

Review article

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Primary ciliary dyskinesia (the immotile cilia syndrome)

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Objective: The purpose of this review is to familiarize the reader with the genetic aspects, clinical manifestations, diagnostic techniques and management of the primary ciliary dyskinesia syndrome. Further, this article illustrates some unusual features of this syndrome and discusses some speculative hypotheses concerning its pathogenesis and clinical presentation.

Data sources: The bibliography includes references in English as well as some references of historical interest in German. Both human and veterinary literature are quoted. Sources included computerized bibliographic searches of recent literature and reviews of literature.

Study selection: Selection of papers was made based on their historic importance in the definition and characterization of the disease, and on reviews of large bodies of novel or interesting information. Some review papers were not included to avoid repetition.

Results: Although the incidence of primary ciliary dyskinesia is low, the inclusion of this condition in the differential diagnosis of chronic and recurrent sinobronchial disease in children and older individuals is very common.

Primary ciliary dyskinesia should be suspected in individuals who present chronic respiratory symptoms already in the neonatal period, develop profuse, chronic mucopurulent rhinorrhea, and chronic otitis media and sinusitis. Chronic cough, obstructive lung disease, and bronchorrhea associated with the aforementioned manifestations should also make clinicians suspect this syndrome. Male sterility is almost universally present and situs inversus is present in 50% of affected persons.

The diagnosis of primary ciliary dyskinesia is clinical and is confirmed by studies of ciliary motility and ultrastructure of the respiratory mucosa. Management is directed to microbial suppression by frequent antibiotic administration, and to clearing of retained secretions.

Conclusions: The diagnosis of primary ciliary dyskinesia requires familiarity with the clinical picture and the specific techniques of identification.

Although the basic mechanism of disease is known, the molecular genetics of primary ciliary dyskinesia and the causes for the phenotypic variability remain to be explained. Future research should be directed to the identification of the gene(s) responsible for the manifestations of the disease and to effective methods of activation, in vivo, of dysfunctional cilia.

INTRODUCTION

Primary ciliary dyskinesia is a genetic disease, characterized by de-

fective motion of ciliated structures. Propulsion of spermatozoa and clearance of mucus from the respiratory tract are impaired. The most common clinical expressions of this condition is chronic upper and lower airway disease and male infertility. Kartagener syndrome, another name commonly used in association with this disease, refers to the presence of situs inversus viscerum in addition to the previously

described abnormalities. This appellation should not be used to describe patients with primary ciliary dyskinesia who have normal visceral situs.

The concomitant presence of chronic sinusitis, otitis, rhinorrhea and bronchorrhea, and situs inversus as a clinical entity has been known since the beginning of the century.¹⁻³ It was the physician, Manes Kartagener, in Switzerland, who first recognized that the concomitant presence of situs inversus, chronic sinus disease, and bronchiectasis was not the product of serendipity but a recognizable, unique clinical syndrome.⁴ The association of situs inversus viscerum, respiratory disease, and sterility was described in 1960 by Arge in men seen in fertility clinics.⁵ He offered no clear explanation for this association. Afzelius, Pedersen and others, later described the absence of dynein arms in the axoneme of immotile human spermatozoa.^{6,7} Subsequently Camner, Mossberg and Afzelius further reported the presence of nonfunctioning respiratory cilia in two subjects with chronic bronchial disease.⁸ The term, "immotile cilia syndrome" was coined by Afzelius⁹ and shortly thereafter, it made its definitive introduction into the North American literature in a hallmark article by Eliasson.¹⁰ These authors presented evidence that support the fact that a congenital, hereditary lack of dynein arms in respiratory tree cilia and the tails of spermatozoa is responsible for both chronic respiratory disease and male infertility. These authors hypothesized that lack of ciliary movement during embryonal life was responsible for random organ rotation

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that would result in visceral displacement in a direction opposite from normal in 50% of affected individuals. This theory would explain the presence of mirror-image visceral situs in 50% of affected patients.

Primary ciliary dyskinesia was defined further by a series of articles in the late 1970s and early 1980s. A variety of axonemal defects was described in individuals affected with this condition. The terms "primary ciliary dyskinesia" and "dykinetic cilia syndrome" appeared in the literature. Several abnormal patterns of ciliary motion (rather than absence of movement) that result in lack of displacement of spermatozoa and lack of effective ciliary action were reported.¹¹⁻¹⁶ Cilia with normal structure but abnormal function have also been described in association with this syndrome.¹⁷

GENETICS

Primary ciliary dyskinesia is an autosomal recessive disease. To date, this condition has not been traced to any specific gene and no specific mutation has been uncovered.

The incidence of primary ciliary dyskinesia has been calculated to be one in 16,000 live births, based on several population studies. Fifty percent of affected individuals have situs inversus or the so-called Kartagener syndrome. The incidence of the latter is one in 32,000 individuals, half the incidence of primary ciliary dyskinesia.^{18,19}

The incidence of situs inversus without any respiratory or other abnormality has been calculated at 1:8,000 live births.^{18,19} The exact incidence of this condition on the North American continent is difficult to ascertain because previous reports have been based on limited population studies in specific geographic areas. Furthermore, it is unclear whether or not conditions that present with other abnormalities of visceral situs have been included in some of these studies. Other syndromes of visceral malposition such

as asplenia and polysplenia are currently believed to be inherited in an autosomal recessive fashion as well. Both situs inversus and a syndrome of ciliary malfunction indistinguishable from the human type have been described in a variety of animals with recurrent pneumonia and reproductive failure.²⁰⁻²⁵ A type of mouse has been described in which situs inversus and ciliary dysfunction is inherited in an autosomal recessive manner; these animals develop secondary hydrocephalus as a result of ciliary dysfunction in the ependymal lining. As in humans, in whom the pattern of ultrastructural abnormality is constant within a sibship regardless of clinical manifestations, the pattern of ultrastructural defects is identical within a litter and within directly related animals.

Whether or not the abnormal situs, the ciliary abnormalities and clinical characteristics of the syndrome are the product of mutations of one single gene is a subject of speculation. The theory of embryonic organ malrotation offered by Afzelius does not explain the genesis of situs inversus in individuals who are otherwise healthy. Neither does the theory explain the presence of abdominal heterotaxia (indeterminate situs) and other aberrations of visceral situs in patients with asplenia or polysplenia. Isolation and cloning of the gene/s responsible for ciliary function and visceral situs

could help explain the variety of clinical expressions.

THE STRUCTURE OF CILIA

Cilia are ubiquitous organelles of species of the animal kingdom. They are also present in a variety of organs and epithelia some of which would not logically come to mind as a site for such structures²⁶ (Table 1). The most common clinical manifestations of the disease originate in the malfunction of respiratory and sperm cilia. Ciliary malfunction in other parts of the body can potentially generate manifestations such as hydrocephalus.^{27,28}

Mucus-propelling cilia measure between 5 and 7 mm in length, and they cluster in patches. About 200 cilia per cell are present in the respiratory epithelium of mammals. Cilia are most numerous in the trachea, where transport velocity is maximal as compared with the respiratory bronchioles, in which ciliary density is more sparse and mucous transport is slower. Ciliary epithelium covers about 150 cm² in the nose, about twice that in the paranasal sinuses and about 50 cm² in the intrathoracic airways.²⁹ The cilium is a prolongation of the cellular surface and shares with the cell the same cellular membrane. The typical cilium has nine peripheral microtubular doublets arranged in a circumference, and two central complete and separate tubules. Each peripheral doublet

Table 1. Ciliated Structures in the Human Body*

Upper airway:	Nose
	Paranasal sinuses, middle ear
	Eustachian tubes
	Pharynx
Lower airway:	From the trachea to the respiratory bronchioles
Ependymal lining:	Brain/spinal cord
Vas deferens	
Endometrium of cervix and fallopian tubes	
Spermatozoa	
Sensory cells:	Olfactory cells
	Vestibular organ
Single cilia (9 + 0 structure) are also seen in a variety of tissues such as ganglion cells, pineal gland, adrenal gland, pancreas, liver, kidney, heart, cartilage, connective tissue, dermis, epidermis, and embryonic tissues.	

* Modified from Afzelius, B: *Int Rev Exp Path* 1979; 19:1-43.

comprises one full microtubule, the A subunit, and an incomplete attached microtubule called the B subunit (a cut across its transversal axis will appear almost as a semicircle). The two central microtubules are almost completely surrounded by a central sheath and comprise the central axis of the axoneme. The integrity of ciliary structure is preserved by the cellular membrane and by a system of inner structures that interconnect the various axonemal structures. Radial spokes or links are projections that connect the central sheath and the peripheral doublets, resembling a wheel. The peripheral doublets are connected to one another by the nexin links, which are bands whose function is to limit sliding and maintain ciliary length and structure. Each A subunit has a set of arms attached to it. These are curved formations that bend clockwise and contain ATPase (essential for ciliary motion) and other polypeptides necessary for the maintenance of the anatomic and functional integrity of the cilium. The outer dynein arms (the ones closest to the external membrane) are longer and resemble a hook, whereas the inner dynein arms are shorter, slightly curved, and attach to the nexin link (Fig 1). The struc-

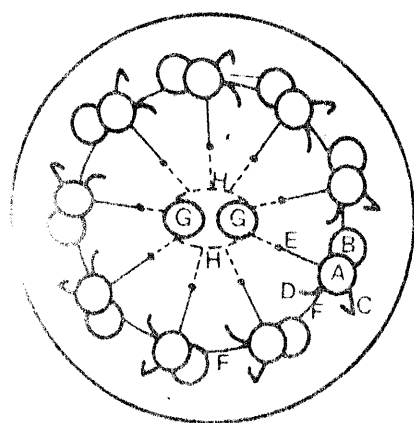


Figure 1. Schematic representation of a cross-section of a cilium. A. Subunit A of microtubular doublet, B. Subunit B of microtubular doublet, C. Outer dynein arm, D. Inner dynein arm, E. Radial spoke, F. Nexin link, G. Central microtubules, H. Central sheath, and I. Outer membrane.

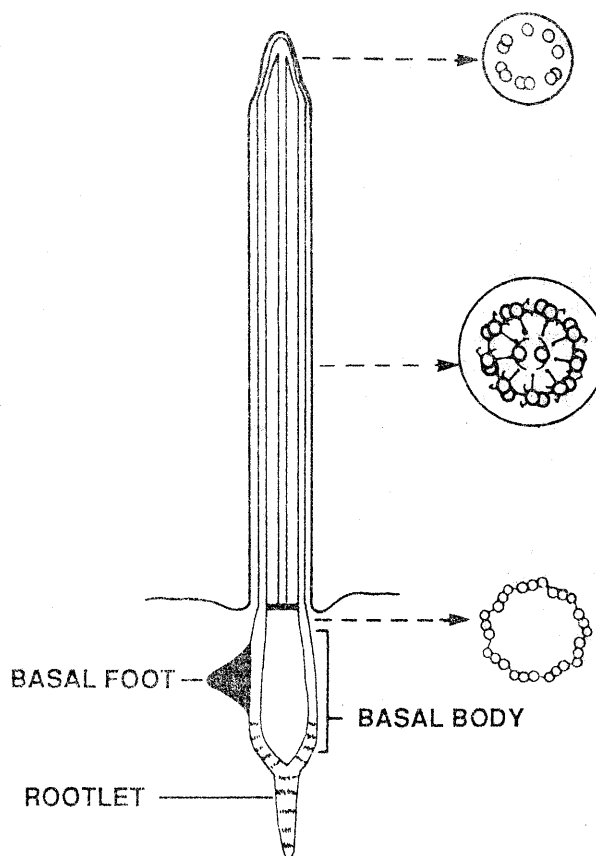


Figure 2. Schematic representation of a longitudinal section across a cilium. The kinetosome or basal body is comprised by the basal foot and the rootlet. The variable microtubular composition at different levels of the cilium is shown.

ture of the cilium is not uniform along its length. At the base, the cilium is anchored to the cell by means of a basal body (kinetosome) which includes a foot (oriented towards the direction of the effective beat) and a rootlet. Microtubular doublets become small triplets: central tubules and all other structures disappear. At the tip of the cilium, the B subunits and other structures are no longer present either, with the exception of single, full tubules (Fig 2).

ABNORMALITIES OF CILIARY STRUCTURE

The most common ultrastructural abnormality associated with primary ciliary dyskinesia is the total absence of dynein arms. This and other abnormalities reported in association with primary ciliary dyskinesia are listed in Table 2 and

some are shown in Figure 3. Abnormalities in the length of cilia adversely affect their ability to move normally.^{33,34} Such abnormalities have been described in association with clinically relevant ciliary dysfunction.

Severe viral infections and chronic inflammation result in changes in ciliary structure including disruption of the cellular membrane, loss or incorporation of microtubules, and formation of compound cilia. Some degree of ciliary dysfunction is also present during inflammatory processes.³⁵⁻³⁸ All these changes, however, are transient, and restricted to a relatively small percentage of respiratory cilia, as compared with the findings in patients with congenitally malfunction of cilia, in which a high percentage of organelles have abnormal ultrastructure and function. Ciliated

Table 2. Reported Structural Defects of Cilia

Congenital	
Abnormal function/normal structure	
Abnormal ciliary length	
Total absence of cilia (defective ciliogenesis)	
Dynein arm defect	
(total or partial absence, fragmentation)	
Radial spoke defect	
(total absence, absent spoke head and inner dynein arm)	
Absence of nexin links and inner dynein arms with axonemal disorganization	
Microtubular transposition	
Acquired	
Compound cilia	
Axonemal disorganization, abnormal number of tubules	

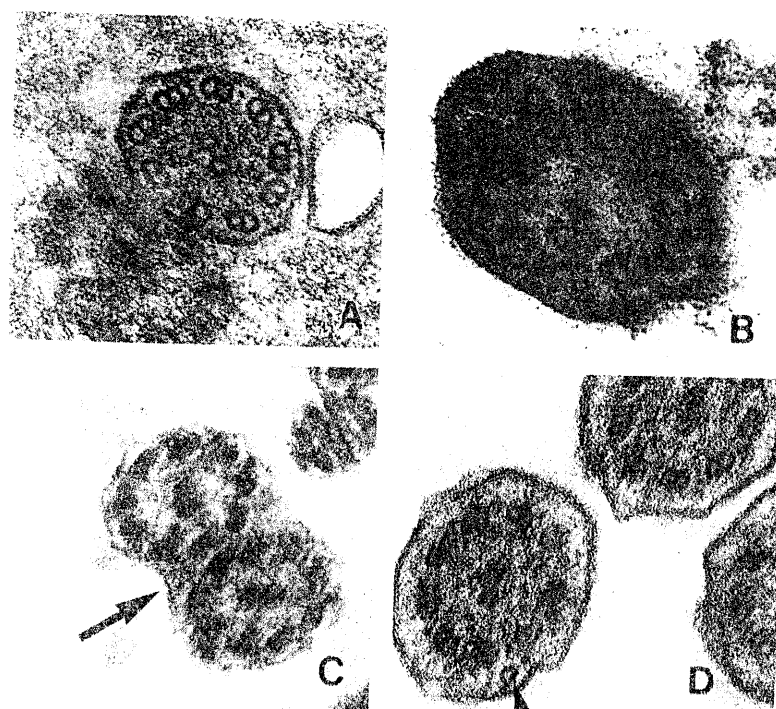


Figure 3. Abnormalities of ciliary ultrastructure. A. Total absence of dynein arms. B. Microtubular transposition. C. Compound cilium—arrow points to fusion of two, and D. Supernumerary tubule.

A and B are hereditary abnormalities, associated with primary ciliary dyskinesia. C and D are acquired abnormalities, secondary to inflammation and disruption of the integrity of cell membranes.

structures in parts of the body not exposed to inflammatory agents are normal in unaffected individuals who exhibit secondary changes, whereas all cilia in individuals with hereditary ciliary dysfunction (with very few exceptions) are abnormal.

The absence of cilia from respiratory epithelium also has been re-

ported in association with ciliary malfunction. Chronic inflammation, especially in the upper air passages can result in the destruction of cilia and virtual denudation of the epithelium. This finding must be differentiated from defective ciliogenesis, which has been reported as a cause of absence of cilia in both

upper and lower respiratory epithelium. In these cases, the precursor cells are absent.³⁹⁻⁴⁴

MUCOCILIARY CLEARANCE

Ciliary beat has a crucial role in the clearance of secretions from the lower respiratory tree and the paranasal sinuses. Mucous flow occurs largely against gravity and depends on the constant forward propulsion generated by ciliary movement. This function is particularly important in the paranasal sinuses and the middle ear, in which ciliary activity is the principal means of clearance.

The beat frequency of normal cilia is between 6 and 8 Hz in the respiratory bronchiole and it increases threefold in the trachea to about 22 Hz. The velocity of transport as a result, increases significantly from the peripheral to the central airways. The overall rate of transport achieves about 20 to 30 mm/sec.

Ciliary activity is the product of two axonemal systems that act in association with one another. The dynein arms and peripheral doublets act as the force-generating system. The dynein arm of subunit A of one doublet links attaches to the B subunit of an adjacent microtubule, which in turn tips upward. The dynein arm acts as a lever, an action mediated by ATP which is hydrolyzed by the ATPase in the dynein arm. The other system, comprised by the radial spokes and nexin links prevents the excessive elongation of the cilium, which would interfere with the bending movement necessary for the whiplash movement characteristic of these organelles.

The cycle has two components, the effective stroke and the recovery stroke. The cilium bends "backwards" against the direction of the movement of mucus during the recovery phase and then proceeds to extend and move forward, very much like a whip, in the direction of the mucous flow (effective stroke phase). This process is pictured in Figure 4. The mucous layer does not actually surround the cilia but

rather, sits on top of a sol layer in which the cilia move more freely. Only the ciliary tips come into contact with the gel (mucous) layer (Fig 5), propelling it in the direction of the effective stroke. When a patch of cilia propels mucus, all the organelles beat in a synchronous manner and their axonemes are parallel to one another, and the basal bodies face in the same direction. This system works best under normal conditions of body temperature and respiratory tree humidity. Any drastic changes in these will interfere with normal ciliary beating and mucous clearance. Anatomic changes in the cilium, whether congenital or acquired, can cause changes in mucous rheology and hydration and interfere with normal ciliary beating.

ABNORMAL MUCOCILIARY CLEARANCE

As previously indicated, the ultrastructural and biochemical integrity of the cilium is essential for proper movement and resulting clearance of mucus. Specific anatomic defects result in conspicuous functional changes in mobility. For example, absence of dynein arms removes the cilium from the needed ATPase to obtain energy for beating, whereas abnormalities in the nexin link structure can cause excessive elongation and inefficient beat se-

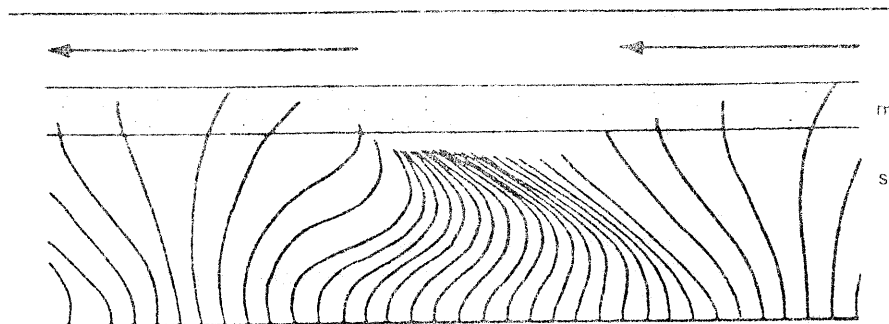


Figure 5. One of the wave patterns generated by ciliary movement. The tip of the cilia propel the mucus over a layer of serous fluid. The arrows represent the effective stroke of the beat. (Reprinted with permission from Sleight MA. The nature and action of respiratory tract cilia. In: Brain JD, Proctor DF and Reid LM. Respiratory defense mechanisms. New York: Marcel Dekker Inc., 1977:283).

quence.^{11,12,45-47} These abnormalities are summarized in Table 3.

The net result is that propulsion of mucus or spermatozoa is impaired by virtue of inefficient or erratic movement.

Vigorous coughing can clear the tracheobronchial tree of secretions even if ciliary clearance is defective (Fig 6).⁴⁸ Forced exhalation, postural drainage, and other chest physiotherapy techniques can also improve mucous elimination; mucus elimination in the paranasal sinuses, on the other hand, is almost exclusively dependent on physiologic mechanisms.

CLINICAL PICTURE

General

The characteristic clinical picture of patients with primary ciliary dyskinesia is one of chronic severe sinobronchial disease (Table 4). Situs inversus, present in 50% of the patients in association with sinobronchial disease, is pathognomonic of this condition. In the absence of malposition of organs, the diagnosis becomes much more difficult.

This condition is one of very few in which symptoms appear in the early neonatal period. Cough, recurrent atelectasis, and pneumonia in neonates are difficult to treat. The only deaths due to primary ciliary dyskinesia I have witnessed have been in two neonates in whom per-

sistent atelectasis and pneumonia led to irreversible respiratory failure. The clinical picture of primary ciliary dyskinesia in the older child, however, can be indistinguishable from that of a child with immunoglobulin deficiency or severe allergic diathesis. Thus, it is very important for clinicians to try to ascertain as accurately as possible the time of onset of symptoms since most symptoms of allergic diathesis will tend to appear later in life.

Nose and Sinuses

One of the most striking characteristics of the clinical picture is persistent mucopurulent rhinorrhea associated with chronic sinusitis and otitis media. Virtually all patients present with sinusitis and otitis media.⁴⁹⁻⁵⁰ Typically, symptoms abate with the administration of antibiotics and reappear very quickly after discontinuation of such therapy. There is no direct correlation between the severity of upper respiratory and lower respiratory symptoms (see below). Pansinusitis (clouding of all cavities and evidence of fluid accumulation) and hypoplasia of the frontal sinuses usually are evident in sinus radiographs and computerized tomograms.

In my clinical practice, sinus disease has proven to be the most difficult aspect of the management of these patients, particularly due to the limitations of therapy of sinus

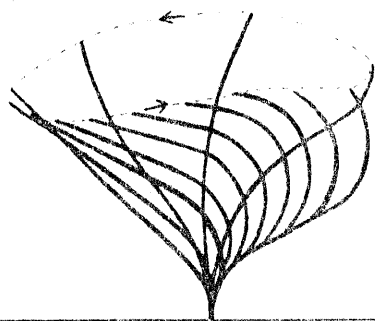


Figure 4. Diagram of beat pattern of a cilium, demonstrating the whip-like movement. (Reprinted with permission from Sleight MA. The nature and action of respiratory tract cilia. In: Brain JD, Proctor DF, Reid LM. Respiratory defense mechanisms. New York: Marcel Dekker Inc., 1977:283).

Table 3. Correlation Between Ultrastructural and Motility Defects in Primary Ciliary Dyskinesia

Ciliary Defect	Motility Defect
Absence of dynein arms	(a) Eggbeater—like rotation (b) Only distal half of axoneme bends at half the beat frequency
Radial spoke defect	Floppy cilia, corkscrew rotation
Translocation defect	Grabbing-type motion at the apex, base is rigid
Normal ultrastructure with abnormal function	Quivering

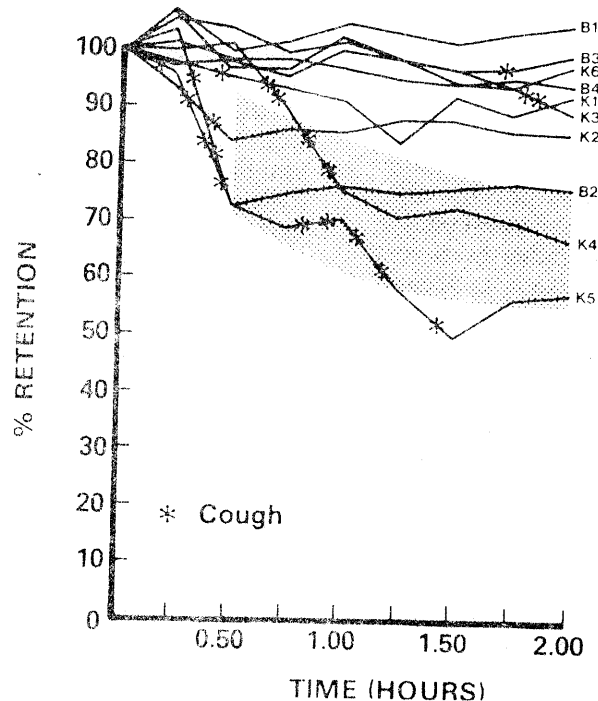


Figure 6. Clearance curves of radioactive material. Decreasing retention over time represents increasing clearance. Stippled area represents clearance of normal individuals.

K and B are individuals with Kartagener syndrome and bronchiectasis of unknown origin; possibly PCD, respectively. Subjects show absent or very decreased clearance. Coughing (asterix) results in brisk elimination of radioactive material. (From Rossman CM et al. *Am Rev Resp Dis* 1980;121:1011-6 by permission of the editor).

disease in younger children.

Otitis media with chronic effusion and conductive hearing loss are present in all patients⁴⁹; almost universally this complication requires the placement of tympanostomy tubes. Hyponasal speech, anosmia, and halitosis are common complaints among severely affected patients.

Nasal polyps have been reported in about 30% of patients with primary ciliary dyskinesia.⁴⁹ Their pathogenesis is not well understood.

Their occurrence is probably the result of chronic inflammatory changes of the mucosa of the nose and paranasal sinuses.

Lower Respiratory Tree

Chronic bronchitis, recurrent pneumonia, and atelectasis as well as reactive airways disease are common. Malfunction of the mucociliary escalator leads to chronic stasis, impaction, and infection which eventually causes erosion and distention of the bronchial wall. Bronchiolectasis is probably common in young

children but very difficult to diagnose. Cylindrical bronchiectasis eventually develops into fusiform or saccular bronchiectasis during adolescence and adult age. An interesting clinical observation is that bronchiectatic changes appear to be most severe in the lower lobes (this is also seen in patients with immunoglobulin deficiency and postinfectious bronchiectasis). In patients with cystic fibrosis, bronchiectasis is most marked in the *upper lobes*. As indicated above, the development of recurrent or persistent atelectasis is quite characteristic in newborn infants.⁵⁰⁻⁵⁴ Airway reactivity is probably due to an increased endobronchial concentration of chemical mediators of inflammation, destruction of epithelium, and receptor stimulation as it occurs in other chronic bronchitic conditions such as cystic fibrosis. Localized crackles can be heard over areas of bronchiectasis and mucous accumulation. The severity of symptoms varies greatly among patients. Some patients have milder lower than upper respiratory disease.

Pulmonary Function

Evidence of obstructive airways disease and air trapping can be elicited during pulmonary function testing. Characteristically these patients have decreased flows and flow rates, and air trapping (increased residual volume and ratio of residual volume to total lung capacity). Flows at low lung volumes are typically reduced (maximal midexpiratory flow rates, forced expiratory flows at 75% and 50% of vital capacity). Airway re-

Table 4. Signs and Symptoms of Primary Ciliary Dyskinesia

Chronic purulent rhinitis—anosmia
Chronic sinusitis
Chronic otitis media—hearing loss
Chronic bronchitis—recurrent pneumonia
Bronchiectasis
Nasal polyps
Clubbing of the fingers
Situs inversus viscerum
Male sterility

sponsiveness to bronchodilator drugs is quite variable. A certain degree of fixed airways obstruction can be expected due to mucous impaction and structural abnormalities of the airway.

Extremities

Digital clubbing is usually present only in older patients who have bronchiectasis. In our experience clubbing is never as severe as that seen in patient with cystic fibrosis and is usually present in older adolescents and adults.

Genitourinary System

Male infertility is the rule, with very rare exceptions.^{55,56} In fact, as indicated in the introduction, this disease was first characterized in fertility clinics where investigators noted the association of male infertility and chronic respiratory symptoms with abnormal sperm motility. The ultrastructural and functional abnormalities of both the respiratory cilia and the tail of the spermatozoa are most commonly identical.

The fallopian tubes are lined with ciliated epithelium. Female infertility and ectopic pregnancy should, theoretically, be more common in affected women because of malfunction of cilia and the oviducts. Displacement of the egg, however, appears to depend more on other mechanisms, such as muscular propulsion, than ciliary beating. No good epidemiologic data are available on this subject.

Leukocyte Function

Defective migration has been reported in primary ciliary dyskinesia secondary to defects in microtubules. It appears that a defect in leukocyte locomotion is present in some individuals.⁵⁷⁻⁵⁹ The bearing of this finding on the clinical picture appears to be negligible. No good correlation studies between defects in leukocyte motility and clinical severity are available. We have failed to detect migration defects in a few of our patients with very severe sinobronchial disease.

Other Organ Systems

Malfunction of ciliary structures has been implicated in abnormality of other organ systems such as the central nervous system. Hydrocephalus has been reported in animals. A few cases of hydrocephalus and ciliary dyskinesia in humans have been published.^{29,30} Again, the paucity of the data does not allow for any conclusions.

DIAGNOSIS

In the absence of situs inversus, the most important historical fact is the onset of symptoms shortly after birth. The rest of the clinical picture can be indistinguishable from that of severe allergic disease, hypogammaglobulinemia, or cystic fibrosis. Symptoms of hypogammaglobulinemia appear after the third month of life, when the maternal immune globulins are no longer circulating. Patients with this condition have scant lymphoid tissue, absent tonsillar tissue and, over time, develop severe infections with unusual organisms, arthritis and other manifestations that make the diagnosis evident. Patients with cystic fibrosis characteristically have a salty sweat, failure to thrive due to intestinal malabsorption, and a picture of recurrent bronchiolitis and bronchitis. The appearance of the patient with primary ciliary dyskinesia and normal visceral situs may resemble most closely that of a patient with severe allergic symptoms who has recurrent sinusitis, otitis media, and bronchitis. It is important to obtain a history of lung disease, sterility, and situs inversus in other relatives. The differential diagnosis in these cases may be very difficult from a clinical viewpoint and requires examination of ciliary structure.

Another condition, reported in adults, is Young syndrome.⁶⁸ This syndrome is defined by sinusitis, bronchiectasis, and obstructive azoospermia. The ciliary ultrastructure is normal and there is no association with the known genetic mutations

of cystic fibrosis. Table 5 summarizes the differential diagnosis.

Biopsy of Respiratory Mucosa— Electron Microscopy

We recommend that patients who have chronic sinobronchial disease undergo sweat testing to rule out cystic fibrosis and determination of serum immune globulins and allergy testing when indicated. If the diagnosis is unclear, electron-microscopic examination of respiratory tree mucosa is required. Biopsy should be ideally obtained from two different sites, for instance the nose and the carina. Denudation or metaplasia of the nasal mucosa is rather common in patients who have chronic rhinosinusitis; therefore, it is not a reliable source of specimens. We usually obtain the biopsies at the time other procedures are done, most commonly tympanostomies, in order not to subject patients to repeated procedures. It is very important that the individual performing the biopsy be cognizant of the diagnosis and the purpose of the biopsy. All too often samples of respiratory mucosa are immersed in formaldehyde rather than in normal saline or glutaraldehyde, 2.5%, the appropriate medium for ultrastructural examination.

The pathologist in charge of processing the samples must be alerted to the suspected diagnosis and should be expert in the examination of the specimen. Transverse as well as longitudinal sections should be obtained; orientation across the axoneme and basal bodies determines the orientation of the basal feet which are usually oriented in the direction of the effective beat⁶⁰⁻⁶³ (Figs 7 and 8). Random orientation of basal bodies is characteristic of ciliary malfunction. The relative angle of neighboring axonemes should normally be 25° or less. Larger angles reflect lack of synchrony of movement.

Studies of Ciliary Movement

The preferred method of study is that of direct examination of respi-

Table 5. Differential Diagnosis of Primary Ciliary Dyskinesia

Variable	Immotile Cilia Syndrome		Cystic Fibrosis		Allergy		Immune Deficiency		Young's Syndrome		Asplenia/Polysplenia	
Onset of symptoms	Birth	Autosomal recessive	Birth	Autosomal recessive	Infancy	?	Infancy	Depends on condition	Adult life	?	Birth/infancy	Autosomal recessive
Genetics	Yes (50%)	+++	No	+	++	+++	No	++/+++	No	+	Yes	(?)
Situs abnormality	+++	+++	+	+	++	+++	++	++	++	++	—	—
Rhinorrhea	+++	+++	+	+	++	+++	++	++	++	++	—	—
Sinusitis	+++	+++	+	+	++	+++	++	++	++	++	—	—
Otitis media	+++	+++	+	+	++	+++	++	++	++	++	—	—
Bronchiectasis	Lower lobes > upper lobes	Lower lobes > upper lobes	Upper lobes > lower lobes	Upper lobes > lower lobes	Rare in lower lobes, right middle lobes (asthma)	++	Lower lobes > upper lobes	Lower lobes > upper lobes	Lower lobes > upper lobes	Lower lobes > upper lobes	—	—
Nasal polyps	++	++	+++	+++	+	+	—	—	—	—	—	—
Spermatozoa	Immotile	Immotile	Absent	Absent	N	N	Opportunistic infections, autoimmune phenomenon	Opportunistic infections, autoimmune phenomenon	Absent	Absent	N	N
Other clinical findings	Males with situs inversus: lower right testicle	Males with situs inversus: lower right testicle	Malabsorption, abnormal food sweat test	Malabsorption, abnormal food sweat test	Skin atopy, allergy	Skin atopy, allergy	↑ lymph nodes (HIV) ↓ lymphoid tissue (B cell deficiency) ± (if bronchiectasis)	↑ lymph nodes (HIV) ↓ lymphoid tissue (B cell deficiency) ± (if bronchiectasis)	Dilated epididymis	Dilated epididymis	Cardiovascular abnormalities, intestinal malrotation, other anomalies	Cardiovascular abnormalities, intestinal malrotation, other anomalies
Digital clubbing	+/++	+/++	+++	+++	—	—	—	—	+	+	—	—

HIV, human immunodeficiency virus; N, normal; +, mild; ++, moderate; +++, severe.

Reprinted with permission from Schidlow DV, Katz SM, and Panitch HP: The immotile cilia syndrome. In Hilman B, Pediatric Respiratory Diseases: Diagnosis and Treatment. Philadelphia: WB Saunders, 1993:554.

ratory epithelium ciliary beating by video-microscopy. This technique requires special videographic attachments, microscopes, and experienced observers. This specialized equipment is usually available only at specialized centers with interest in ciliary motility and is not justified as a routine laboratory test. Some investigators have used stroboscopic light to determine the pattern of ciliary beating. Again, this kind of study can become quite involved and is usually of more scientific interest than clinical usefulness.

Some clinicians have reported visualization of ciliary beating in scraped nasal cells, under proper magnification as a means to diagnose dyskinesia. This method appears not to be widely used.

The saccharin test is a simple test that can be done in the office very easily. A particle of saccharin is placed on the anterior portion of the inferior nasal turbinate. A sweet flavor is felt by normal individuals within 20 to 30 minutes. In patients with faulty clearance, this flavor takes a much longer time to appear. This "poor man's mucociliary clearance test" has received much attention by clinicians but it is fraught with technical problems and is not very reliable.^{64,65}

Semen Analysis

The ejaculate in mature males can be used to assess the sperm motility as well as a sample for electron microscopic examination of ciliary ultrastructure. The abnormalities of the sperm are similar to those of the respiratory tree in affected individuals with very rare exceptions.

Chest Radiography

Dextrocardia is immediately evident in patients with situs inversus. The apex of the heart is in the right midclavicular line. The aortic arch is to the right, the liver is located in the left upper quadrant of the abdomen and the gastric bubble in the right upper quadrant. If these anomalies are detected, further contrast studies of the gastrointestinal tract or tomograms are superfluous.

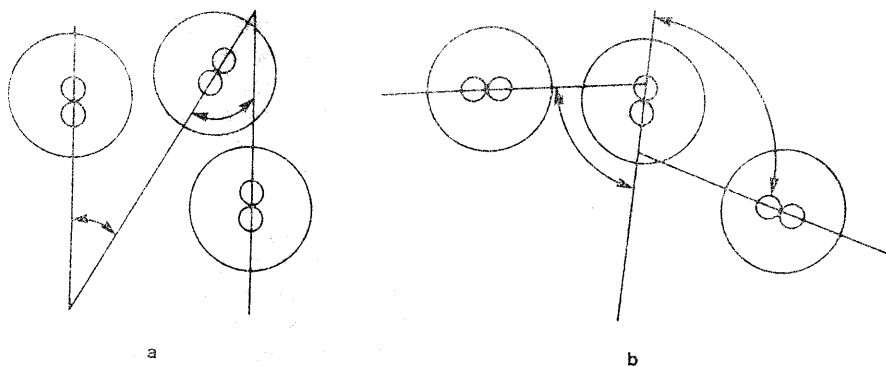


Figure 7. Diagrams of transverse sections of ciliated epithelium. The axonemal axis is determined by the direction of the pair of central doublets. (a) Normal angle (0-25°) and (b) abnormal angle (random orientation; angle larger than 25°). (Reprinted with permission from Schidlow DV, Katz SM, Panitch HP. The immotile cilia syndrome. In: Hilman B. Pediatric respiratory diseases: diagnosis and treatment. Philadelphia: WB Saunders 1993:554).

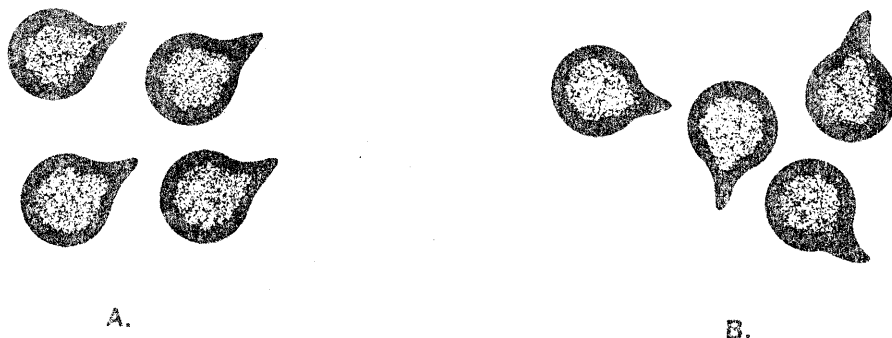


Figure 8. Diagrammatic representation of cuts across the basal bodies of ciliated epithelium. a. Basal feet point in the direction of ciliary beat in normally synchronized movement (normal orientation). b. Basal feet are randomly oriented, representing asynchronous beating characteristic of primary ciliary dyskinesia. (Reprinted with permission from same source cited in Figure 7).

A schematic representation of a longitudinal section across a cilium. The kinetosome or basal body is comprised by the basal foot and the rootlet. The variable microtubular composition at different levels of the cilium is shown.

Areas of atelectasis, peribronchial thickening, nodular cystic shadows, consistent with bronchitic changes, interstitial infiltration and overaeration of varying degrees can also be present.⁵²⁻⁵³ The appearance of situs inversus must be distinguished from that of "discordant visceral situs." This condition is seen in patients with asplenia or polysplenia in whom there is interruption of the inferior vena cava with great variability of organ position. The most common abnormalities include dextrocardia with the gastric bubble

in its normal position and the liver in the midline. Intestinal malrotation is very common. Some ciliary abnormalities have been described in association with this syndrome but it is currently unclear whether these are serendipitous or truly represent a cause and effect relationship. These patients have no associated respiratory disease unless they have associated reactive airways disease or other conditions. Chronic respiratory disease and infertility are not features of this syndromes. Children with asplenia can

have severe cardiac defects and suffer overwhelming systemic infections.

Bronchography

This radiographic modality should be reserved for circumstances in which surgical resection is being considered and delineation of the bronchial anatomy is deemed necessary.

Computerized tomography of sinuses and chest. The computerized tomography of the sinuses usually shows complete opacification of the paranasal sinus. A normal paranasal sinus almost rules out the diagnosis of primary ciliary dyskinesia. Computerized tomography of the chest is helpful in detecting early and late changes in bronchial anatomy and also is useful if surgical resection is being considered.

Cultures of respiratory secretions. Most patients with primary ciliary dyskinesia have normal flora or non-typable *Hemophilus influenzae*. As time goes by these patients become colonized with *Staphylococcus aureus* and *Pseudomonas aeruginosa* of the nonmucoid variety. This is an important finding because patients with cystic fibrosis characteristically present with the mucoid variety of *Pseudomonas aeruginosa*. All efforts must be made to obtain a good sample of respiratory secretions. The absence of pathogenic organisms does not rule out the diagnosis. The presence of pathogenic organisms, however, is more likely to be associated with a serious dysfunction of defenses such as is seen in primary ciliary dyskinesia, cystic fibrosis, or immunoglobulin deficiency rather than with an allergic diathesis.

MANAGEMENT

The management of primary ciliary dyskinesia is essentially symptomatic. Antimicrobial drugs are useful in suppressing bacterial colonization and recurrent infection; they need to be administered frequently or continuously. Intravenous administration of antibiotics may be

necessary in cases of acute bacterial exacerbations.

The choice of antimicrobial drugs must be based on the flora identified in cultures of respiratory sections. Bronchodilator drugs are useful in curbing airway reactivity. Choices and modes of administration do not differ from those used in the treatment of asthma. Other measures to improve mucus elimination are useful, such as physical therapy and postural drainage, assisted cough, exhalatory maneuvers, and other mucous clearance techniques.

Tympanostomy is almost universally needed in those individuals with recurrent otitis media. Paranasal sinus inflammation and infection often presents a difficult management problem. Endoscopic sinus surgery can be of assistance in older patients refractory to medical treatment.

Surgical resection of bronchiectatic areas should only be undertaken if the area in question acts as a persistent source of recurrent pneumonia, jeopardizing the health of the patient. Otherwise, a conservative approach is preferable.

Alpha dornase (Pulmozyme), a drug recently introduced for the treatment of cystic fibrosis, which helps liquify purulent secretions by cleaving long strands of DNA, has great potential as a coadjuvant therapy. No experience exists to date in the use of this drug in patients with primary ciliary dyskinesia.

PROGNOSIS

Primary ciliary dyskinesia is not, in itself, a lethal disease. Many people live long lives, especially if their disease is relatively mild or stable, and proper therapy is administered. The deterioration of pulmonary function tends to be slow and many patients enjoy long periods of clinical stability.

SUMMARY

Primary ciliary dyskinesia is an uncommon, clinically heterogeneous genetic disorder. Its most salient clinical features are expressed in the

respiratory tree and the male reproductive system.

To date, the fact that about one-half of affected individuals exhibit situs inversus of the viscera is not well understood. The theory of embryonal malrotation, advanced several years ago, fails to reconcile the fact that in the animal kingdom situs inversus can occur in isolation. Whether or not more than one mechanism plays a role in visceral malrotation remains to be determined.

The involvement of organ systems outside the respiratory tract appears limited and of little clinical consequence. Reports of hydrocephalus, presumably due to impaired circulation of fluid, for instance, have been sporadic.

Likewise, the findings of impaired neutrophil locomotion are not uniform and their clinical significance is unclear. Further investigation will be necessary to find effective ways to restore normal activity to defective cilia.

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