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Diagnostic approach to primary ciliary dyskinesia: a review

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Abstract Primary ciliary dyskinesia (PCD) is a heterogeneous disease with impaired mucociliary transport leading to respiratory disorders, hearing impairment and male infertility. PCD can be diagnosed by clinical features together with functional and structural analysis of the cilia. To prevent bronchiectasis with a marked reduction in quality of life, early diagnosis is essential. The rarity of PCD and the costs of ultrastructural analysis of cilia require a rational diagnostic concept. We therefore reviewed the literature and compared clinical manifestations as well as functional and structural analyses of the cilia in 28 patients (23 children, 5 adults) investigated between 1990 and 1998. All were thoroughly examined for other possible diseases before biopsy, and ten patients (35.7%; eight children, two adults) were diagnosed as having PCD. From the literature review and our findings we conclude that ciliary investigation is indicated (a) in patients who remain suspected of having PCD despite thorough clinical examination and exclusion of other disorders such as cystic fibrosis, allergy, immunologic disorders and α_1-antitrypsin deficiency; (b) in patients with situs inversus suffering from chronic and/or recurrent airway infections; and (c) in patients with neonatal respiratory distress syndrome of ''unknown'' cause (i.e. after exclusion of hyaline membrane disease, aspiration syndromes, neonatal pneumonia, and pneumothorax as well as cardiovascular and metabolic diseases).

Conclusion The combination of extensive clinical examination with functional and ultrastructural analysis of the cilia results in a high degree of accuracy in diagnosing PCD.

Key words Ciliary dyskinesia · Respiratory tract infections · Diagnostics · Ciliary ultrastructure · Ciliary movement

Abbreviations *PCD* primary ciliary dyskinesia · *CBF* ciliary beat frequency

Introduction

Primary ciliary dyskinesia (PCD) is an autosomal genetic disorder characterized by impaired mucociliary transport. It has been described as a heterogeneous disorder clinically manifested by chronic respiratory tract infections beginning in early childhood and leading to chronic bronchitis and/or bronchiectasis, chronic rhinosinusitis and otitis media (e.g. otitis media with effusion), as well as by situs inversus and male infertility in a high percentage of cases [1, 18, 21]. Bronchiectasis occurs in adults and is the most important factor for impaired quality of life. The incidence of each single

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manifestation differs from one patient to another, even among siblings.

PCD is of particular interest to the otorhinolaryngologist as many of the clinical manifestations fall into this field. The association of situs inversus with sinusitis and bronchiectasis was first described by Siewert [30] in 1904 and in more detail by Kartagener [15] in 1933, and was subsequently named after him. In 1975 Afzelius et al. [1] and Camner et al. [2] suggested that ciliary immotility is the underlying cause of Kartagener's syndrome and in 1977 Eliasson et al. [8] proposed the term immotile cilia syndrome for all congenital ciliary alterations that lead to defective mucociliary clearance. However, in vivo studies showed that immotility was not absolute because ciliary movement occurred in a number of patients [22, 26, 28]. But since this ciliary movement did not lead to effective mucociliary transport the name was changed to dyskinetic cilia syndrome [25]. Sleigh [31] introduced the name "primary ciliary dyskinesia" for the autosomal recessive inherited syndrome and "secondary ciliary dyskinesia" for acquired ultrastructural abnormalities in cilia when these are caused by respiratory infections, mechanical injury of the mucosa, or locally applied drugs.

Although this congenital autosomal recessive disease has been known for many years, diagnostic criteria and clinical presentation are sometimes confusing. The rather unspecific clinical signs of PCD can lead to an overestimation and to unnecessary examination. However, lack of awareness of this disease may lead to delayed diagnosis, which will have consequences for the long-term result (bronchiectasis). In a review article Jorissen and Cassiman [14] summarized the different structural ciliary abnormalities and pointed out the contradictions, lack of knowledge and confusing data on primary and secondary ciliary dyskinesia.

To elaborate a reasonable diagnostic concept for PCD we reviewed the literature and compared it with our own experience of clinical and ultrastructural material collected between July 1990 and May 1998. During this period we diagnosed in 10 patients as having PCD. The clinical examinations were performed at the Childrens Hospital and the ENT Department of the University Hospital of Zürich and the function and ultrastructure of mucosal biopsy material were analyzed in the Morphology Laboratory of the ENT Department.

Literature review

Clinical features

Because the clinical features of PCD can mimic other diseases (e.g. cystic fibrosis, allergy or immunologic disorders) there is some risk that the patients' symptoms may be either overestimated or underrated. To prevent an increase in health-care costs it is necessary to select patients carefully, using screening methods to exclude other diseases with a higher incidence before investigating ciliary function [35]. Thus, chronic rhinosinusitis is a rather unspecific manifestation unless it is present immediately after birth, with consecutive impaired feeding of the infant, or if it occurs in combination with other signs such as situs inversus. Kroon et al. [16] pointed out that situs inversus can be found in 50% of PCD patients, whereas 23% of all patients with situs inversus have PCD. In 1997 El-Sayed et al. [9] suggested that otitis media with effusion and conductive hearing loss should be considered as common sequelae in PCD patients. It was Van der Baan [37] who found a discrepancy between poor subjective middle ear complaints and objective middle ear performance in adult PCD patients. The coincidence of neonatal respiratory distress of unclear cause [23] with PCD has been described in only a few cases [17, 39]. The clinical picture is very similar to that of wet lung disease [5], also known as transient tachypnea of the newborn. Although bronchiectasis, nasal polyps and in particular the combination of both are considered highly indicative of PCD they both usually occur not earlier than the second decade of life.

Biopsy

Some investigators prefer to take ciliated cells by brush cytology [7] whereas others strongly recommend taking a biopsy of intact ciliary epithelium attached to the basement membrane [13]. The most reliable functional results were obtained from bronchial biopsies [35]. It is also of importance to investigate at least two different mucosal sites because some of the findings in secondary ciliary dyskinesia resemble those characteristic of primary ciliary dyskinesia. The characteristic features of secondary non-inherited ciliary dyskinesia, however, are focal and reversible [14]. The patients should be free of respiratory tract infections before mucosal biopsy, because many etiologic factors for secondary ciliary abnormalities exist that are mainly of an infectious or inflammatory nature [3, 4, 19]. Patients should be advised not to use any topical drugs (for bronchi or nose) before biopsy.

Ciliary beat frequency and quality of ciliary movement

Analysis of ciliary wave form in PCD patients showed either no motility or impaired movement (fast or slow oscillation) which did not lead to mucociliary transport. Ciliary beat frequency (CBF) can be measured with phase-contrast microscopy. The CBF values from the different sites are very similar but vary greatly between individuals. We have shown in an earlier report that the inter-subject CBF variation for each specific site was much greater than the inter-site CBF variation in any one patient [11]. Although ultrastructural analysis of cilia is important for the diagnosis of PCD, ciliary motility is a prerequisite for mucociliary transport [7].

Structural ciliary defects

The most common ultrastructural features, and the sine qua non for PCD, are defects in outer and inner dynein arms, as has been described by several authors [10, 20, 34, 38]. In a few cases of PCD, radial spoke defects and translocation can be found [32, 33] which are ultrastructural features described as characteristic of PCD [12, 24]. Random ciliary orientation changes [6, 29] in the number of peripheral microtubules as well as a large number of compound cilia were found not only in patients with PCD but also in patients with chronic respiratory disease not due to PCD. Rautiainen et al. [24] described random ciliary orientation as being more prominent in PCD patients than in other patients with chronic respiratory disease.

Our experience

All patients referred for ciliary investigation first underwent careful selection to exclude other possible underlying disorders such as clinically presented allergy, cystic fibrosis or α_1-antitrypsin deficiency. Clinical examinations and tests on 28 patients seen between July 1990 and May 1998 did not allow a clear diagnosis. These patients were therefore selected for mucosal biopsies, undertaken in the Morphology Laboratory of the ENT Department of the University Hospital, Zürich, to analyze the function and ultrastructure of the cilia. Ten of these patients were found to have PCD, which indicates that this selection produced a high rate (35%) with PCD. In these ten PCD patients the occurrence of clinical features was comparable with the features reported in the literature (see Table 1). We therefore recommend that special attention should be paid to patients suffering from a combination of suspicious clinical features (e.g. situs inversus and chronic airway diseases). Our finding that the cilia were immotile or dyskinetic in all specimens from PCD patients is in good agreement with that of several other investigators [20, 27, 28, 36]. In our ten PCD patients, cilia were immotile in four, only oscillation was shown in five, and one specimen was not analyzed in our institution. Ciliary beat frequency could only be determined in the cases which were not diagnosed as PCD. In all our non-PCD patients ciliary beat frequency was within the normal range and effective mucociliary transport could be visualized. The variability in CBF was wider between subjects than between sites of biopsy. We compared ultrastructural findings from nine PCD patients with those from eight non-PCD patients. All PCD patients showed partial or total absence of dynein arms, with the inner and outer dynein arms missing in over 70% of the ciliary cross-sections (Fig. 1).

Three out of nine patients had radial spoke defects and in four translocation could be seen. Disorientation of the ciliary axis and absent or additional microtubules were found in eight patients, while compound cilia were found in six patients. Except for the dynein arm and radial spoke defects the ultrastructural anomalies showed a similar incidence in the non-PCD.

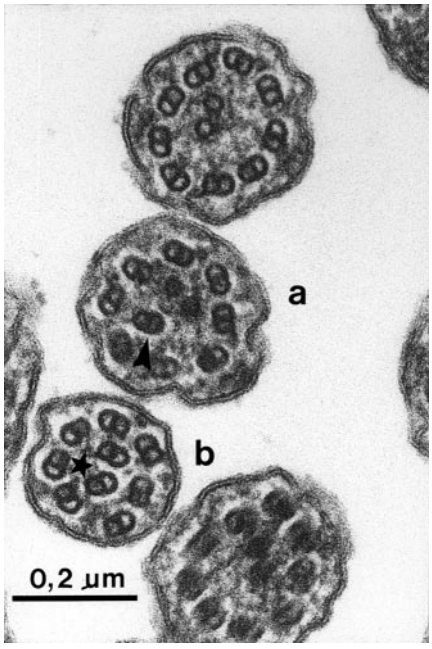

Fig. 1a, b Electron micrograph of cross-section of cilia from a child with PCD. In all cilia the peripheral microtubules show partial loss of dynein arms. **a** Transposition of a pair of peripheral microtubules (*arrow head*) due to radial spoke defect. **b** Translocation (* absence of central microtubules)

Table 1 Clinical manifestations in 10 patients with PCD (1990–1998)

Clinical signs and symptoms	No. of patients
Chronic rhinosinusitis	10
Chronic productive cough	9
Neonatal respiratory distress	9
Chronic otitis media with effusion	8
Recurrent suppurative bronchitis	8
Situs inversus	5
Bronchiectasis	4
Nasal polyps	3

Conclusions

Primary ciliary dyskinesia is a rare and heterogeneous disease. Diagnosis can be made with high sensitivity using the combination of a thorough clinical examination and functional and ultrastructural analysis of the cilia. According to the literature and our experience a careful selection of patients, with exclusion of other underlying disorders (e.g. cystic fibrosis, allergy, immunologic disorders, α_1-antitrypsin deficiency), is mandatory before biopsy. Patients with situs inversus who also suffer from chronic and/or recurrent airway infections do not need additional examination before being tested

for PCD. Neonatal respiratory distress syndrome of "unknown" cause (i.e. after exclusion of hyaline membrane disease, aspiration syndromes, neonatal pneumonia and pneumothorax as well as cardiovascular and metabolic diseases) should be considered as a suspicious sign for PCD. The finding of immotile or dyskinetic cilia by phase-contrast microscopy and the significant absence of dynein arms allow PCD to be diagnosed with high sensitivity.

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