

Case report

**Apparent X-linked primary ciliary dyskinesia associated with retinitis pigmentosa and a hearing loss**

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**Abstract.** Three brothers, one 10-year-old and a pair of 14-year-old dizygotic twins – expressed the classical, early-onset retinitis pigmentosa (RP) with typical ophthalmoscopic findings, night blindness, visual field constricted to 10° and flat ERG response. All three brothers were also diagnosed with primary ciliary dyskinesia (PCD) and had recurrent respiratory infections, chronic sinusitis and bronchiectasis. In all of them, resection of the middle lobe of the right lung was performed. A similar clinical picture of coexisting RP and PCD was noted in the brother of the probands' mother. All probands displayed *situs solitus*. Consistent with the X-linked mode of RP inheritance, there were also three obligatory female carriers of the disorder in this family: the mother of the affected boys, her mother and a daughter of her brother. In all of them, retinitis pigmentosa “*sine pigmento*” was found with milder but clinically significant symptoms (mild night blindness, visual field constricted to 30°, and scotopic and photopic ERG responses reduced to 30-60%). No extraocular symptoms were detected in any of the heterozygous female carriers. This family presents an example of two rare phenomena: X-linked dominant retinitis pigmentosa (with milder expression in females) and a rare combination of RP with recurrent respiratory infections due to PCD.

**Key words:** hearing loss, primary ciliary dyskinesia, retinitis pigmentosa.

Primary ciliary dyskinesia (PCD) (MIM #244400), formerly known as immotile cilia syndrome (ICS), is the only known human disorder caused by a primary dys-

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function of the ciliary apparatus. The frequency of PCD is estimated at 1/12,500 live births. Inheritance in most cases appears to be via a single major locus with an autosomal recessive mode of transmission, although pedigrees showing autosomal dominant or X-linked modes of inheritance have also been reported (NARAYAN et al. 1994).

Clinically PCD is recognized on the basis of a classical triad of symptoms: *situs inversus* (in case of the Kartagener syndrome, a subtype of PCD), bronchiectasis, and chronic sinusitis. In practice, PCD often remains unrecognized, hence underdiagnosed and poorly treated. The following groups of patients require in-depth screening towards PCD: newborns with sital congenital anomalies; children with treatment-resistant asthma; allergic subjects; individuals with rhinosinusitis and/or chronic severe otitis media; children/adults with a chronic respiratory infection, either with or without bronchiectasis, particularly those producing purulent sputum; subfertile/infertile males and females, particularly when chronic respiratory infections coexist. In differential diagnosis, PCD should be distinguished from cystic fibrosis, allergy, immune deficiency, Young's syndrome, and asplenia/polysplenia (SHIDLOW 1994).

Chronic rhino sinusitis is one of the most frequent clinical findings in PAD patients, combining nasal congestion and discharge of a mostly thin nasal secretion with chronic or recurrent involvement of mainly maxillary and ethmoid paranasal sinuses; frontal sinuses frequently fail to develop and the mastoid cells display poor aeration (MYGIND et al. 1983). The radiological signs of sinusitis can be recognized as early as at 6 months of age. Hyponasal speech is very common, but anosmia is an occasional feature. Chronic and severe secretory otitis media, frequently with continuous, long-lasting and offensive discharge from the ears after insertion of the tympanostomy tube, is almost always present in childhood, with occasional eruptions of the acute form of the disease. Sclerosis of the mastoid/middle ear region is often present on radiological examination. A moderate conductive hearing loss between 10 and 40 dB has been documented (PEDERSEN, MYGIND 1983). The sense of balance is normally unaffected. Anyway, PCD patients usually grow out of most of these symptoms at puberty.

Here we present a Caucasian family of Polish origin with an apparently X-linked inheritance of coexisting retinitis pigmentosa (RP) and primary ciliary dyskinesia (PCD). Hearing loss coexists with both disorders.

In the family presented in this report, three brothers – one 10-year-old and a pair of 14-year-old dizygotic twins – expressed the classical, early-onset retinitis pigmentosa (RP) with typical ophthalmoscopic findings, night blindness, visual field constricted to 10, and flat ERG response (Figure 1). In parallel all three brothers were diagnosed with primary ciliary dyskinesia (PCD) resulting in recurrent respiratory infections, chronic sinusitis and bronchiectasis. The boys suffered from chronic productive cough and rhinitis from early childhood. Sweat chloride, IgE and humoral and cellular immunity were normal. On CT scan, frontal, maxillary, and partly also ethmoid sinuses were consistently shadowed. Lung

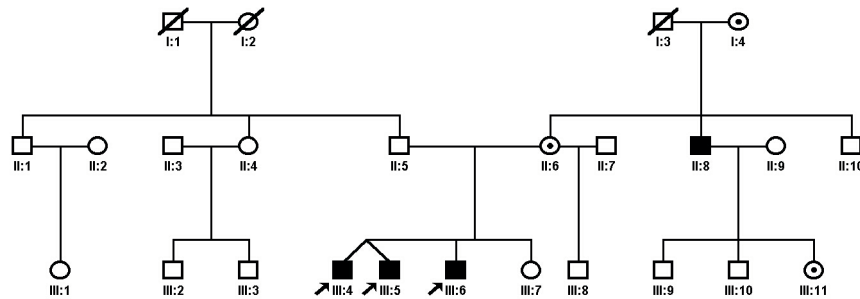


Figure 1. The pedigree of the studied family. Arrows point to family members affected with both PCD and RP

function revealed airway obstruction. Periodically *Haemophilus influenzae* and methicillin-sensitive *Staphylococcus aureus* were cultured from the patients' sputum. In all of them, resection of the middle lobe of the right lung was performed because of bronchiectasis. Despite evident similarity of clinical symptoms, the youngest brother displayed the most severe course of respiratory infections. Under the light microscope, investigation of bronchial scrapings revealed short and immotile cilia. A very similar clinical picture of coexisting retinitis pigmentosa and primary ciliary dyskinesia was noted in the brother of the probands' mother. All probands displayed *situs solitus*.

Consistent with the X-linked mode of RP inheritance, there were also three obligatory female carriers of the disorder in this family: the mother of the affected boys, her mother and a daughter of her brother. In all of them, retinitis pigmentosa "sine pigmento" was found with milder but clinically significant symptoms (mild night blindness, visual field constricted to 30°, and scotopic and photopic ERG responses reduced to 30-60%). No extraocular symptoms were detected in any of the heterozygous female carriers. All four affected males presented a slowly progressive hearing loss.

The family described above presents an example of two rare phenomena: X-linked dominant retinitis pigmentosa (with milder expression in females, as described by SOUIED et al. 1997) with recurrent respiratory infections due to primary ciliary dyskinesia. Only a few cases of such a combination have been described so far (DRY et al. 1999, Van DORP et al. 1992, ZITO et al. 2001). This might imply the presence of one of the PCD loci within the X-chromosome, although no X chromosome-linked candidate loci have been described so far (for a review see WITT 2004).

The outer segments of retinal photoreceptor rods and cones are formed from primary cilia (PAZOUR, ROSENBAUM 2002). It has been recently shown that transport defects within these organelles can be a major cause of retinal degeneration leading to retinitis pigmentosa (SUNG, TAI 2000). We have already described an-

other, seven-generation family, with apparently X-linked inheritance of coexisting retinitis pigmentosa and primary ciliary dyskinesia (KRAWCZYŃSKI, WITT, in press).

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