RETINITIS PIGMENTOSA AND BRONCHIECTASIS: A CASE REPORT ON A RARE ASSOCIATION SUGGESTIVE OF A COMMON UNDERLYING PRIMARY CILIARY DYSKINESIA (PCD)

DE BRAUWER P.J., BLAISE P.,* HERMANS G.,***
*BONIVER V., *** BARTSCH P., **** RAKIC J.M.**

SUMMARY

We describe a case of retinitis pigmentosa, associated with bronchiectasis, as the first sign of primary ciliary dyskinesia (PCD). Only a few cases were described in the literature and the association of both diseases is not obvious at first sight, although a common ciliary dysfunction of both respiratory epithelium and photoreceptors of the retina seems to be the common factor. It is important to recognize the association and to question patients with retinitis pigmentosa about their respiratory functions, because an early diagnosis of PCD can prevent recurrent infections and development of bronchiectasis with daily physiotherapy.

RÉSUMÉ

Nous rapportons un cas de rétinite pigmentaire, associé à des bronchectasies, comme premier signe d'une dyskinesie ciliaire primaire (DCP). Quelques cas seulement ont déjà été décrits dans la literature et l'association des deux maladies n'est pas évidente à première vue. Le dysfonctionnement ciliaire commun des photorécepteurs rétiniens et de l'épithélium respiratoire semble être à la base de l'association des deux maladies. Il est important de reconnaître cette association et d'interroger les patients, atteints de rétinite pigmentaire sur leur function respiratoire, car un diagnostic précoce de DCP pourrait prévenir des infections récurrentes et le développement des bronchiectasies par physiothérapie journalière.

KEY WORDS

Retinitis pigmentosa,bronchiectasis,primary ciliary dyskinesia, PCD

MOTS-CLES

Rétinite pigmenaire ,bronchiectasies,dyskinésie ciliaire primaire, DCP

.....

* *Department of Ophthalmology, CHU Liège, Belgium*
** *Department of Anatomopathology, CHU Liège, Belgium*
*** *Department of Otorhinolaryngology, CHU Liège, Belgium*
**** *Department of Pneumology, CHU Liège, Belgium*

Submitted: 09-11-09
Accepted: 01-03-10

INTRODUCTION

Bronchiectasis is a chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal permanent dilatation of these airways. They can be the result of various conditions including primary ciliary dyskinesia (PCD), a disease characterised by ciliary dysfunction, generally (but not always) associated to structural abnormalities of the cilia.

The association between PCD and retinitis pigmentosa (RP) is not obvious at first sight. However, some rare cases have already been reported (5,11,12,13). Some authors have already suggested a possible X-linked inheritance of both disorders (11,12,13). We report the case of a patient suffering from retinitis pigmentosa and bronchiectasis as the first apparent symptom of PCD.

CASE REPORT

A 40 year-old man was addressed to us for a multidisciplinary advice about his bronchiectasis and retinitis pigmentosa. His retinitis pigmentosa, existing since childhood, was already avanced. Best-corrected visual acuity was relatively conserved at 7/10 in both eyes. The refraction with cycloplegics was -2(-0.5)90°D for the right eye and -2.5 spheric D in the left eye. The visual fields were reduced to a small central area of 20 degrees and a crescent-shaped area in infero-temporal field. Funduscopy showed the classical picture of osteoblasts in the periphery and mid-periphery of the retina (*Figure 1*). The ERG was flat, both in scotopic and photopic circumstances. (*Figure 2*)

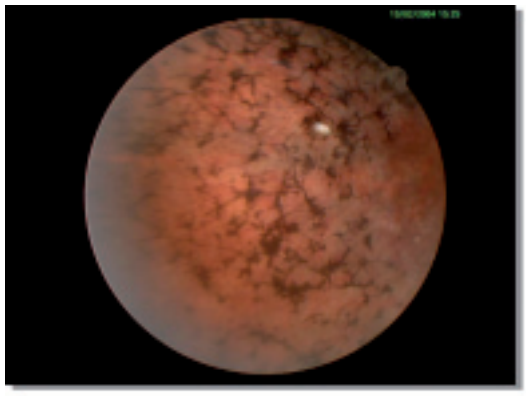

Fig. 1: fundus showing the classical peripheral and mid-peripheral osteoblasts.

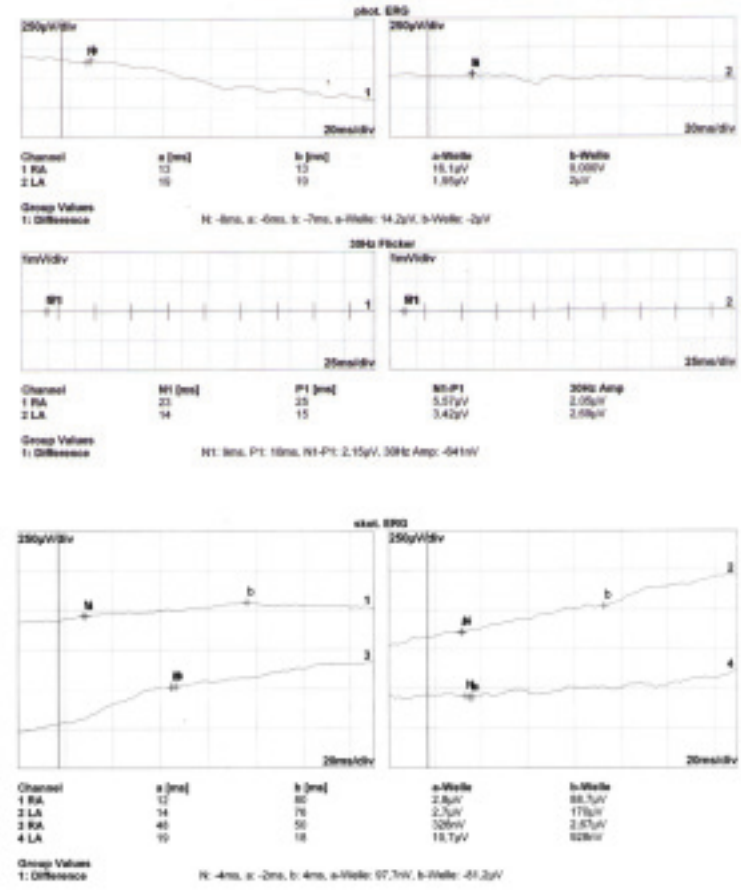

Fig. 2a and 2b: ERG of the patient showing no respons in photopic(a) and scotopic(b) circumstances.

His first respiratory symptoms appeared during the third decade and presented as recurrent respiratory infections and chronic sinusitis. High resolution computed tomography (HRCT) showed diffuse bronchiectasis (*Figure 3a and 3b*). The bronchic biopsy showed that the bronchic cilia were considerably diminished in number, disoriented, but there was still a normal histologic structure of these cilia (*Figure 4a and 4b*).
Unfortunately, ciliary beat frequency was not measured. Serum protein electrophoresis did not show alpha1-antitrypsin deficiency whereas the pilocarpine iontophoresis (sweat test) was normal. An immunodeficiency state or bronchopulmonary aspergillosis could not be demonstrated. The audiometry did not reveal any defect.

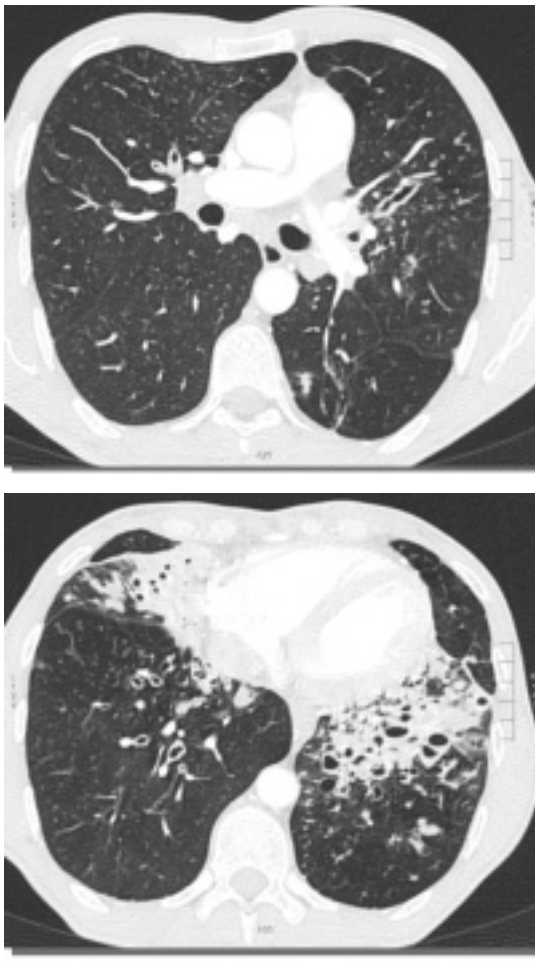

Fig. 3a and 3b: showing severe bronchectasis, predominantly in the left pulmonary lobe (see arrows) of the patient. The impaired mucociliairy clearance wa responsible for recurrent infections (arrowheads in fig 3b).

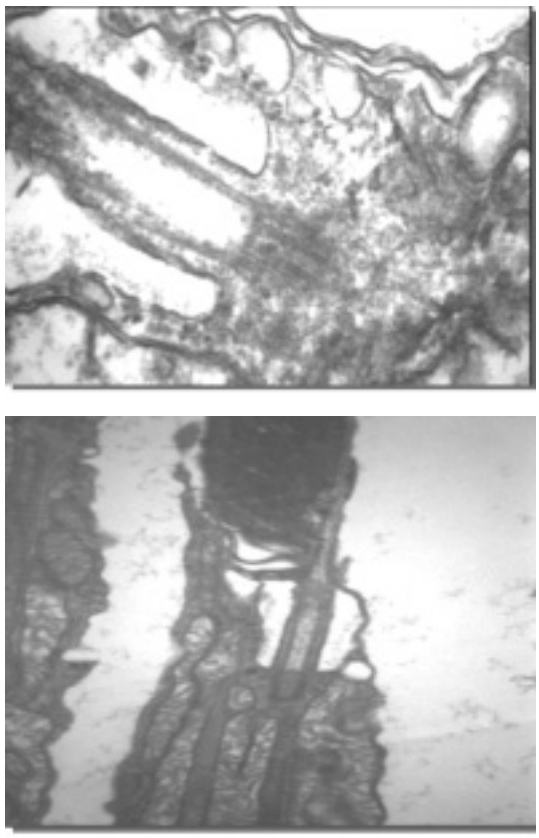

Fig. 4a and 4b: electron microscopy showing preserved normal structure of the bronchic cilium in our patient.

This patient was an only child and had three daughters. One of them who was 11 years-old and the oldest of the three, also suffers from retinitis pigmentosa with reduction of visual functions, osteoblasts in the peripheral retina and reduced amplitudes on ERG. Her best- corrected visual acuity was 8/10 in both eyes with a refraction of -1,5 (-0,25)90°D for the right eye and -1(-0.5) 90°D for the left eye with cycloplegia. She did not present currently any respiratory disturbance. The two youngest daughters, 5 and 8 years old, were also screened for RP and PCD, but all findings were negative. The mother of the patient died at age of 30 and did not present any visual problems. The father did not present any retinal pathology either until

now. Other members of the family have not been investigated regarding PCD or RP.
We hypothesized tha our patient has an X-linked dominant form of retinitis pigmentosa with a milder expression of XLRP in the daughters, only visible in the oldest until now. The DNA analysis of RPGR has been planned in a near future.

DISCUSSION

Cilia and cilia-like structures are present in various human organs and tissues. Classically, cilia are divided into two main types, according to the geometry of microtubules within the ciliary axonemes: (9+2) or motile cilia composed of nine microtubule doublets, surrounding a central pair, and (9+0) or primary and nonmotile cilia composed of nine microtubule doublets without a central pair (*figure* 5). The primary cilia also lack dynein arms that are found on motile cilia (1,6).
The function of the (9+2) cilia is to move fluid across an epithelium, whereas the (9+0) cilia act as antennae, sensing the external environment (6).
The outer segments of retinal photoreceptor rods and cones are formed from primary (9+0) cilia. In the rods and cones of the retina, photoreceptor discs and visual pigments are synthesised in the inner segment and transported to the distal outer segment through a narrow (9+0) or primary cilium. Disruption of this process leads to retinitis pigmentosa (1,6). Other locations of primary cilia are the principal cells of the nephron, the hair cells of the inner ear and the olfactory sensory neuron. Disruption of these cilia can lead to cystic disease of the kidney, hearing loss and anosmia (1,6). In some ciliopathies with RP, there is therefore an association of retinal degeneration with other systemic abnormalities mostly of the inner ear and the kidney leading to different syndromes such as Usher, Bardet-Biedl, Alström, Nephronophthisis and others (see below).

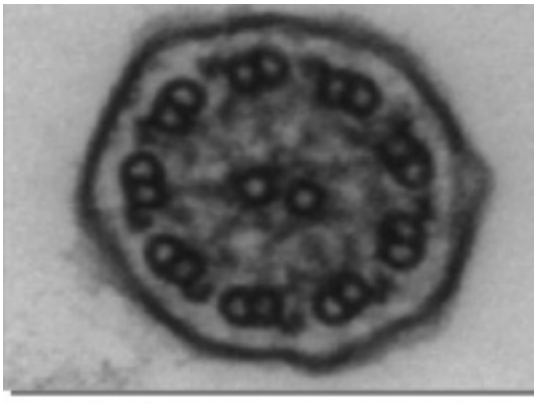

Fig. 5: electron microscopy of a normal ciliairy ultrastructure, showing central microtubules (little black arrow), inner-and outer dynein arms (big white arrows) and the radial spokes (long black arrow)

Disruption of the 9+2 (motile) cilia, which move mucus across respiratory epithelia, leads to rhinitis, sinusitis and bronchiectasis (6). Other motile cilia are present in the epithelium of the oviduct and the efferent ductules of the testis, in the oviduct and the ependymal lining of the brain (6). Disruption of these cilia is associated with infertility or other reproductive system disorders (ectopic pregnancy, due to disorientation of the cilia in the ovaria) and hydrocephalus (1,6).Therefore, patients with PCD mostly present also with male infertility ,with spermatozoa that are immotile or have reduced motility and sometimes with hydrocephalus. In several cases, a situs – inversus (Kartagener syndrome) is also present (1,3,11) In our patient, none of these associated features were found. However, the present association of PCD and RP in our case is not classic at all and has only been described in some few cases (5,11,12,13).

In conclusion, having not exactly the same structure and the same function, defect in ciliary ultrastructure does not generally affect both respiratory epithelium and photoreceptors, and most cases of primary ciliary dyskinesia have no retinitis pigmentosa and inversely.

In the last years, the localisation of numerous proteins implicated in retinal degenerations relate to the retinal cilium has incited a tremendous amount of research. While the functions of many of the proteins located in the cilia are poorly understood, disruption of the function of these proteins may result in a wide variety of phenotypes ranging from isolated retinitis pigmentosa to more pleiotropic phenotypes with

different systemic disorders and giving rise to several syndromes, all associated with a retinal ciliopathy(1). The most important are Usher syndrome, Bardet-Biedl syndrome and Alström.

Usher syndrome is an autosomal recessive disorder, characterized by bilateral deafness and RP and is considered as being the most common cause of combined blindness and deafness (1,4,8,15). Here, apart from the retinal ciliopathy, the cilia of the cochlea and vestibule are also affected (1,4,8). These ciliary abnormalities were demonstrated both on nasal biopsy in living patient and on retinas postmortem (4) The retinal findings in Usher syndrome demonstrate a remarkable degree of variability. Most common characteristics include peripheral bone spicule formation associated with arteriolar narrowing. Pachy atrophic changes or yellow to grey-white flecks as in a retinitis punctata albescens have also been described (1,4). It is classified into three main categories. Type I is characterised by early childhood onset of RP associated with profound congenital deafness and absent vestibular function. Type II is characterised by a later onset of RP, often in the late second decade of life, with moderate to severe congenital deafness but normal vestibular function. In type III, the onset of vision loss is variable, while often both vision and hearing are initially normal and progressively deteriorate over decades (1,4,8,10). Another important retinal ciliopathy is the Bardet-Biedl (BBS) syndrome. This is an autosomal recessive disorder that affects numerous tissues and often, but not allways displays RP. The diagnosis is based on the presence of four to six primary clinical features: rod-cone dystrophy, postaxiale polydactyly, mental retardation, renal abnormalities and hypogonadism. The presence of RP often begins in childhood in these patients and is the most common clinical finding in BBS patients, often present in over 90% of the patients with BBS (1,9).
Aldström syndrome is an autosomal recessive disorder that shares many similarities with BBS, such as RP, obesity, diabetes mellitus, and renal failure. However, BBS features of polydactyly, hypogonadism and neurological impairments are not features of Alström syndrome. The RP in Alström syndrome is often severe and of early onset, associated with nystagmus. While peripheral bone spicule formation can occur, an atrophic maculopathy often appears early and is considered a universal finding by the second decade of life (14).

Other ciliopathies that present an association of RP with different systemic disorders are Nephronophthisis (RP and chronic cystic disease of the kidney), Edwards-Sethi syndrome (RP and neurosensory hearing loss, diabetes mellitus, hypogonadism, neurologic impairment), Ellis-van Creveld (RP, polydactyly and chondrodysplasia) and Merckel-Gruber syndrome (RP and cystic kidney disease, hypogonadism, cardiac abnormalities, occipital encephalocele) (1).

However, not all patients with retinal ciliopathies can be attributed to an already existing syndrome.

In 2004, Witters et all described a case of progressive cone dystrophy with sensorineural hearing loss, upper respiratory tract infection and male infertility, and also suggested a possible common ciliopathy, not corresponding to already described entities (15). Similarly, in our case, the association of retinitis pigmentosa and PCD is not very well understood, especially because it concerns a mixed ciliopathy of motile and immotile cilia. This combination has only been described in a few cases so far (Moor et al. 2006, Krawczynski et al. 2004, Dry et al 1999,Van Dorp et al. 1992) (5,11,12,13). Krawzinski and Moor both described this association and found that an X-linked inheritance of both disorders where a mutation on the RPGR gene is the presumable explication of this rare disorder (11,12,13).

In contrast to the normal autosomal recessive form of PCD, the putative X-gene neither interferes with lateralisation nor affect fertility which explains the clinical findings of our patient(no signs of male infertility or situs inversus) (11).

In our patient, the low number of respiratory cilia, their disorientation, and the absence of any other possible cause of chronic sinusitis and bronchiectasis and recurrent pulmonary infections plaid for an abnormality of ciliary function. Absence of ciliary ultrastructural defect, as in our case, may not exclude the diagnosis of PCD, numerous cases of PCD with normal ciliary structure having already been reported (3,12,13).

CONCLUSION

In conclusion, this case is one of the very few that describe a combination of RP and PCD. Understanding the underlying concept of ciliopathies leads the ophthalmologist to have a high degree of suspicion that a systemic finding may be present in a patient with retinitis pigmentosa. As such it becomes imperative to look for associated disorders of the cilia: neurosensory hearing loss, anosmia, developmental delay, mental retardation, infertility and other reproductive system disorders, obesity, cystic kidney disease and sometimes respiratory disease. In our patient, the interrogation about his respiratory functions, lead to the diagnosis of PCD. An early diagnosis of PCD is essential to prevent recurrent infections and development of bronchiectasis by daily physiotherapy and antibiotic treatment as soon as the first sign of deterioration in the lung function appears (3). Inversly, a patient with PCD should have a carefull ophthalmologic examination for signs suggestive of RP.

REFERENCES

(1) ADAMS N.A., AWADEIN A.HASSANAIN S.T.- – The retinal ciliopathies.Ophthalmic Genetics 2007, 28:113-125.

(2) BARRONG SD, CHAITIN M.H, FLIESLER S.J., POSSIN D.E., JACOBSON S.G., – Ultrastructure of connecting cilia in different forms of retinitis pigmentosa. Arch Ophthalmol. 1992; 110:706-10.

(3) BUSH A., COLE P., HARIRI M., MACKAY I., PHILLIPS G., O'CALLAGHAN C., WILSON R., WARNER JO. – Primary ciliary dyskinesia: diagnosis and standards of care. Eur Respir J. 1998; 12:982-8.

(4) BONNEAU D. R. F., KREMER C., KLOSSEK J.M., KAPLAN J., PATTE F. – Usher syndrome type I associated with bronchiectasis and immotile nasal cilia in two brothers. J Med Genet. 1993; 30:253-4.

(5) DORP VAN D.B., WRIGHT A. – A family with RP3 type of retinitis pigmentosa: an association with ciliary abnormalies

(6) ELEY L., YATES L.M.,GOODSHIP J.A. – Cilia and disease. Curr Opin Genet Dev, 2005; 15:308-314.

(7) FOX B., BULL T.B., ARDEN G.B. – Variations in the ultrastructure of human nasal cilia including abnormalities found in retinitis pigmentosa. J Clin Pathol. 1980; 33:327-35.

(8) GORLIN R.J., TILSNER T.J. – Usher syndrome Type III. Arch Otolaryngol. 1979; 105:353-354

(9) IANNACONE A., DE PROPIS G. – The ocular phenotype of the Bardet-biedl syndrome. Comparison to non syndromic retinitis pigmentosa. Ophthalmic Genet. 1997; 18:13-26

(10) KREMER H., VAN WIJK E. – Usher syndrome; molecular links of pathogenesis,proteins and pathways. Hum Mol Genet. 2006; 15:262-270

(11) KRAWCZYNSKI M.R., DMENSKA H., WITT M. – Apparent X-linked primary ciliary dyskinesia associated with retinitis pigmentosa and a hearing loss. J Appl Genet. 2004; 45:107-10.

(12) KRAWCZYNSKI M.R., WITT M. – PCD and RP:X-Linked Inheritance of both disorders? Pediatric Pulmonology 2004; 38:88-89.

(13) MOOR A., ESCUDIER E., ROGER G. – RPGR is mutated in patients with a complex X-linked phenotype combining primary ciliary dyskinesia and retinitis pigmentosa. J.MedGenet 2006; 43:326-333.

(14) RUSSEL-Eggit I., CLAYTON P. – Alström syndrome. Ophthalmology. 1998; 105:1274-1280

(15) WITTERS J.A., DE JAEYTIJD J., LEYS M. – Progressive cone dystrophy and sensorineural hearing loss.

.....

Correspondence and reprints:
Dr. P. J. DE BRAUWER
Dept. Of Ophthalmology
CHU Sart-Tilman,
Domaine universitaire, batiment B 35
B-4000 Liège
Email:peterjan_debrauwer@hotmail.com