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REVIEW

Primary ciliary dyskinesia. Ciliopathies

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KEYWORDS
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Oncogenesis

Abstract
Primary ciliary dyskinesia is a genetically inherited syndrome characterised by ciliary immotility or dysmotility. Deficiency in mucociliary clearance produces chronic respiratory infections from birth, male sterility by spermatozoid immotility and situs inversus in 40%-50%of patients (Kartagener's syndrome). Diagnosis is made by analysing ciliary motility with high-speed digital video and ciliary ultrastructure. The wide distribution and functions of the cilia in the body mean that this dysfunction can generate other ciliopathies apart from primary ciliary dyskinesia.

PALABRAS CLAVE
Síndrome de Kartagener;
Sinusitis;
Bronquiectasias;
Situs inversus;
Síndrome de Usher;
Retinitis pigmentosa;
Oncogénesis

Discinesia ciliar primaria. Ciliopatías

Resumen
La discinesia ciliar primaria es un trastorno genéticamente determinado que se caracteriza por un movimiento ciliar alterado o ausente. Genera un déficit en el aclaramiento mucociliar que se manifiesta clínicamente como infecciones crónicas de vías aéreas constantes desde el nacimiento, así como esterilidad masculina por inmovilidad del espermatozoide y situs inversus en el 40-50% de los pacientes (síndrome de Kartagener). El diagnóstico se basa en el estudio de la movilidad ciliar mediante vídeo de alta resolución digital y alta velocidad, complementado con el estudio de la ultraestructura ciliar. La amplia distribución ciliar en el organismo y sus numerosas funciones hacen que su patología origine, además de la discinesia ciliar primaria, otras ciliopatías.

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Introduction

Cilia and flagella are projections of the cell, surrounded by the cell membrane, which have different biological functions. They are present in protozoa, animals and some plants. In the human body, there are at least 9 categories of cilia or derived organelles with different characteristics and biological functions, although almost all cells, at some point in their evolution, have ciliary structures that are involved in cellular division[1] (Table 1).

The cilium is involved in embryonic development, the polarity of many cells, the maintenance of homeostasis, sensory functions (hearing, sight, smell), transport and cell division. This wide variety of functions involves great morphological and genetic complexity.[2] The carrier function gives mobility to a cell (as in the case of sperm cells), or to the materials located on the cell surface (as in the case of ciliated cells in the respiratory tract that convey mucus, the cells in the fallopian tubes that transport the ovum, or cerebrospinal fluid transporters in the cerebral ventricles). The homeostatic and visual sensory functions are based on another property of the cilia: the intraflagellar transport protein present in them generates a movement of molecules and proteins in an anterograde and retrograde direction, relative to the cell, capable of maintaining them.[3] In addition, they can act as mechanoreceptors and chemoreceptors, as is the case in the cilia of the inner ear and the olfactory receptors, respectively.[4]

The respiratory cilium emerges as an external cellular growth from a basal body to which it is attached (also known as centriole), consisting of 9 triplets of peripheral microtubules. The part that emerges from the cell surface (known as the axoneme), has the classic structure of "9+2": 9 pairs of peripheral microtubules surrounding a central pair, all enveloped in the cell membrane. Each peripheral doublet of tubules has two dynein arms (outer and inner) that contain the motor protein of the cilium. The dynein arms cause the microtubules to slide over each other and the cilia to move. There are also nexin links, which maintain the cilium intact during the beat. The central tubules are surrounded by a central sheath that binds to the peripheral doublets by radial arms and that acts as the skeleton that preserves the structure of the cilium (Figure 1).

Along with this ciliary pattern, we can also find cilia in the organism with structure "9 +0", that is, without the pair of central microtubules. Most of them, except for embryonic nodal cilia, are immobile. Their functions are not well understood, although in many cells they have a sensory role.[5]

The widespread distribution and physiological functions of the cilium cause its dysfunction to be related with a wide range of diseases, in addition to primary ciliary dyskinesia (PCD). They are currently known as ciliopathies[1,6-8]:

- Congenital hydrocephalus.
- Progressive blindness (retinitis pigmentosa).
- Sensorineural hearing loss (Usher syndrome).
- Mental retardation.
- Chronic renal failure (polycystic kidney disease and nephronophthisis).
- Polydactyly.
- Bardet-Biedl syndrome: obesity, hypogenitalism, mental weakness, cranial defects, retinitis pigmentosa, syndactyly.

Table 1 Cilia or organelles derived from cilia in the human body

Category	Pattern	Mobile	Size	Location
Mucus-propelling cilia	9+2 DY	Yes Ciliary beat	6 µx2 µ (200/cell)	Respiratory cilia of the upper and lower airways, middle ear
Water-propelling cilia	9+2 DY	Yes Ciliary beat	10-15 µ (1 or more/cell)	Ependyma, cerebral ventricles, testicular ducts, Fallopian tubes
Nodal cilia	9+0 DY	Yes In apex	5 µ (1/cell)	Embryo, 7-8 days postcoitus
Monocilia	9+2/9+0 DY	Yes	1/cell	Corneal follicular endothelium, thyroid
Rudimentary cilia	9+0 No DY	Improbable	2-3 µ (various/cell)	Glial cells, chondrocytes, fibroblasts, almost all cells
Olfactory cilia	9+2 No DY	No	50 µ (20/cell)	Olfactory epithelium
Photoreceptor cilia	9+0 No DY	No	1/cell	Retina: cones and rods
Sperm cell flagellum	9+2 DY DY	Yes Flagellar	45 µ (1/cell)	Sperm cell
Kinocilia	9+2 DY DY	?	1/cell	Internal ear

DY indicates dynein.

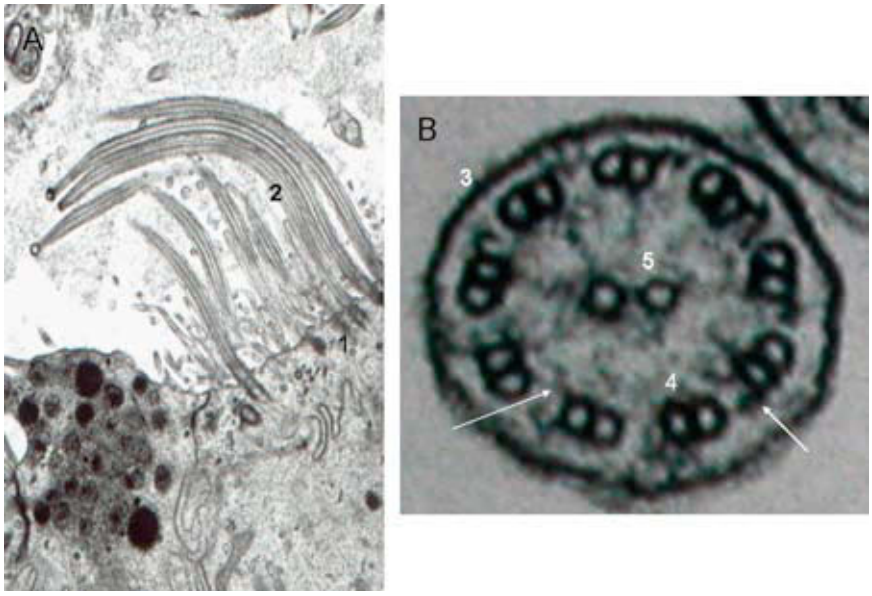

Figure 1 Longitudinal (A) and transverse (B) sections of nasal respiratory cilia. 1: basal body. 2: ciliary axoneme. 3: cell membrane. 4: pairs of peripheral tubules. 5: pair of central mounds. Arrows: internal and external dynein arms.

- Complex congenital heart diseases, especially disorders of laterality.
- Biliary atresia.
- Oesophageal atresia, severe reflux.

However, PCD is the most common clinical syndrome, and also that with the most impact, associated with ciliary dysfunction. PCD, also known as ciliary immotility syndrome (CIS), is an inherited, autosomal recessive disorder that affects approximately 1/10,000-60,000 individuals.[9] It includes a group of diseases in which the respiratory cilia are immobile (CIS), ciliary motion is dyskinetic and inefficient (PCD) or there are no cilia (ciliary aplasia); the last entity is of extreme rarity.[1,6,9,10] PCD and CIS are synonymous terms from the clinical and pathogenic point of view: immotility and dyskinesia lead to a lack of mucociliary transport and stasis of respiratory secretions with its consequences: chronic infections of upper and lower respiratory tract from birth.[10,11] The mobility disorder also affects sperm cell flagellum and fallopian tube cilia; in these cases, infertility is common in men and reduced fertility in women.

The ineffectiveness of embryonic nodal cilia causes the asymmetry of internal organs to be placed at random, so that approximately 50% of these patients have total *situs inversus*. For many years, the association of sinusitis, bronchiectasis, and *situs inversus* has been known as Kartagener's syndrome. However, bronchiectasis does not appear at birth but develops subsequently as a result of chronic infection, so this syndrome is currently defined by the coexistence of PCD and *situs inversus*,[12,13] with a prevalence of 1/20,000-40,000 individuals.[10]

Although the clinical presentation is fairly homogeneous (chronic productive cough, rhinorrhea and chronic rhinitis from birth, chronic sinusitis, frontal sinus agenesis and *situs inversus* in 50% of patients), its morphology is very heterogeneous. The most common ultrastructural defect is the complete or partial absence of dynein, but there are cases with a normal ciliary structure.[1,13,14] In addition, there are numerous acquired ciliary defects from the action of germs or toxins (secondary ciliary dyskinesia [SCD]), which must be discriminated from the congenital. The large number of polypeptides involved in the formation of cilia also implies a large number of genes that determine their function, thus hampering the also heterogeneous genetic diagnosis.

Early diagnosis of PCD has significant beneficial effects on disease morbidity. Pulmonary function in these patients is much worse when they are diagnosed in adulthood and have not followed adequate treatment.[6] However, the rarity of this syndrome often causes its diagnosis to be delayed and its incidence to be underestimated.[15,16] It is necessary, therefore, to establish points of early diagnosis for the disease in all countries.

Genetic bases of PCD

PCD has an autosomal recessive pattern, with no predilection for gender or race,[9] although cases have been reported with possible X-linked inheritance.[17] The molecular complexity of the ciliary axoneme, in which at least 250 proteins have been described, implies that there are many candidate genes; therefore, PCD is genetically very heterogeneous.[17,18] Until now, mutations in three genes coding for dynein (*DNAI1* on chromosome 9p13-21, *DNAH5* on chromosome 5p15-5p14 and *DNAH11* on chromosome 7p15.3-21) have been

associated with a minority of PCD cases (30%). Alongside these, a variant of PCD transmitted by the X-chromosome linked with retinitis pigmentosa has been reported, caused by mutations in *RPGR* (guanosine triphosphatase regulator gene of retinitis pigmentosa).[17] There are many other candidate genes that encode components of cilia: *DNAH7*, *DNAH9*, *DNNI2*, *AK7*.[6,12,17-19]

The sensory cilia are more ubiquitous in the organism and are found in many tissues (kidney, olfactory epithelium, inner ear and retina) and their dysfunction generates a large number of phenotypes. Thus, different mutations of the *RPGR* gene have been found in patients with retinitis pigmentosa, sometimes in relation to sensorineural hearing loss (Usher syndrome).[20,21]

Clinical manifestations

The manifestations of congenital ciliary dysfunction are characterised by their presence from birth, by their chronic and constant clinical course and their wide distribution (simultaneously affecting all organs in which the cilia exert their function). The most characteristic clinical presentation that is always present is simultaneous upper and lower respiratory tract infection, permanent and from birth. Although the clinical condition may vary throughout life, this common denominator always remains (Table 2). Table 3 presents the clinical findings that should make us suspect PCD in childhood, especially if they occur in combination in a single patient.

In the prenatal period, *situs inversus* is an indication of PCD. Although in most cases with this asymmetry there is no ciliary dyskinesia, it is always a sign of suspicion, given that situs inversus affects 0.001% of the general population but almost 50% of these patients.

During the neonatal period, it is common to present dyspnoea or pneumonia without any other "predisposing cause". *Situs inversus* or a family history positive for the disease should guide our diagnostic suspicion. Constant rhinorrhea from the first day of life is a very suspicious sign of PCD; parents often say that the child "was born with a cold".

Chronic, productive, daily cough with mucopurulent sputum is characteristic in childhood, increasing as the child grows. The symptoms increase during the day, contrary to what occurs in smokers, in whom they are stronger in the morning. Children are sometimes diagnosed with atypical asthma, unresponsive to habitual treatment.[6,12] "Idiopathic" bronchiectasis occur in 10% of these children and is an important feature in the screening of PCD[22]; another important feature is rhinitis with persistent, mucopurulent rhinorrhea, which responds poorly to standard treatments, often complicated with sinusitis in older children who do not improve with treatment or surgery. Nasal polyposis is rare and more common in cystic fibrosis. Secretory otitis media, complicated by recurrent acute otitis media, is also characteristic during childhood. Placing transtympanic drainage does not improve the otitis, which is followed by permanent otorrhea until the drains are extruded. Ear problems improve with age, but do not disappear, and permanent transmission hearing loss is the norm.[23]

Table 2 Manifestations of primary ciliary dyskinesias in the different human organs

Organ	Clinical manifestation
Lung	Neonatal respiratory distress Recurrent bronchitis Bronchiectasis
Ear	Secretory otitis media Chronic otitis media
Fossae and sinuses	Chronic sinusitis Hypoplasia of sinuses, specially the frontal
Genital-urinary tract	Male infertility Female: reduced fertility, ectopic pregnancy
Organic laterality	*Situs inversus totalis* *Situs ambiguus* (heterotaxia)
Central nervous system	Hydrocephalus (rare)

Table 3 Symptoms and suspicious signs of primary ciliary dyskinesia in children. The evidence increases when they are present in combination

Neonatal and continuous rhinitis
Respiratory distress in healthy newborns to term
Productive cough from birth and rhinitis
Situs inversus
Prolonged otorrhea after tympanic drainage
Bronchiectasis "without cause"
Children with recurrent problems and recurrent lung infections that require continuous antibiotic treatment "without cause"

The symptoms described remain during adolescence and adulthood, and other problems appear. Partial or total occupation of all paranasal sinuses by soft tissue and secretions is characteristic. Another characteristic feature is hypoplasia of the paranasal sinuses in general and, especially, frontal sinus aplasia, evidenced when performing a computed tomography scan (CT) (Figure 2), due to the lack of the eutrophic pneumatising effect of the diseased mucosa.

Although bronchiectasis can appear in childhood, it is during adulthood that it becomes constant in all patients and generates the characteristic clinical features and complications. Auscultation reveals crepitation, occasionally with wheezing that may mimic asthma. Cylindrical or saccular bronchiectasis involves the middle and lower lobes and the lingula (Figure 2), unlike cystic fibrosis, in which it is located in the upper lobes. Other radiographic findings in the chest of these patients include multiple diffuse nodules over 2 mm in diameter, probably from bronchiolitis, moderate hyperinflation, peri-bronchial condensations and atelectasis.[24,25] Lung function can be normal, but there is often poor pulmonary ventilatory function, ranging

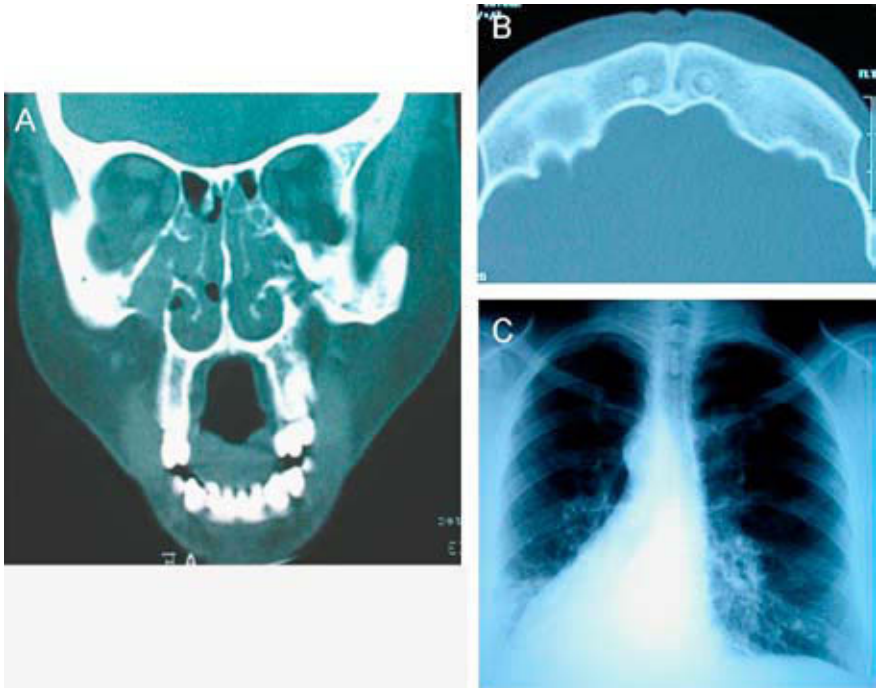

Figure 2 Radiographic findings in primary ciliary dyskinesia and Kartagener's syndrome. A: paranasal sinus hypoplasia occupied by inflammatory tissue. B: aplasia of frontal sinuses. C: dextrocardia and bilateral bronchiectasis.

from mild to severe, by the third decade of life. It is a consequence of the high concentrations of inflammatory mediators generated by the permanent infection.

Headache is a common complaint among these patients. It may be related with the exacerbation of chronic sinusitis, but can persist in stable periods. One possible cause of cephalgia in these patients is hydrocephalus, which has been described in some patients with PCD; this is related to ependymal cilia dysfunction and cerebrospinal fluid drainage.[26] Different studies indicate, however, that the incidence of hydrocephalus in PCD is scarce.[1]

Fertility problems are apparent in adults, whose study may lead to the diagnosis. Most men have sperm that are alive but immobile, thus making them infertile. A small percentage (<20%) are fertile, since the structures of the cilia and sperm are similar, but their polypeptide composition is different.[27] Another factor contributing to male infertility is the absence of ciliary activity in the testicular efferent ducts, which impedes the exit of sperm cells.[3] The deficient activity of the cilia in the fallopian tube interferes with the normal transport of the ovum to the uterus, so that female fertility is also reduced by 50% and the number of ectopic pregnancies is incremented.[3,9,28]

Diagnosis

Except in cases with clear clinical evidence with concomitant *situs inversus* and respiratory symptoms, before starting specific ciliary studies, it will be necessary to exclude other causes of chronic respiratory infection, mainly cystic fibrosis, respiratory allergy and immune deficits.[6,29] There are specific tests to diagnose these diseases:

- Sweat test: chloride concentrations > 80mmol/l are typical of cystic fibrosis. The diagnosis is confirmed by the finding of a genotype compatible with the disease.
- Quantification of immunoglobulins and their subclasses in blood to rule out an immune deficit. This can coexist with PCD.
- Allergy tests to rule out an allergy. This can coexist with PCD.

There are screening tests for PCD, useful in environments where there are no specific tests. However, the final diagnosis is based on the study of ciliary mobility and ultrastructure and should always be carried out to confirm the disease.

Screening tests

Determination of exhaled nitric oxide and measurement of nasal mucociliary transport.

1) Exhaled nasal nitric oxide (nNO): nNO is very low or absent in patients with PCD. Its determination has a sensitivity of 95% and a specificity of 90% in patients with clinical suspicion of PCD.[30-32] However, a confirmation test is always required, since nNO can be also very low in other conditions such as cystic fibrosis.[6,12] Furthermore, it cannot be determined accurately in small children,[33] who are in the period when the diagnosis is most important.

2) Measurement of mucociliary clearance: There are various methods to study nasal mucociliary transport. The classic saccharin test is always difficult to interpret and unfeasible in children, since it requires a level of patient cooperation impossible in small children.[33,34] Radioisotope tracer methods are the most profitable and objective and can be performed at any age, even in newborns.[34,35] However, the study of mucociliary transport is a test with high specificity but low sensitivity: normal nasal mucociliary transport rules out PCD; however, if the test is altered, we cannot diagnose PCD, since there are many other diseases that can produce transport disruption, especially SCD.

Diagnostic tests

PCD diagnosis is based on analysing the frequency and shape of ciliary action. Studying ciliary structure by electron microscopy (EM) is also diagnostic if it shows ciliary defects typical of PCD, but 10%20% of patients with PCD show normal ultrastructure,[12] so normality does not exclude the diagnosis. Both require the sampling of respiratory epithelium ciliated cells from nasal passages (much more accessible) or from bronchial tubes. Given that these samples should contain only ciliated cells, brushing and (more profitably) curettage are the most suitable techniques for obtaining them. Part of the sample can also be used for cell culture studies on which to carry out subsequent studies.

1) Study of ciliary action: high-resolution, high-speed digital video imaging system (DHSV: digital high-speed video). This allows precise study of the ciliary action, which can be viewed on different planes, at different speeds and even frame by frame.[36] The sample is deposited, immediately after being taken, in a solution of cell culture medium, where more samples can be obtained for direct microscopic observation. A high-speed digital camera coupled to the microscope will let you record ciliary movement for later analysis. A computer program implemented on the images will facilitate the determination of:

   - Frequency of ciliary beating action: each laboratory determines its normal values. As a guidance, a beat frequency above 9 Hz (540 beats per minute) should be considered normal.
   - Pattern-shape of the ciliary beat. Precise study, frame by frame, to determine that the beat is normal and in the two characteristics cycles: an effective movement phase, in which the cilium extends throughout its length, and a recovery phase, when the cilium bends and returns to the starting position to start the beat again. Both determinations are necessary, because the frequency of the beat may be normal, while the movement is dyskinetic.[37]
   - There is an alternative, indirect method of determining an effective ciliary beat: the test of cell rotation. If the cells rotate on themselves in the culture medium, this means that ciliary movement is adequate.[12] If it is not possible to obtain loose cells in the first sample, then the cells are cultured and treated a few weeks later with pronase to separate the cells: healthy cells rotate constantly.[38]

2) Study of ciliary ultrastructure: the biopsy is immersed in glutaraldehyde and processed for EM study. The cross-sections of cilia are examined and the different components of the axoneme are analysed. An accurate assessment of a possible alteration requires expert personnel and specific criteria (both quantitative and qualitative) on the various ciliary structures to be studied from a diagnostic point of view. Between 10 and 100 cross sections should be analysed per patient. Absence of dynein is considered when the average number of dynein arms counted is less than 2 per cross-sectional cut. The assumptions that follow establish partial dynein deficits: *a*) we consider the absence of internal dynein arms when this average is <0.6 per cross-sectional cut and <1.6 referred to the outer arms; *b*) few external or internal dynein arms if the average is <7 and 3, respectively, and *c*) short dynein arms mean a short projection compared with normal cilia. Ciliary orientation determined by the pattern of central tubules is normal if the variation is less than 28º. Alterations of the 9+2 pattern are considered significant if they affect more than 30%of the ciliary axonemes.[13,14,38]

PCD is morphologically heterogeneous, so we can find various congenital ciliary abnormalities described in the literature.[1] The most common ciliary defects, which affect 80%-95% of patients with PCD, are dynein deficiencies: complete absence, associated with immobility, or partial absence (of internal or external arms, little dynein or short arms), which is associated with dyskinesia (Figure 3). Other ultrastructural abnormalities are less prevalent and include the absence of radial arms, ciliary transposition and agenesis of central tubules.[1,6,12,14,20,39] However, from the purely morphological point of view, only the total deficit of dynein can be considered diagnostic.[1] Numerical alterations of microtubules, ciliary complexes, ciliary membrane evaginations and others must be regarded as secondary. In case of diagnostic doubts, cell cultures are useful, since newly-formed cilia reproduce the congenital ciliary alterations but not the acquired.[38]

Although some authors consider EM as the ultimate test for diagnosis,[1,6] 10%20% of patients with PCD show a normal ultrastructure,[1,12,13,20,40,41] and in some series this figure reaches 28%.[38] From this we can deduce that only in cases where there are congenital ciliary defects will they be diagnostic, but a normal ultrastructure does not preclude PCD. Therefore, studies of the frequency and pattern of ciliary beat provide the final diagnosis of SCD, complemented by ultrastructure studies. In doubtful cases, both variables should be studied in cilia obtained from cell cultures from the individual's ciliated cells.

Genetic tests

In specialised laboratories, it is possible to perform genetic studies of mutations in genes *DNAI1* and *DNAH5*.[19] The diagnosis is established if the mutation affects both alleles, but if it only affects one allele, it is necessary to investigate other trans-allelic mutations.[12]

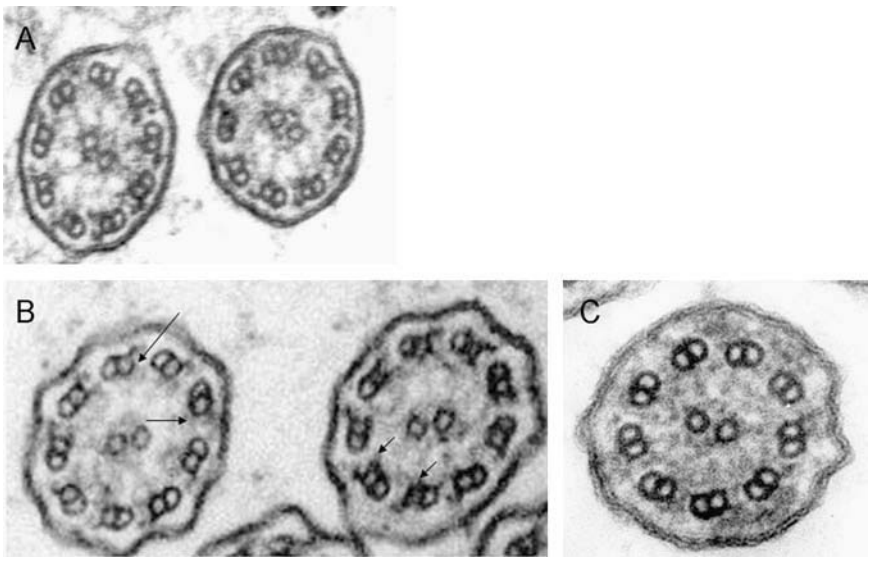

Figure 3 he most common ultrastructural abnormalities in primary ciliary dyskinesia compared with normal cilia. A: normal cilia. B: lack of internal dynein arms (arrows). C: absence of dynein.

Differential diagnosis

This is established with acquired ciliary alterations and secondary ciliary dyskinesia. Ciliated cells are exposed to the environment since they act as a first line of defence against it. Numerous agents, including bacteria, viruses, harmful and irritating gases, various types of suspended matter and physical agents such as cold, heat and changes in atmospheric humidity can damage them. The resistance of these cells is extraordinary, but they may suffer changes under certain conditions, mainly dependent on infection, which can damage the entire depth of the mucosa and cause injuries that take weeks to resolve.

It is therefore very important to apply the diagnostic methodology described in previous lines, based on clinical suspicion, given that, in childhood, respiratory infections are chained and it can be difficult to differentiate PCD from SCD. Numerical alterations of microtubules and ciliary complexes are considered characteristics of SCD (Figure 4).

Treatment

There is currently no pharmacological treatment that restores normal ciliary mobility. However, the therapeutic measures described below improve disease evolution and decrease its morbidity.[42] The treatment of these patients is based on three actions that are applied simultaneously[6]:

1) Periodic monitoring of general condition, respiratory function and auditory function.
2) Promotion of drainage of secretions through respiratory physiotherapy and physical exercise.
3) Aggressive antibiotic treatment of respiratory infections.

Periodic medical monitoring

- Regular visits to the paediatrician, in the case of children, pulmonologist, otolaryngologist and primary care physician, who must be fully informed about the patient's illness and the treatments prescribed.
- Regular assessments of pulmonary ventilation and performance of pulse oximetry, for the early detection of respiratory function deterioration.
- Regular sputum cultures to monitor infectious flora.
- Chest CT scan only if there are signs of disease progression.
- Otoscopic and audiometric review.
- Regular clinical assessment of chronic rhinosinusitis.

Medical treatment of PCD

We must select antibiotics that penetrate into the respiratory tract effectively and that will remain stable and bioactive in the presence of beta-lactamase producing bacteria. They should be prescribed whenever there are signs of respiratory infection and for as long as necessary. Antibiotic prophylaxis should be considered if repeated courses of antibiotics are needed.

Antibiotics should be selected according to sputum culture. Occasionally, in children who do not expectorate, a bronchoalveolar wash will be needed to obtain a sample. If *Pseudomonas aeruginosa* is detected, the treatment protocol is the same as in cases of cystic fibrosis.[6] The most common bacteria found in infections of the airways of patients with PCD vary depending on whether the patient is a child or an adult.[16] In children, the most common are *Haemophilus influenzae* and *Staphylococcus aureus*; in adults, they are *Streptoccocus pneumoniae*, *P. aeruginosa* and non-tuberculous mycobacteria.

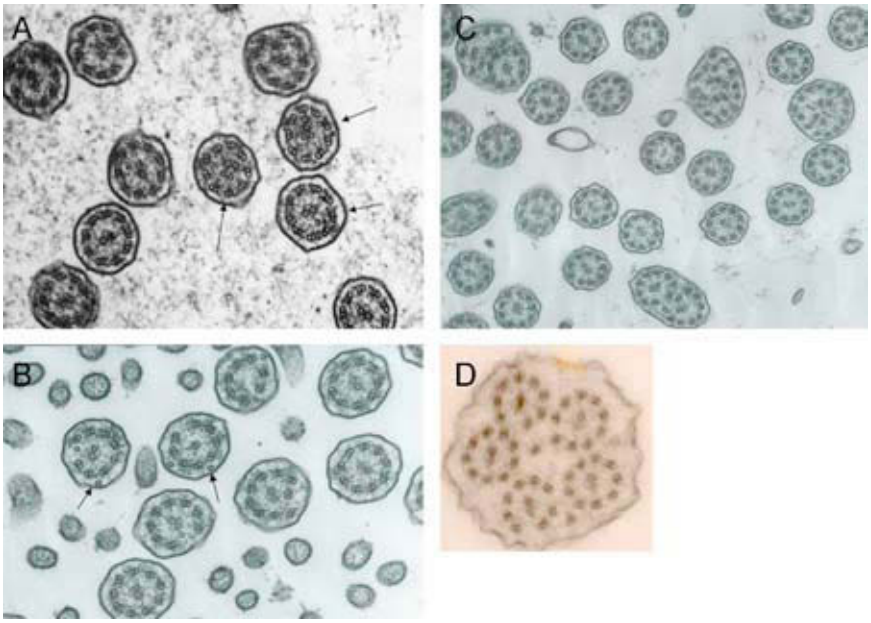

Figure 4 Secondary or acquired ciliary alterations. A: supernumerary peripheral tubules (arrows). B: supernumerary central tubules (arrows). C and D: ciliary complexes: several axonemes surrounded by a single cell membrane.

Bronchodilators are not beneficial and should be withdrawn if they had been started by a misdiagnosis of asthma. Saline sprays are beneficial, as they improve mucus clearance through cough.

PCD patients should receive all protocol immunisations, including those against influenza A virus and pneumococcus type A virus.

The complications of bronchiectasis and chronic lung disease increase with age, but rarely require surgical treatment (lobectomy or lung transplantation). Although the inflammatory pattern of PCD and cystic fibrosis is similar, with a clear predominance of neutrophils in secretions, the evolution of PCD tends towards stability. In contrast, the trend is towards progressive deterioration in cystic fibrosis.

Respiratory physiotherapy

Adults and parents of affected children should know the different techniques that favour the elimination of the bronchial secretions, although the beneficial effects of constant respiratory physiotherapy still remain to be demonstrated.[6] A healthy lifestyle, avoiding the consumption of tobacco and—bove all—physical exercise have proven to be factors that facilitate stabilisation of the pulmonary disease.[43]

Otolaryngology treatment

Secretory otitis media (SOM) appears in all patients, especially in children. It is manifested by hearing loss, with a consequent delay in language acquisition, and by repeated acute otitis media. In many patients, placement of transtympanic drains is followed by a persistent mucoid otorrhea as well as a significant increase in tympanic perforations.[44] Surgical intervention should be avoided wherever possible, but recurrent acute otitis media can make it inevitable. Hearing aids may be needed for the treatment of hearing loss. Ear problems experience a clear improvement in adults.[45]

Chronic mucoid, mucopurulent rhinorrhea is treated with frequent nasal clearing and saline serum washes.[46] Sinus exacerbations are scarce; they are treated with systemic antibiotics. Surgical treatment is rarely required and when it is employed, the results are usually poor. Nasal polyposis is infrequent in PCD.

Infertility treatment

Infertility is the rule in men with PCD, who must be informed and should be offered the opportunity of a semen analysis. In vitro fertilisation techniques, especially intracytoplasmic sperm injection, are useful; however, they should be preceded by the appropriate genetic counselling because this is a hereditary disease. In women, in addition to genetic counselling, close pregnancy monitoring is required due to the increased possibility of ectopic pregnancy.

All patients with PCD, especially children, should be encouraged to lead a normal life and carry out the activities appropriate to their age since, with proper treatment, they will enjoy a long, active life.

Other ciliopathies

Four types of cilia related with diseases have been identified in the human body[2]: 1) motile cilia in 9+2 structure

(respiratory, Ependyma, fallopian tube, testicular efferent duct and sperm cell flagellum cilia) whose dysfunction generates PCD; 2) motile 9+0 cilia (embryonic nodal cilia), which are responsible for determining the laterality of the various internal organs; 3) immotile 9+2 cilia (kinocilia in the ciliated cells of the inner ear), involved in auditory and balance functions; and 4) immotile 9+0 cilia (renal monocilia and retinal photoreceptor cilia) involved in homeostatic and visual functions. In future, more ciliary functions and more diseases related to them will probably be described, since most of the polarised cells of the organism have these structures and they have roles in development, morphogenesis and homeostasis.[47] Diseases related to cilia-ciliopathies can affect many organs simultaneously. This is the case in PCD, in which there are infertility, laterality disorders *(situs inversus)* or hydrocephalus in addition to respiratory infections, as has been commented in the preceding section. Alternatively, they can be expressed in a single organ preferentially, as occurs in some patients with renal cysts, ophthalmic disorders, anosmia or cochleovestibular alterations, which are only rarely associated with PCD.[4]

Renal ciliopathies

Glomerular and tubular cells produce a single cilium with a 9+0 structure, which projects into the lumen of the tubule and acts as a mechanoreceptor or chemoreceptor.[5] The protein products of genes mutated in polycystic kidney disease (polycystin 1, polycystin 2 and fibrocystin) and nephronophthisis (nephrocystin 1 and inversin) have been found in this renal cilium.[48,49] The mechanism by which these diseases occur concerns calcium-mediated cell polarisation: normally, cilia generate an influx of extracellular calcium that culminates in cell hyperpolarisation, but this signal is abolished in the absence of cilia or if they function incorrectly,[50] although other pathogenic mechanisms also related to the cilium may be implicated.[5]

Ocular ciliopathies

The association PCD-keratoconus has been reported sporadically. It is believed to be related to the monocilia of the corneal endothelium and their role in maintaining corneal integrity.[51]

However, undoubtedly the most significant ocular ciliopathy is retinitis pigmentosa (RP). Rods and cones are modified neurons that act as photoreceptors. Both have an internal proximal part and a distal external one in relation to the cell, which are connected by a 9+0 cilium. The photoreceptor discs and visual pigments are synthesised exclusively in the inner part and then transported through the cilium, by the action of the intraflagellar transport protein (ITP), to the external segment.[52] There is continuous, active replacement between the two segments. ITP failure results in an accumulation of substances in the inner segment and a deficit in the external that leads to the death of the photoreceptor cell.[53] The degeneration of photoreceptors is characteristic of RP, clinically translating into progressive blindness. Recently, the proteins that cause RP types 1 and 3 (RP1 and RPGR, respectively) have been identified in photoreceptor-connecting cilium.[54,55] RP can appear combined with sensorineural hearing loss, in which case it is known as Usher syndrome. In type 1B Usher syndrome, we find a mutation in the myosin VIIa gene, which is located in the photoreceptor-connecting cilium and is involved in opsin transport from the inner to the outer segment of the photoreceptor. RP is also a part of Bardet-Biedl sydrome.[5]

Ciliopathies and olfaction

Olfactory receptor cells are bipolar neurons that have a tuft of between 8 and 30 cilia of structure 9+2, but without dynein and, therefore, immotile. Olfactory receptors are located in the cell membrane of the apical segment of the olfactory cilia[1] and act as a calcium-dependent mechanism that transforms into an electrical signal.[56] Patients with PCD usually suffer hyposmia, but probably as a result of chronic rhinosinusitis. Only patients with ciliary aplasia are anosmic.[1] Moreover, aplasia of the olfactory cilia is common in congenital anosmia, although not accompanied by PCD.[57]

Ciliopathies and the internal ear

The sensory cells of the inner ear characteristically have highly specialised mechanoreceptors on their surface. In vertebrates, these receptors consist of a single kinocilium with a 9+2 structure and numerous microvilli or stereocilia, ordered depending on the kinocilium.[1,5] It has been shown that the basal body of the kinocilium is needed to establish an orderly bundle of stereocilia that functions as an efficient mechanoreceptor.[58] Other evidence is offered by the Usher syndrome and by deaf mutant mice that have lost the characteristic order of the inner ear receptors.[59]

Cilia, cell division and oncogenesis

The role of cilia in cell division has also implicated these organelles in oncogenesis.[2] Most cells of vertebrates generate a cilium in the G0-G1 phase of the cell cycle. The centriole from a prior cell division can act as the basal body on which a cilium is assembled in a cell in quiescent state, and the centriole arising from the disassembly of cilia from the G1 or previous phase or from the S phase can act as microtubule organising centres essential for spindle formation in cellular division.[60] Primary cilia are thus actively assembled and disassembled during the cell cycle. A deregulation of this process may be crucial in oncogenesis, for example, as a result of centrosome amplification and the consequent genomic instability observed in many types of cancer.[2]

Conclusions

Cilia are highly complex organelles involved in numerous biological functions, from cell division to sperm transport, to mucociliary clearance of the airways. Their dysfunction generates numerous disorders that are known as ciliopathies, and which range from primary ciliary dyskinesia to oncogenesis, although their number is expected to increase

in the future. Otolaryngologists, due to the accessibility of ciliated samples in the nasal fossae and because many ciliopathies are manifested in their field, have a key role, both clinically and in research, in the development of of ciliopathy knowledge.

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