammation and severity of congenital ciliary defects. To diminish the infection effect, it is suggested that the specimen is taken for study after a full course of antibiotic therapy. Finding the same ultrastructural defect in spermatozoa as in respiratory cilia would be a helpful evidence to make a diagnosis of PCD. In patients with PCD, we can also find the same uniform ultrastructural defect in both upper and lower respiratory

cilia. This will not happen in patients with SCD. Because nasal mucosa is the primary respiratory tract exposed to injuries, some investigators advised epithelial cell culture as a tool to evaluate ciliary dysfunction and differentiate PCD from SCD[17,25]. They cultured the native ciliated cells which showed abnormal beating pattern and frequency. The regrowth ciliated cells in the culture media with antibacterial drugs would be free from infection and any other external stimuli. As a result, the cultured ciliated cells are in an ideal condition for functional and ultrastructural studies.

Dynein arms and radial spokes defects have been proven to be the major ultrastructural defects specific to PCD[7,14,18,22]. The number of nexin links per cilium in PCD is not significantly different from the patients with chronic respiratory diseases and healthy persons[22]. Abnormal arrangements of microtubule including transposition, which mean displacement of one of the peripheral pairs of microtubule centrally with absence of the central microtubule, incomplete microtubule, incomplete central sheath and ciliary disorientation are also found to be non specific to PCD[22]. Compared with healthy people, these abnormalities were found in significantly high percentage of cilia in the PCD and SCD patients, however, no significant difference between these two groups was demonstrated.

Early diagnosis is important for management which consists of vigorous sinunasal and pulmonary toilet and prompt antibiotic therapy of exacerbations. Management of PCD is essentially symptomatic in order to keep the upper and lower respiratory tract free of excessive infected secretion. Superinfection with *H. influenzae, S. pneumoniae* or *P. aeruginosa* are common. Appropriate antimicrobial drugs, based on gram staining, culture, and sensitivity testing, should be initiated to treat acute bacterial infection while prophylactic measures such as vaccination against influenza virus and *Streptococcus pneumoniae* could prevent common pathogens causing upper respiratory tract infection. In chronic, severe or repeated infection cases, intravenous antibiotics may be necessary. Antibiotics could be administered frequently or continuously depending on the severity of infection. Physical therapy, postural drainage assisted cough, exhalatory maneuvers and other mucosal clearance technique such as nasal saline irrigation would be beneficial for the patients. Endoscopic sinus surgery, polypectomy, antrostomy, tympanotomy tube insertion, and surgical resection of bronchiectasis are performed in selected cases. With proper treatment the prognosis of PCD is very good. Patients with PCD could enjoy a nearly normal life expectancy.

CONCLUSION

PCD is a genetic disease. Chronic repeated upper and lower respiratory tract infection with or without male infertility and situs inversus lead the physician to suspect this disease. Electron microscopic study is still an important tool to establish the final diagnosis of PCD. Early diagnosis with proper treatment with respiratory toilet and antibiotic therapy is crucial to allow the patients to live a nearly normal life.

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