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Primary Ciliary Dyskinesia/Kartagener Syndrome - Clinical and Genetic Aspects

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1. Introduction

The epithelium of the respiratory tract forms a large surface area that maintains intimate contact with the environment. Through the act of breathing, this mucosal surface encounters an array of pathogens and toxic particulates. In response to these challenges many strategies have evolved to protect the host. These include the barrier functions of the epithelium, cough, mucociliary clearance, resident professional phagocytes, and the secretion of a number of proteins and peptides with host defense functions (Bartlett et al., 2008). The respiratory epithelium is lined with cilia that normally carry out an integrated and coordinated mechanism called mucociliary clearance. Mucociliary clearance, the process by which cilia transport the viscous mucus blanket of the upper airway to the gastrointestinal tract, is the primary means by which the upper airway clears itself of pathogens, allergens, debris, and toxins. Cilia are evolutionarily conserved structures that play a role in diverse cell types. Cilia are complex and powerful cellular structures that serve a multitude of functions across many types of organisms. In humans, one of the most critical roles of cilia is defense of the airway. The complex structure and regulatory mechanisms that dictate the form and function of normal cilia are not entirely understood, but it is clear that ciliary dysfunction results in impaired respiratory defense. Ciliary dysfunction may be primary, the result of genetic mutations resulting in abnormal cilia structure, or secondary, the result of environmental, infectious or inflammatory stimuli that disrupt normal motility or coordination.

2. Primary Ciliary Dyskinesia (PCD)

Ciliary abnormalities are classified into two categories; specific congenital defects of ciliary structure incident to the "primary ciliary dyskinesia" and acquired nonspecific anomalies of the ciliary apparatus (Afzelius, 1985; Ghadially, 1997). Chronic sinusitis, bronchiectasis, and *situs inversus* are known as the clinical triad of Kartagener's syndrome (KS) (Kartagener, 1933). KS is now recognized as a clinical variant of primary ciliary dyskinesia (PCD). PCD is an autosomal recessive disorder characterized by inefficient or absent mucociliary clearance (Armengot et al., 1999). The coexistence of PCD and *situs inversus* is called KS and occurs in 50% of PCD patients (Afzelius, 1995). *Situs inversus* can be defined as the random distribution of internal organs during embryogenesis, probably due to the absence of the ciliary activity that is responsible for normal organ distribution (Afzelius, 1995).

In this chapter, four cases with PCD/KS diagnosed in our institution were reported. A literature review of clinical and genetic aspects of PCD/KS was performed.

3. Case reports

Case 1 (Taniya et al., 1984)

This case is an anatomical observation on a Japanese male cadaver (61-year–old) with chronic sinusitis, bronchiectasis and *situs inversus viscerum totalis*. Figure 1 showed the associated abnormalities of this case.

Case 2 and Case 3 (Tanaka et al., 2007)

They are the cases of two sisters (Case 2; 25-year-old and Case 3; 19-year-old) who had a healthy brother. The saccharin clearance time (SCT) was measured to examine the mucociliary function. In both cases, the SCT lasted over 60 minutes. Roentgenography and CT scans revealed that both patients had the clinical triad of chronic sinusitis, chronic bronchitis with bronchiectasis, and *situs inversus.* Case 2 (elder sister) had dextrocardia and scoliosis (Fig. 2a,b), while Case 3 (younger one) had *situs inversus* of the lung, liver and stomach as well as dextrocardia (Fig. 3a,b). Chest CT scans showed the bronchitis with bronchiectasis (Fig. 2c,d and Fig. 3c,d).

Case 4

This case is a Japanese male (30-year-old) who had chronic sinusitis and bronchiectasis without *situs inversus*.

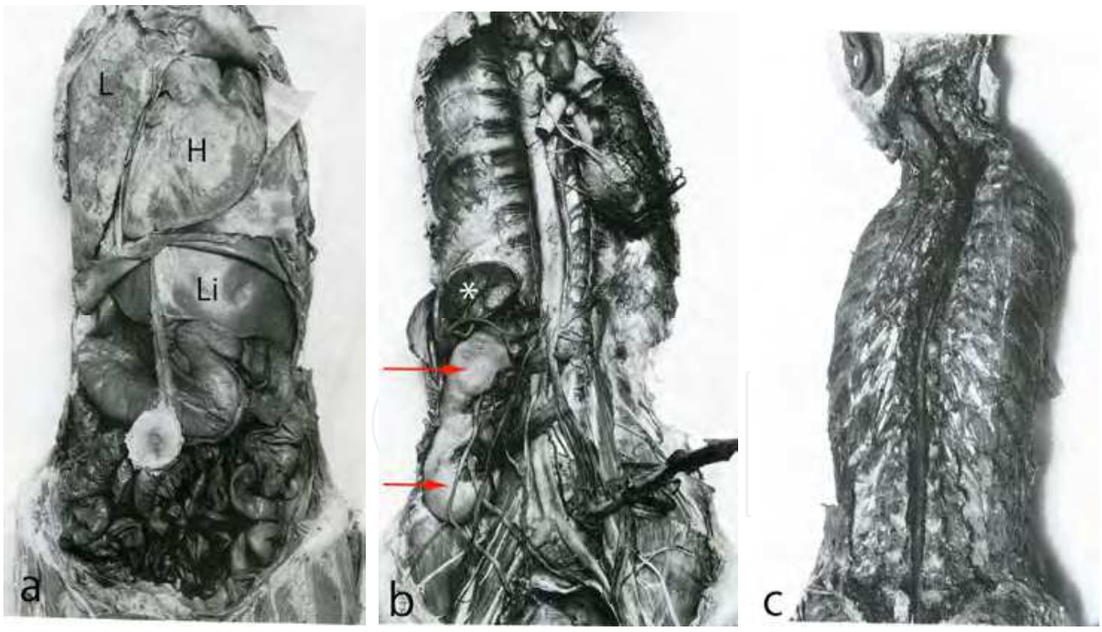


Fig. 1. Case 1. a) The heart (H) showed dextrocardia. There was no lung in the left hemi-thorax. The right lung (L) with two lobes weighed 1,375 g. The left bronchus was ended at approximate 3 cm distance form the bifurcation of trachea. Consequently pulmonary artery also pulmonary veins were missed, but the pleura remained on the left side. The liver (Li) was located in the left side. b) The left kidney was missed, and unilateral fused kidney (arrows) was observed on the right side. The spleen (*) was located in the right side. c) Scoliosis was observed.

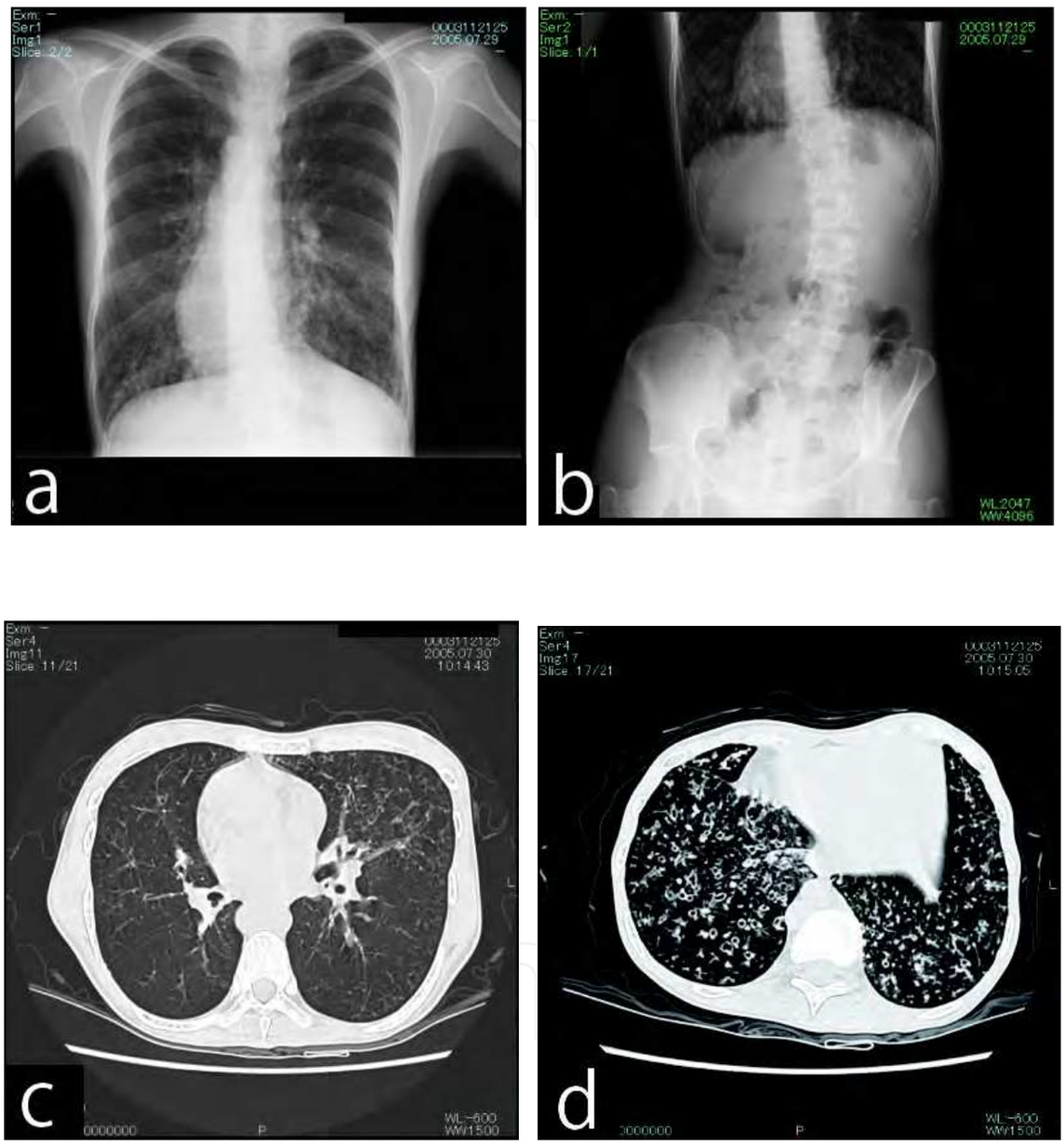


Fig. 2. Case 2. a) Chest roentgenography showed dextrocardia. b) Abdominal roentgenography showed scoliosis. c) , d) Chest CT scans showed bronchiectasis, bronchial wall thickening and diffuse panbronchiolitis in both lung fields.

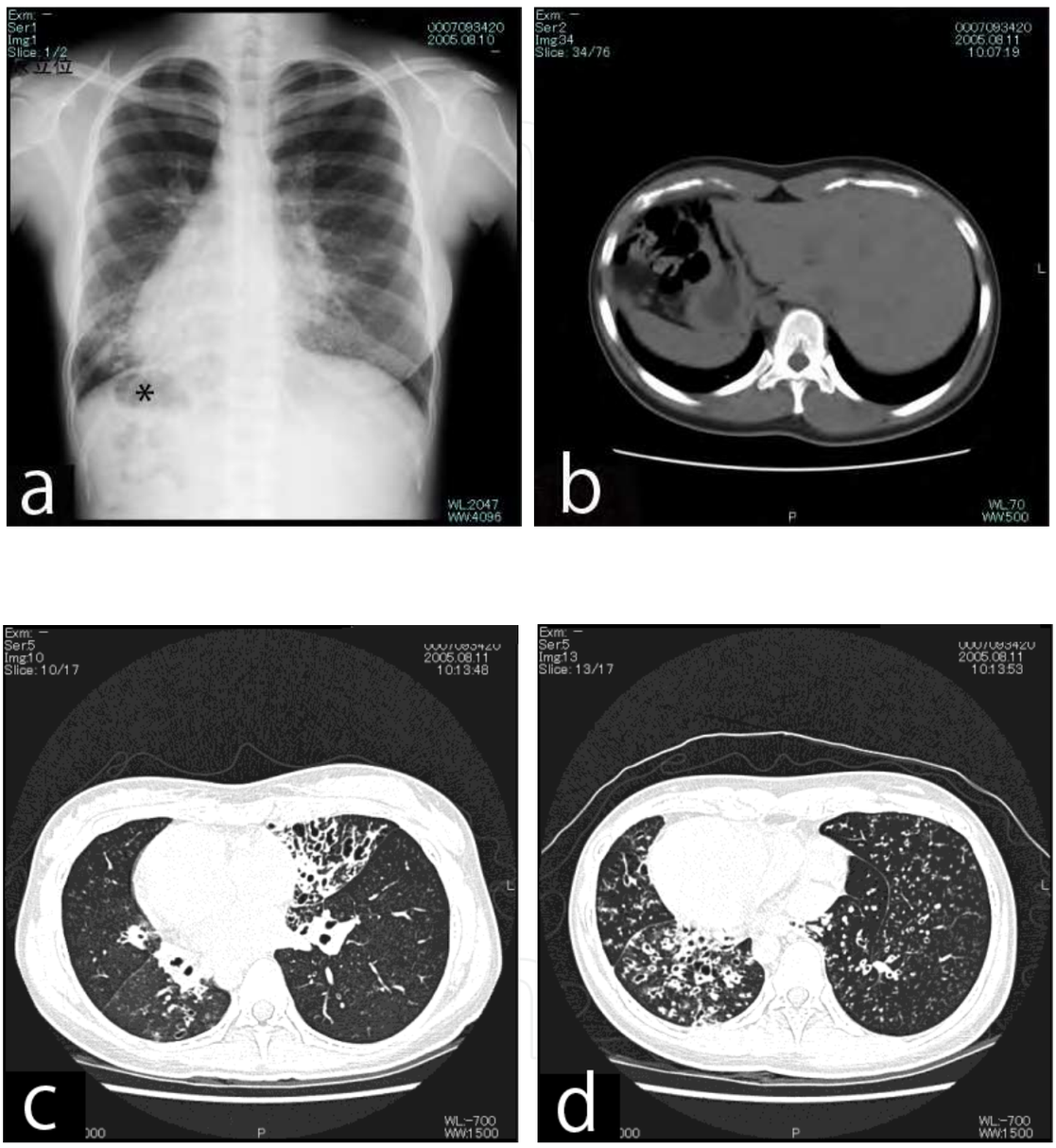


Fig. 3. Case 3. a) Chest roentgenography showed dextrocardia. Gastric bubble (*) was seen at the right side. b) Abdominal CT scan showed *situs inversus* of the liver and the descending aorta located at the left side and the right side, respectively. c) Chest CT scans showed bronchiectasis, bronchial wall thickening and diffuse panbronchiolitis in both lung fields as shown in the Case 2.

4. Electron microscopy

Transbronchial lung biopsy (Case 2 and Case 3) and nasal epithelial biopsy (Case 4) were performed. The tissue samples were fixed by immersion in 0.1 M phosphate-buffered 2.5% glutaraldehyde for 1 hour. They were then rinsed in the same buffer for 30 minutes and fixed in 1% osmium tetroxide for 1 hour. Biopsy samples were stained with 4% uranyl acetate *en block* for 1 hour. The samples were dehydrated in graded ethanol and embedded in Epon. Semi-thin sections from all the samples were stained with toluidine blue and the most representative areas were selected to make the ultra-thin sections. After staining with uranyl acetate and lead citrate, the ultra-thin sections were examined with an electron microscope. The following characteristics of the ciliary axonemes were evaluated according to Armengot et al. (2005) ; dynein arms (inner and outer), the central pair of microtubules (presence or absence and location), radial spokes (presence or absence), peripheral microtubules (position and number), compound cilia, ciliary orientation (relative to the orientation of the central pair), and other factors (ciliary membrane evaginations and incomplete axonemes). At least 100 ciliary cross sections per patient were observed, and dynein arms (inner, outer, or both) were considered absent when the mean number of dynein arms counted in all cross sections was less than 2 per cross section (Lurie et al., 1992).

4.1 Abnormal dynein arms

Electron microscopy revealed that the Case 2 and Case 3 had defect of inner dynein arms. The outer arms were present (Fig. 4a, b). In the Case 4, the outer arms were absent, while the inner arms were present (Fig. 4c).

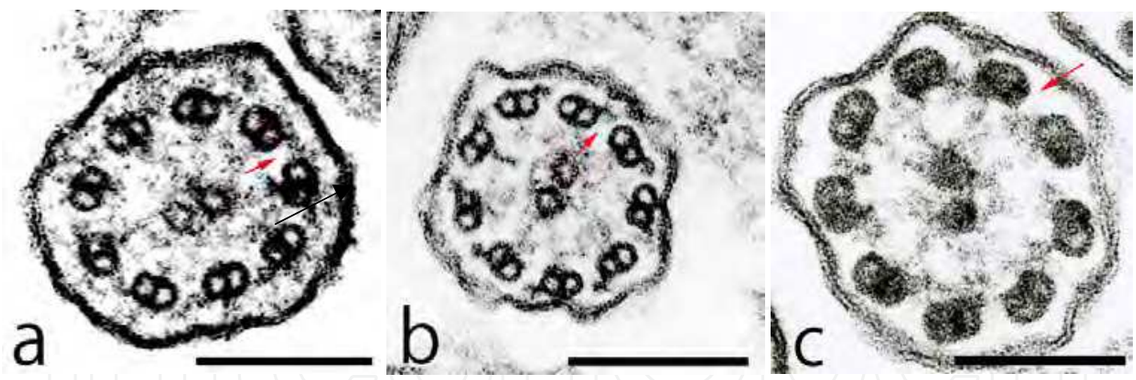


Fig. 4. a) Case 2 and b) Case 3. Cross section of a ciliary axoneme in which the absence of inner dynein arms can be observed. c) Case 4. The outer dynein arms were absent. Arrows indicate the empty space where the inner dynein arm (Case 2 and Case 3), outer dynein arm (Case 4) should be. Scale bar = 200 nm

4.2 Other abnormal features of cilia

Abnormal number and distribution of peripheral microtubule pairs (supernumerary microtubules) and central pair were observed in the Case 2 and Case 3 (Fig. 5a). Abnormal cilia called swollen and compound cilia were frequently observed, especially in the Case 2 (Fig. 5b). Compound cilia showed multiple axonemal structures enclosed by a common ciliary membrane (Fig. 5c).

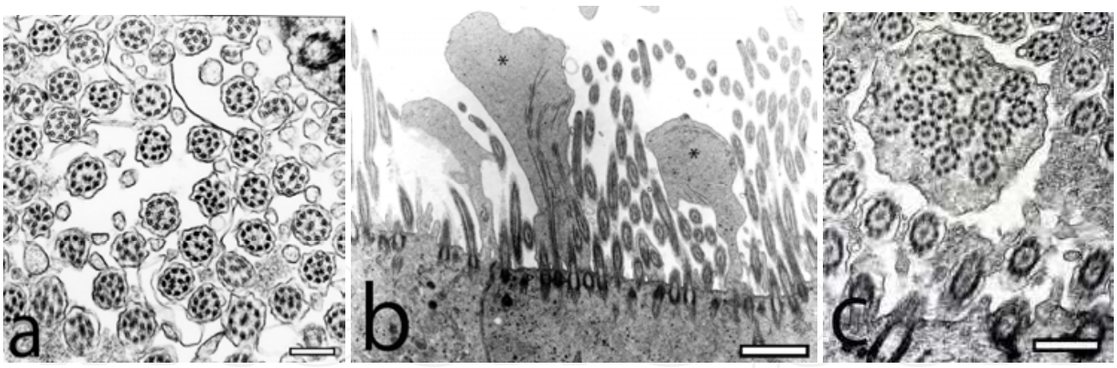


Fig. 5. a) Case 3. Cross section of cilia. Cilia with excess numbers of peripheral microtubules. Cilium lacks a pair of central singlet microtubules. Abnormal number and distribution of peripheral microtubule pairs and central pair were also observed in the other cases. Scale bar = 250 nm, b) Case 2. Electron micrograph of bronchial epithelium. Asterisks indicate enlarged cytoplasmic projections (so called swollen or compound cilia) from the surface of ciliary cells. Scale bar = 2 μm, c) Case 4. Multiple axonemal structures enclosed by a common ciliary membrane. Scale bar = 500 nm

5. Ciliary structure and function

5.1 Normal ultrastructure of motile cilia

Cilia and flagella are evolutionarily ancient organelles whose structure and function have been rigidly conserved across the phylogenetic spectrum. Historically recognized for their role in cell motility and transport of fluids over mucosal surfaces (Leigh et al., 2009). Fig. 6 shows the lower airway and respiratory epithelium with cilla. The core, or axoneme, of the cilia and flagella consists of a "9+2" microtubule structure with a ring of nine microtubule doublets surrounding a central pair of single microtubules. The nine microtubule doublets are studded with dynein arms that contain adenosine triphosphatases and act as molecular motors to effect the sliding of the peripheral microtubular pairs relative to one another. The outer dynein arms (ODA) are positioned proximal to the ciliary membrane and the inner dynein arms (IDA) proximal to the central apparatus of the A microtubule. The dynein arms are large protein complexes each comprised several heavy, light, and intermediate chains. Cilia were classified as motile and non-motile. The classification is depicted in Figure 7.

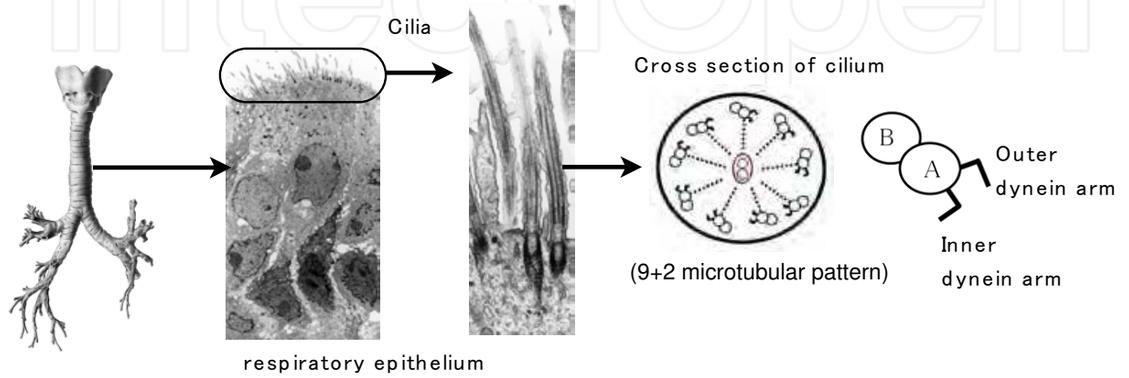


Fig. 6. Diagrammatic view of the lower airway and respiratory epithelium with cilia.

There are three basic groups of cilia (see Fig. 7); motile 9+2 cilia with attendant dynein arm structures (e.g., airway), nonmotile 9+0 primary cilia lacking dynein arms.
In contrast to the 9+2 pattern of motile cilia with dynein motors, there are structural variants without dynein motors that have a 9+0 microtubular (e.g., kidney tubules), and motile 9+0 primary cilia possessing dynein arms (e.g., embryonic node). Unlike the numerous motile cilia present on airway epithelial cells, these primary cilia are borne as solitary appendages. Historically thought to be nonfunctional or vestigial, they have been rediscovered in recent years as structures central to organ positioning during embryologic development and to the detection of mechanical and chemical gradients. Thus, primary cilia are now recognized as structures modulating detection, orientation, and positioning (Leigh et al., 2009).

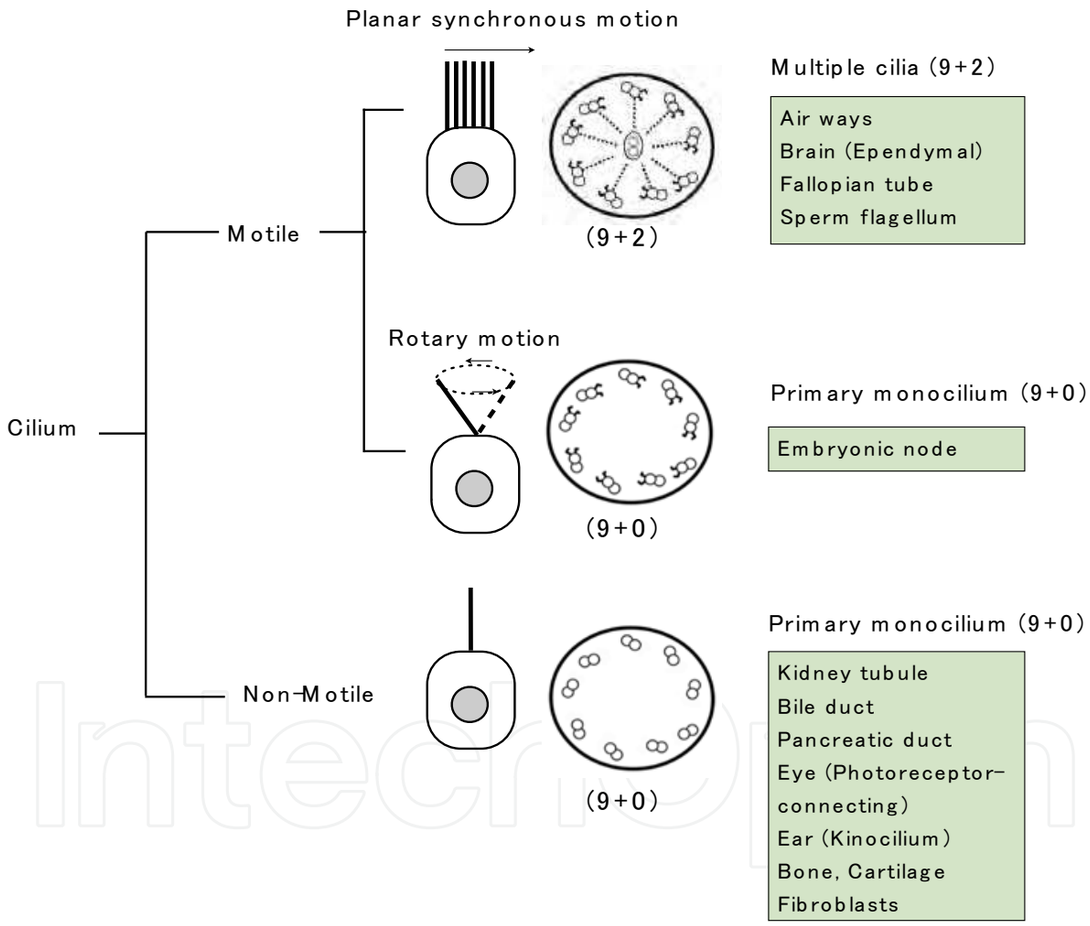


Fig. 7. Diversity of cilia. Cross section of motile cilia (9+2 and 9+0 arrangement) and non-motile (9+0 arrangement) is shown. This diagram is modified from the review (Leigh et al., 2009).

5.2 Ciliary abnormalities

Ciliary abnormalities are classified into two categories; specific congenital defects of ciliary structure incident to the "primary ciliary dyskinesia" and acquired nonspecific anomalies of the ciliary apparatus (Afzelius, 1985; Ghadially, 1997). Acquired nonspecific ciliary

abnormalities. Acquired nonspecific ciliary abnormalities include swollen cilia, compound cilia, intracellular ciliated vacuoles, intracytoplasmic axoneme, cilia within periciliary sheaths or intracellular cilia, abnormalities in the number and arrangement of axonemal microtubules, and others (Hagiwara et al., 2000; 2004). The formation of nonspecific abnormal cilia is reversible and such cilia are almost absent in new ciliated cells that are formed by *in vitro* ciliogenesis (Jorissen, 2000). The peripheral microtubule alterations and the presence of swollen and compound cilia are characteristic of ciliary dyskinesia secondary to chronic infection of the epithelium. The absence of dynein arms was the first ciliary defect associated with KS (Afzelius, 1976). This deficiency can involve the inner or outer dynein arms or both (Jorissen & Bertrand, 1997). The ultrastructural defects of the ciliary axoneme observed in this study are the absence of inner dynein arms（Case 2 and Case 3）, which were often observed in PCD. The outer arms are absent in the Case 4. Ciliary ultrastructural analysis in most patients (>80%) reveals defective dynein arms, although defects in other axonemal components have also been observed. The axonemal dynein arms are composed of heavy, intermediate, and light dynein chains (Holzbaur &, Vallee, 1994). A defect in any one of these proteins could lead to an abnormal dynein arm and/or defective beating activity of the axoneme. The complete absence of dynein arms is associated with immotile cilia. Other ciliary defects are associated with abnormal and inefficient ciliary beat patterns (Chilvers et al., 2003). Immotile cilia and cilia that have an inefficient beat produce the stasis of respiratory secretions.

6. Genetics

Mutations have been identified in eight genes in PCD. Most of the disease-causing mutations identified to date involve two gens. These are genes coding for the dynein axonemal intermediate chain 1 (DNAI1) (Pennarun, 1999; Guichard, 2001; Zariwala, 2001) and the dynein axonemal heavy chain 5 (DNAH5) (Olbrich et al., 2002) in ciliary outer dynein arms, although a few mutations have been noted in other genes. Mutations in two genes have been associated with KS. Mutations in the coding region of DNAH11 account for situs inversus totalis and probably a minority of cases of PCD（Bartoloni, 2002). To date, only two autosomal genes, DNAI1 and DNAH5 encoding axonemal dynein chains, have been shown to cause PCD with defective outer dynein arms (Moore, et al., 2006). Other defects of the ciliary ultrastructure associated with KS include absence of radial spokes, ciliary disorientation, and ciliary transposition (Noone et al., 2004) This extensive morphological variety comes about because the ciliary axoneme is a biological structure consisting of at least 130 distinct polypeptides (Afzelius, 1995). Clinical molecular genetic testing for primary ciliary dyskinesia is available for the most common mutations. Lee et al. (2008) show that the PCD phenotypes of hydrocephalus, male infertility, and respiratory ciliary dysfunction result from the loss of a single, novel gene named primary ciliary dyskinesia protein 1 (Pcdp1). They also demonstrate expression of the gene in spermatogenic and motile ciliated cell types and show protein localization in flagella and motile cilia in both mice and humans.

7. Clinical features

Ciliated cells line the nasopharynx, middle ear, paranasal sinuses, larynx, trachea and bronchi. Planar synchronous motion of the cilia sweeps the periciliary fluid and overlying

mucus, resulting in vectoral movement of mucus out of the lower respiratory tract. The mucociliary escalator is the primary defense mechanism of the airways (Knowles & Boucher, 2002) and any functional disruption, primary or acquired, can lead to chronic sinopulmonary symptoms. PCD is a genetically heterogeneous disorder of motile cilia. Most patients with PCD have a history of neonatal respiratory distress. The respiratory manifestations of PCD are chronic bronchitis leading to bronchiectasis, chronic rhino-sinusitis, and chronic otitis media.

7.1 Upper respiratory tract

Rhino-sinusitis and otitis media are cardinal features of the disease in PCD, and are responsible for much of the morbidity associated with PCD in early childhood (Noone et al., 2004; Coren et al., 2002). Nasal congestion and/or rhinorrhea are very common, and some patients have nasal polyposis. Middle ear disease is described in virtually all cases of PCD with varying degrees of chronic otitis media and persistent middle ear effusions. The middle ear disease often leads to multiple sets of pressure-equalization tubes in early childhood, (Noone et al., 2004; Jain et al., 2007).

7.2 Lower respiratory tract

Most patients report a chronic, productive cough as a prominent symptom of PCD, because cough compensates for the lack of effective mucociliary clearance. Impaired mucociliary clearance of the lower respiratory tract leads to recurrent episodes of pneumonia or bronchitis. Bacterial cultures of lower respiratory secretions most commonly yield nontypeable *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. *Pseudomonas aeruginosa* infection, including mucoid strains, has also been reported, most often in older individuals (Noone et al., 2004).

7.3 Other organs

Genitourinary tract; Male infertility is common and reflects defects in sperm tail axonemes.
Central nervous system; Cilia on ependymal cells lining the ventricular surface of the brain facilitate cerebrospinal fluid flow. Several reports have linked hydrocephalus with PCD, hypothetically due to impaired cerebrospinal fluid flow secondary to dysfunctional motile cilia that line the ventricular ependymal cells (De Santi et al., 1990; Greenstone et al., 1984). Hydrocephalus is frequently found in murine PCD models, but its incidence or clinical relevance in patients with PCD is unclear.
Eye; Some individuals with PCD also develop retinitis pigmentosa. Retinitis pigmentosa has recently been linked to some forms of PCD (Moore et al., 2006; Zito et al., 2003; Iannaccone et al., 2003; Krawczynski et al, 2004).
Kidney; Bronchiectasis was reported in 37% of patients who have autosomal-dominant polycystic kidney disease (Driscoll et al., 2008).
Laterality defects; Cilia on the embryonic node play a critical role in left-right patterning during early development. *Situs inversus totalis*, heterotaxy with or without congenital cardiovasucular abnormalities were observed. In this study, scoliosis was found out in two cases. In the search of adolescent idiopathic scoliosis (AIS), some workers have focused on mechanisms initiated in embryonic life including a disturbance of bilateral (left-right or mirror-image) symmetry highly conserved in vertebrates. The prevalence of right and left

scoliosis curve laterality associated with *situs inversus* (Burwell et al., 2006). However, the relationship between scoliosis and PCD is not clear.

8. Conclusion

In this chapter, four cases with PCD/KS diagnosed in our institution were reported. They contain the anatomical observation on a Japanese male cadaver with *situs inversus viscerum totalis*, and the clinical and electronmicroscopic observation on two sisters with heterotaxy and a male with PCD diagnosed without heterotaxy. PCD is a genetically heterogeneous disorder of motile cilia. Motile cilia play a role in fluid clearance. They reflect impaired mucociliary clearance owing to defective axonemal structure in cilia. Ciliary ultrastructural analysis reveals defective dynein arms. Approximately 50% of patients with PCD have laterality defects (including *situs inversus viscerum totalis* and, less commonly, heterotaxy, and congenital heart disease), reflecting dysfunction of embryological nodal cilia. Scoliosis was found out in two cases. The relationship between scoliosis and PCD is not clear. Until recently, the only definitive diagnostic test had been electron microscopy to define ultrastructural defects in cilia. The diagnostic approach to PCD is evolving. Genetic testing, nasal NO measurement, immunofluorescent analysis, and high-speed videomicroscopy are emerged.

9. Acknowledgment

The author thanks Mrs. Kayoko Tanaka for her skillful technical assistance with electron microscopy.

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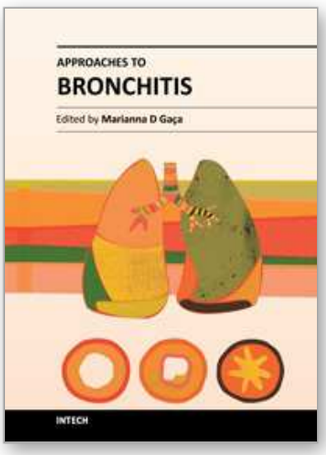
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Approaches to Bronchitis

Edited by Prof. Marianna GaÃ§a

ISBN 978-953-307-770-3
Hard cover, 70 pages
Publisher InTech
Published online 17, October, 2011
Published in print edition October, 2011

The aim of this book is to present some recent and interesting findings in the field of bronchitis, which will serve as a supplement to the book Bronchitis. In particular, this volume focuses on the successful use and development of novel tools in the diagnostics and treatment of bronchitis. Contributions include clinical case studies, the impact of air pollution on bronchitis, the presentation and diagnosis of the respiratory disease eosinophilic bronchiolitis, primary ciliary dyskinesia, the development of a method for the swift detection of the infectious bronchitis virus and studies investigating the successful use of alternative medicines in the treatment of bronchitis. The editor would like to thank the authors of the chapters who have contributed to this book and hopes that this will book not only supplement the book on Bronchitis, but may increase interest in the subject.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Masumi Akita (2011). Primary Ciliary Dyskinesia/Kartagener Syndrome - Clinical and Genetic Aspects, Approaches to Bronchitis, Prof. Marianna GaÃ§a (Ed.), ISBN: 978-953-307-770-3, InTech, Available from: http://www.intechopen.com/books/approaches-to-bronchitis/primary-ciliary-dyskinesia-kartagener-syndrome-clinical-and-genetic-aspects

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