Primary ciliary dyskinesia in children

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Abstract

Objectives: to point out primary ciliary dyskinesia as a cause of chronic respiratory disease in children.

Methods: a 10 year literature review on Medline and by direct research about the subject.

Results and Conclusions: primary ciliary dyskinesia is a disorder characterized by an abnormal mucociliary clearance. It affects both the upper and lower respiratory tracts and usually the clinical manifestations start in the first years of life. It can progress to bronchiectasis. Kartagener’s syndrome is the typical genetic manifestation. The diagnosis may be based on an abnormal saccharin test, but its confirmation depends on abnormal ultrastructure of the cilia or abnormal ciliary function. Many ciliary defects are currently known. The treatment is supportive, with measures to enhance mucociliary clearance, such as chest physiotherapy, prevention of infections by immunizations and prompt antibiotic therapy in the acute respiratory infections.


Introduction

Ciliary dyskinesia is the name attributed to diseases involving alterations in ciliary ultrastructure and/or function. As a consequence of these abnormalities, mucociliary transport is also affected.

Mucociliary clearance constitutes one of the most important defense mechanisms of the respiratory tract, whereby bacteria, viruses, allergens, and pollutants are driven to the oropharynx, where they are swallowed. The interruption of this mechanism, as in ciliary dyskinesia, results in clinical disease.¹

The study of primary ciliary dyskinesia began about 90 years ago with the clinical observation of syndromes that included pulmonary diseases, sinopathy, situs inversus, and male infertility. Situs inversus and bronchiectasis were first described by Siwert in 1904.¹ Kartagener, in 1933, carefully studied 11 patients with sinusitis, bronchiectasis, and situs inversus, suggesting that the existence of a common factor affecting all these patients. The triad became known as Kartagener’s syndrome.¹

Kartagener’s syndrome had been previously called “immotile cilia syndrome,” until researchers concluded that most cilia presented uncoordinated or dyskinetic movements, not necessarily being immotile.¹ It was only at that point that the name “primary ciliary dyskinesia” was proposed.² Primary ciliary dyskinesia is an autosomal recessive inherited disease, with an approximate incidence of 1:15-30,000 individuals.³⁻⁵ It is classified as primary (congenital) or secondary (acquired). The most common defect is a deficiency in the number of dynein arms, resulting in weakening of the respiratory cilia and in spermatozoa motility.
Dyskinesia occurs in all sites presenting ciliated epithelium, i.e., nasal fossae, paranasal sinus, middle ear, tracheobronchial tree, ependyma, efferent ducts, uterine tube, cervix endometrium, and prolongations of retina cells. In the present article, the literature concerning ciliary dyskinesia is reviewed taking into consideration the importance of the subject and the little knowledge about this disorder in the differential diagnosis of recurrent or chronic infections of the respiratory tract.

Pathophysiology

Before describing the main ciliary alterations that lead to ciliary dyskinesia, we review the current knowledge about morphology and normal mucociliary function.

a) Normal cilium ultrastructure

Cilia are cellular projections that have intrinsic motility. The movement of microtubules modifies their shape, resulting in the propulsion of mucus. Flagella and cilia present the same basic structure, although flagella present different movements and some additional elements. On traditional microscopy, ciliated cells present extensions of 0.25 mm in diameter and 5 to 7 mm in length, similar to the bristles in a paintbrush. A ciliary axis and a basal body compose each cilium. Between the ciliary axis and the basal body, there is a transition zone. The ciliary axis, or axoneme, is constituted of a set of longitudinal microtubules, dipped in the cytoplasmic matrix, and surrounded by an extension of the cell membrane. The axoneme has other structures as well, such as the radial spokes, central sheath and hood (Figure 1).

The internal structure of the axoneme presents microtubules arranged in an array of nine couplets surrounding two central singlets, establishing a characteristic “9 + 2” cilia pattern. The microtubules are formed by protofilaments made of tubulin protein. The outer couplets are divided into A and B. Each A microtubule presents two projections (dynein arms), which are classified as internal or external and arranged clockwise. The two arms are asymmetric, and have different polypeptide compositions.

Dynein is a protein found in the arms of microtubules. It is involved in the splitting of adenosine triphosphate molecules, and it is responsible for the liberation of the necessary amount of energy for the transport process. The outer microtubule couplets are linked by a slender filament composed of a protein called nexin.

Radial spokes are microstructures that connect the outer A microtubules to the central sheath. The central sheath is a discontinuous structure consisting of two rows of projections along each central microtubule. The ciliary hood involves the distal extremities of the central microtubules and of the A microtubules in the outer couplets.

The basal body is constituted by the basal corpuscle, which is similar to the centriole, involved in the formation of microtubules, and by the basal foot, a conic, short, dense, and striated structure, laterally projected from the medial region to the basal corpuscle. The basal foot seems to act as a supporting base during the stage of effective ciliary beating. The ciliary roots provide the axoneme anchorage. The transition zone ranges from the end of the basal corpuscle to the beginning of the central microtubules (Figure 2).

b) Ciliary movement

The exact series of mechanochanical phenomena that allow microtubules to move remains unknown. Ciliary power-stroke seems to be generated by the sliding of outer microtubule couplets, modulated by the dynein arms and assisted by accessory axoneme structures. This hypothesis, known as “sliding filament,” was postulated by Afzelius in 1959.

The waveform movements of the cilia are similar to that of the wind on a wheat field. A normal cilium moves forward in effective movement (1/5 of the cycle); then, it slowly recedes (4/5 of the cycle), in a sequential and metachronous recovery movement, reaching a peak length of approximately 20 mm. On average, cilia beat 20 times per second. Half of the dynein arms are involved in the effective movement, and the other half in the recovery movement (Figure 3).

During the effective movement, the arms extend at (approximately) 40º. This requires ATP hydrolysis, accomplished by the action of dynein, which is an ATPase. Radial spokes, which connect the outer microtubules to the central sheath, provide enough resistance to cause the cilia to bend as a result of the sliding process. The combination
of sliding and microtubule resistance (tubulin-dynein interaction) is at the base of ciliary motility. The 5 mm thick mucosal surface moves upward at a speed of 0.5 mm to 1 mm per minute; thus, a particle adhered at the level of the bronchioalveolar junction takes about 20 to 30 minutes to reach the pharynx, and about 30 minutes to reach the larynx.

Whenever there is an alteration in ciliary structure or function, there will be an alteration in mucociliary clearance, with stasis of the respiratory tract secretions, which will be responsible for the clinical manifestations of the disease.

c) Ultrastructural alterations in primary ciliary dyskinesia

Six important ultrastructural abnormalities have been identified:

1. Absence of or defect in the dynein arms. This affects inner, outer, or both arms.

2. Defect in the radial spokes. Causes disorientation of the cilium center, leading to eccentric positioning of the central microtubules.

3. Transposition of the outer microtubules to a central position.

4. Absence of the axoneme structures.

5. Supernumerary microtubule couplets.

6. Defect in the basal body.

Recently, other ciliary alterations have been described as causing primary ciliary dyskinesia, such as presence of short nasal respiratory cilia and ciliary disorientation.

d) Ultrastructural alterations in acquired ciliary dyskinesia

Acquired ciliary defects may develop immediately after an aggression, or in the course of chronic diseases, such as cystic fibrosis or carcinoma, usually disappearing with proper treatment.

Bacterial or viral infections of the respiratory tract result in destruction of the ciliated epithelium and in altered ciliary beating rate, leading to mucociliary clearance delay. Other causes of acquired ciliary dysfunction are represented by the inhalation of cigarette smoke, toxic gases, environmental pollutants, or drugs, such as opium, atropine, cocaine and alcohol.

The most commonly acquired defects include compound cilia, addition and subtraction of microtubules, random orientation of the central microtubules, and alterations in the structure of the ciliary membrane. These defects are common in the general population, and their contribution to the increase of respiratory tract dysfunctions is more important than that of primary ciliary dyskinesia.

For differential diagnosis between primary and acquired ciliary dyskinesia, multiple samples of respiratory mucosa must be collected, at least twice, from different sites (nose, trachea, and bronchi). The percentage of abnormal cilia must be evaluated in a sample containing a large number of cilia. The presence of the main ciliary defect in all analyzed samples will confirm the diagnosis. In male patients, a concomitant spermatozoa alteration excludes the possibility that ciliary defects are secondary to the infection.

Signs and symptoms

Primary ciliary dyskinesia may appear early in the neonatal respiratory distress syndrome. However, in most cases, symptoms emerge during childhood. The severity of the symptoms varies considerably.

Upper respiratory tract

The nose, paranasal sinus, and ear are affected in most children. Nasal congestion and coryza are frequent,
with some or no seasonal variation. Frequently, children also present mouth breathing and nasal speech. Nasal polyps are found in approximately one-third of the patients. Anosmia is an occasional symptom, usually observed in older children.

Sinopathy and recurrent or chronic otitis media, with suppuration and obstruction of the auditory tube, are also common. These disorders are attenuated with time. Some children may present permanent tympanic membrane perforation, or they might need multiple tympanostomies, with the insertion of a ventilation tube. As a consequence, these patients may suffer an auditory loss.15,18

Lower respiratory tract

The predominant symptom in these patients is chronic cough, usually productive. Wheezing is not common. Recurrent pneumonia is a frequent finding in the history of primary ciliary dyskinesia patients.

Both lungs are equally involved, with predominant alterations on the lower and middle lobes and on the lingula, due to the greater difficulty in the drainage of secretions.3

The bacterial flora of primary ciliary dyskinesia patients resembles that of individuals suffering from chronic bronchitis. *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus viridans* are the usual pathogens.15

Dyspnea is an uncommon symptom. However, in some cases, an obstructive pattern is observed in pulmonary function tests.17

Physical exam may reveal signs of chronic pneumopathy, with an increase in the antero-posterior diameter of the thorax and digital clubbing in cases of greater pulmonary compromising. In cases of bronchiectasis, stertor can be observed on pulmonary auscultation. Bronchiectasis occurs in less than one-third of the children, and is usually more segmental than generalized. In adults, its incidence is greater, and indicates progressive lung damage. In some individuals, segmental and subsegmental atelectasis may be present.4,15

Cardiovascular system

Situs inversus is found in approximately 50% of primary ciliary dyskinesia patients; its incidence seems to be occasional, and not related to a familial pattern.3,15 The relation between primary ciliary dyskinesia and dextrocardia has not been clarified yet. Afzelius proposed that situs inversus may result from the inability of embryonic cell cilia to execute the rotation of viscera to the adequate anatomic position.4

Congenital cardiopathies in association with primary ciliary dyskinesia were also reported.20

Reproductive system

The ultrastructure of the tail in spermatozoa is similar to the ultrastructure of respiratory cilia. Men with primary ciliary dyskinesia present decreased or absent spermatic motility, which may be accompanied by oligospermia, leading to infertility.21,22

Similarly, female infertility is probably influenced by ciliary motility in primary ciliary dyskinesia, which is present in a great number of patients.15,17

Nervous system

The brain ependyma has a ciliated epithelium; however, little is known about the neurological manifestations of primary ciliary dyskinesia in pediatric populations. Reports of hydrocephalus can be found in these patients.4,23

Primary ciliary dyskinesia patients might report severe cephalaea, which may reflect decreased circulation of cerebrospinal fluid, associated with impaired ciliary activity. Chronic infections of the frontal sinus also contribute to the appearance of this symptom.4

Digestive system

Gastroesophageal reflux has been described in some cases.20

Genetic syndromes

Primary ciliary dyskinesia is present in some genetic syndromes, listed below.

Kartagener’s syndrome

Kartagener’s syndrome was first described by Manes Kartagener in 1933. Kartagener’s is an autosomal recessively inherited syndrome. A classic triad characterizes this syndrome: sinopathy, bronchiectasis and situs inversus. Usually, situs inversus is total, with the inversion of all thoracic and abdominal organs.24,25. The most common alterations are structural modifications in the dynein arms.26

Other congenital anomalies associated with the syndrome include transposition of large vessels and pyloric stenosis.27,28

Young’s syndrome

Young’s syndrome is characterized by male infertility, as a result of obstructive azoospermia. A chronic disease of the upper and lower respiratory tract may accompany it. The etiology of this syndrome is unknown. The cause of the epididymal obstruction is not entirely clear. Bronchial mucosa cilia and spermatozoa flagella of patients with Young’s syndrome have a normal ultrastructure, but are immotile or dyskinetic.29

Usher’s syndrome

Autosomal recessive disease characterized by congenital neurosensory deafness and progressive visual loss due to retinitis pigmentosa. Speculations of a possible association
between primary ciliary dyskinesia and Usher’s syndrome have been made, based on the presence of bronchiectasis and chronic sinusitis, and on the decrease in nasal mucociliary clearance in some patients.30

**Diagnosis**

Diagnosis of primary ciliary dyskinesia must be based on the patient’s clinical history. Frequently, several specialists evaluate the child before a definitive diagnosis is established. However, the most common causes of respiratory diseases should be ruled out before the performance of more specific exams.

The selection among several diagnostic methods depends on the available laboratory resources.1,15,31

**Unspecific methods**

*Simple thoracic X-ray:* reveals the degree of pulmonary involvement, with thickening of the bronchial walls, hyperinflation, possibly also showing bronchiectasis, atelectasis, condensation, and situs inversus. It usually shows greater damage in the middle lobe and lingula (Figure 4).

*Frontal sinus X-ray:* reveals mucous thickening or opacity of the paranasal sinus.

*Thoracic computed tomography:* useful for a better evaluation of the presence of segmental bronchiectasis and atelectasis (Figure 5).

*Bronchography:* occasionally indicated for patients with bronchiectasis, in order to evaluate surgical indications.

*Pulmonary function test:* evaluates the degree and type of ventilatory malfunctioning, usually obstruction.17,18

*Audiometry:* evaluates the degree of auditory impairment.4

**Specific methods**

*a) Screening tests*

1 - *Saccharin test*

In this test, a saccharin particle is placed in the anterior third of the inferior nasal turbinate. Time interval is counted in minutes, from the moment of saccharin insertion to the report of a sweet or slightly bitter gustatory sensibility in the oropharynx. Normal transit takes up to 30 minutes. Since saccharin tests require patient cooperation, they are usually restricted to patients above the age of six.36,37

2 - *Radioisotopic test*

Particles marked with radioisotopes are used in a procedure similar to the saccharin test. A gamma camera or serial X-ray accompanies the progression of the particles to the nasal cavity, and the speed of mucociliary clearance is determined in cm/minute. This method requires expensive and sophisticated equipment.38

*b) Specific exams*

1 - *Ultrastructural evaluation of the cilia*

In order to assess the ultrastructure of cilia, a biopsy of the respiratory mucosa must be carried out, usually a nose biopsy, because of technical simplicity. Biopsies of nasal mucosa may be performed by means of a curette, at the medial or inferior nasal turbinate level, or with the brush technique.32-34 The latter is technically more simple, frequently dispensing with local anesthesia. The biopsy fragment must be conserved in glutaraldehyde and submitted to electronic transmission microscopy, in order to evaluate the presence and nature of the ciliary defect.35 Electronic microscopy is usually available only in large centers, making this type of assessment more difficult.
Usually, when most cilia are abnormal, the study of nasal ciliated cells is sufficient to establish a diagnosis. Therefore, nasal biopsy must always come first, since it is less invasive than other techniques and can be performed in an outpatient setting, often dispensing with the use of topic anesthesia, which could influence ciliary clearance. However, nasal biopsy has one disadvantage: since the nasal mucosa is the site of frequent viral and bacterial infections, ultrastructural alterations in the cilia secondary to infectious processes may be observed. Therefore, nasal biopsy should be performed only after at least one month without acute respiratory infection. In cases of chronic rhinosinusitis, the nasal mucosa epithelium might already have suffered metaplasia, with few viable cilia for ultrastructural evaluation. In these cases, patients should undergo a treatment with antimicrobials for at least 2 weeks before biopsy, so that secondary ciliary alterations are minimized. Tracheal or bronchial biopsy is indicated when the analysis of the nasal biopsy is not enlightening.

2 - Functional evaluation of cilia

In addition to the study of ciliary ultrastructure, it is important to perform a functional analysis, since dyskinetic cilia may be morphologically indistinguishable from normal ones.

A fragment of respiratory mucosa biopsy should be placed in a specific medium, capable of maintaining the vitality of the cells, and then quickly sent to a laboratory for analysis.

Several methods have been developed to measure ciliary beat frequency and to analyze the shape of the ciliary motion. These are sophisticated methods, demanding extensive training, and available in very few centers in Brazil or elsewhere. These methods are high-speed cinematography, laser light spectroscopy, photoelectric measurements, and stroboscopy. Ciliary beat frequency can be measured by any of these methods, but the analysis of ciliary movement can only be performed using high-speed cinematography; a video system can be used to evaluate the motion shape of ciliary beating. The analysis of ciliary movement is fundamental to understand ciliary function, since the cilia that seem to be immotile or even normal on optic observation might actually be uncoordinated or dyskinetic. Normal ciliary beat frequency usually ranges from 12 to 15 Hz, and in patients with primary ciliary dyskinesia, it is normally under 10 Hz.

Differential diagnosis

Primary ciliary dyskinesia must be differentiated mainly from the following chronic pulmonary diseases: cystic fibrosis, asthma, immunodeficiencies, chronic aspiration, and bronchiektasis of other etiologies.

Treatment

Until this moment, there is no specific treatment to correct ciliary dysfunction. Development of a treatment will depend on further genetic and molecular research.

Flowchart of primary ciliary dyskinesia investigation

Patient with signs and symptoms suggestive of primary ciliary dyskinesia

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Thoracic X-ray

→ normal

→ situs inversus ⇒ Thoracic tomography to evaluate bronchiektases, atelectases

→ suggestive of bronchiektasis

+ Altered frontal sinus X-ray

+ Pulmonary function test: normal or obstructive

+ Audiometry (in the presence of chronic otitis)

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Saccharin test

→ > 30 minutes (twice)

→ < 30 minutes (twice): other etiologies for the respiratory disease are ruled out

→ the patient is too young to perform the test and there are strong signs of primary ciliary dyskinesia

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Nasal biopsy ® electronic microscopy and functional evaluation of the cilia
Patients benefit from the removal of secretion through regular respiratory physical therapy. In patients with ciliary dysfunctions, physical therapy should be similar to that used with cystic fibrosis patients, using classic techniques, such as thoracic percussion, postural drainage, and techniques of forced expiration, and instruments such as the flutter and the positive expiratory pressure mask, which make physical therapy more efficient. Patients must be stimulated to cough and to practice exercises that stimulate coughing, since this is an efficient mechanism for eliminating secretions. Prior to respiratory physiotherapy, inhalations with physiologic solution, mucolytics, or bronchodilators must be performed. Antitussive agents are strictly contraindicated.

Prophylactic measures, such as immunization against hemophilus, pneumococcus, and influenza, should be followed. Patients should be advised to avoid exposure to smoke, pollutants, and allergens.

At the first sign of infection, therapy with antibiotics is indicated. The most commonly, *Haemophilus influenzae* and *Streptococcus pneumoniae*, deserve special attention. In patients presenting *Haemophilus influenzae* and *Streptococcus pneumoniae*, a regular sputum culture should be performed in order to monitor the bacterial flora of their respiratory tract and help in the selection of an antimicrobial agent when indicated. Antibiotics are usually used for two-week periods during acute exacerbations. In some cases, long-term prophylactic therapy with antibiotics may be required.

Adequate hydration must be stimulated to maintain secretions fluid and easy to eliminate. Mucolytics may be used in some cases. Bronchoscopy is indicated if atelectasis does not respond to intense respiratory physical therapy.

Resection of pulmonary segments or lobes may be indicated in cases of unsuccessful clinical treatment of localized bronchiectasis, atelectasis, or hemoptysis. Meatl antrostomy or removal of inferior nasal turbinates may be carried out to alleviate paranasal sinus obstruction. In cases of recurrent otitis media, myringotomy with insertion of a ventilation tube may be useful. Nasal polypectomy and sinus drainage may help patients with severe sinusitis non-responsive to antibiotic treatment.

Due to the chronic status of primary ciliary dyskinesia, patients should be followed by a multidisciplinary team including psychologists, speech therapists and otorhinolaryngologists.

In conclusion, primary ciliary dyskinesia may progress to chronic pulmonary disease; therefore, it should be considered in the differential diagnosis of chronic and repeated pneumopathies of the child. Early diagnosis and treatment can avoid, or at least delay the evolution of the disease into irreversible pulmonary lesions. A complete evaluation for the diagnosis of primary ciliary dyskinesia is sophisticated and expensive, leading to a situation of subdiagnosis of the disease in our setting. In cases of clinical suspicion based on suggestive signs and symptoms and on altered screening tests, the patient must be directed to a medical center equipped to perform ultrastructural and functional evaluation of cilia. Despite the evolution to chronic pulmonary disease, with bronchiectasis and some degree of respiratory failure, the course of primary ciliary dyskinesia is highly variable, and in many patients life expectancy is very close to normal.

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