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Up to date on primary ciliary dyskinesia in children ☆

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a congenital, clinically and ultrastructurally heterogeneous disease due to abnormal structure and/or function of cilia, with impaired mucociliary transport leading to several respiratory disorders. PCD can be diagnosed by the combination of thorough clinical examination with functional and ultrastructural analysis of the cilia. This paper shows progresses in PCD diagnosis obtained by ciliogenesis in culture evaluation of ciliated respiratory cells and by genetic analysis of mutations in candidate genes. Moreover, since to date no specific treatments are available to correct the ciliary dysfunction, the paper shows the proper therapeutical approach by the use of respiratory physiotherapy and regular exercise to favour airways clearance, by antibiotics administration to control acute airway infections. Macrolides administration as antinflammatory option is suggested.

1. Introduction

Primary ciliary dyskinesia (PCD) (OMIM no. 244400) is a genetically heterogeneous, autosomal recessive disorder characterized by dysfunction of respiratory cilia and impaired muco-ciliary clearance [1]. Poor clearance leads to various clinical manifestations and recurrent airway infections. Since ciliated epithelia are present in many body sites, ciliary dysfunction may be cause of several disorders collectively known as "ciliopathies" [2–4]. Further, approximately 50% PCD patients show abnormal or mirror placement of body organs with situs inversus (Kartagener syndrome) [5].

PCD manifests early in life and, if improperly diagnosed and treated, may lead to chronic sinusitis and severe bronchiectasis with extensive impairment of pulmonary function. Its incidence is estimated at 1/16,000 births with around 70 new cases born per year in white population, and we may assume that there are about 4000 PCD patients in Italy [6–8]. However, since its diagnosis is still challenging, PCD is largely underestimated [9,10].

2. Respiratory cilia: normal ultrastructure and function

Motile cilia are long thin protrusions, extending up to 20 micrometers from the cell surface. They concentrate in large numbers on the apical cell surface and beat in coordinated waves to organize fluid flow across the cell surface. These cilia are basically constructed from a "9 + 2" arrangement of microtubules, in which nine microtubule doublets surround a central inner pair (Fig. 1). The outer doublets are connected by inner (IDA) and outer dynein arms (ODA), recognizable on electron micrographs of ciliary cross sections: dynein is thought to participate in the provision of energy for microtubule sliding through adenosine triphosphatase activity. Ciliary bending results from the longitudinal displacement of adjacent periferal microtubular doublets. Moreover, the outer and inner doublets are connected by radial spokes which can regulate the direction of ciliary beating [1,11].

3. When to suspect PCD

Children with PCD can be asymptomatic at birth, but often they show respiratory distress in the neonatal period. Usually lower airway infections appear early in life and wet cough is their main symptom, and these patients tend to develop chronic bronchitis which may lead to bronchiectasis in several years, which can be demonstrated by high resolution computed tomography (HRCT). Recurrent middle ear infections, chronic sinusitis and nasal polyps may also be frequently found in these patients.

In general, PCD clinical features don't differ much from those in patients with chronic respiratory diseases where secondary ciliary abnormalities may be found. Nevertheless, some of the clinical manifestations must be properly magnified for diagnostic purposes (Table 1). In fact, diagnosis is easier when there is abnormal or mirror placement of body organs with abdominal situs inversus or situs inversus totalis, which may be due to the loss of embrional ciliary motion and of its role in the asymmetric positioning on body organs [10].

4. Diagnosis

The ERS PCD Task Force has published in 2009 consensus recommendations for the diagnosis of PCD [12]. Diagnosis was formerly

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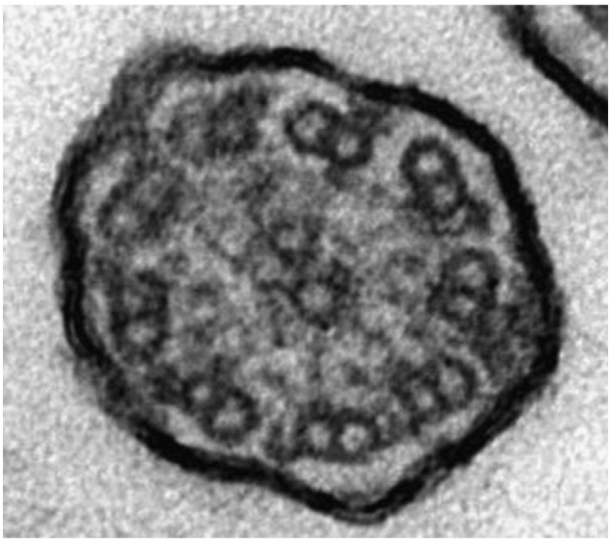

Fig. 1. Transmission electron micrograph of ciliary ultrastructure showing normal axonemal ultrastructure (magnification × 94.000).

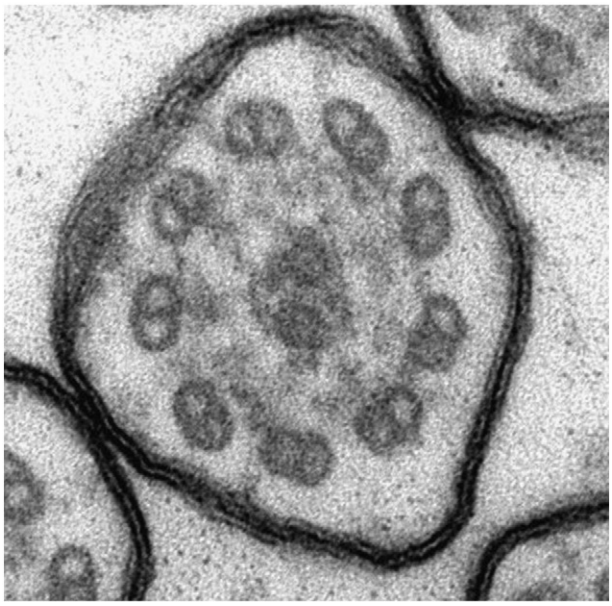

Fig. 2. Transmission electron micrograph of ciliary ultrastructure showing axonemal ultrastructure in PCD with lack of ODA and IDA (magnification × 110.000).

made by ultrastructural and functional analysis of respiratory cilia obtained by nasal or bronchial brush biopsy. To date, however, none of the two can be considered as a gold standard test in the diagnosis of PCD. Besides typical cilia and axoneme abnormalities, such as deficiencies of the dynein arms (Fig. 2) and alterations of the central pair (Fig. 3), there are many other minor alterations, often undetectable by electron microscopy, which have profound impact on ciliary motion [5,12–15]. This has been recently confirmed by other examination techniques in patients with suspected PCD. In particular, despite normal structure, cilia with hyperkinetic beat and reduced bending capability were demonstrated [13,16]. Finally, a subset of PCD patients showed normal structure and beat frequency but random orientation [1]. As a consequence, sometimes, even when using both ciliary motion and ultrastructural analysis, PCD diagnosis can be challenging and requires to repeat ciliary evaluation in doubtful cases [1].

In those difficult cases, genetic evaluation could represent the ideal diagnostic solution, but PCD is a very heterogeneous condition, and in spite of all considerable efforts made in the last couple of years by some research groups, only a few mutations are known as certainly connected with the disease. Therefore, this evaluation can't be considered as a tool in the diagnostic process, and must be reserved as a confirmatory test when available [12].

In fact, there are several hundreds of diverse polypeptides interacting in precise and coordinated way in cilia axoneme only [3,12], and there is a growing number of genes implicated in PCD etiopathogenesis [1,17,18].

Actually, despite high conservation across the phylogeny spectrum and structural identity of cilia and flagella, our understanding of the molecular composition of cilia is far from complete. Depending on technology used, organism and tissue examined, and database searched for tissue-specific expression, the number of genes ranged from 99 to 1000 [18]. Several genes important for normal motility, frequency and coordinated beat [5,11,13,15,19,20] have also been linked to PCD (Table 2). In fact, clinical PCD could be caused by assembly genes whose products are not found in cilia at all, and by mutations which cause abnormal function of a normally constructed cilium.

Currently the majority of the known genes are localized in dynein, axonemal, intermediate chain 1 (DNAI1) and 2 (DNAI2), heavy chain 5 (DNAH5) and 11 (DNAH11), and thioredoxin domain containing protein 3 (TXNDC3). Other genes are external to axoneme but important for cytoplasmic preassembly of axonemal dyneins (chromosome 14 open reading frame 104 [KTU]) and central microtubular pair (radial spoke head 9 homologue [RSPH9] and 4 homologue A [RSPH4A]) [3]. Other genes have also been recognized in a small number of cases [12,15]. Genetic testing can be reserved until after the clinical

Table 1
Signs and symptoms suggestive of PCD.

Time period	Signs and symptoms
Neonatal	Respiratory distress or pneumonia in term neonates with no predisposing cause; rhinitis and/or nasal congestion that remain constant over time; *situs inversus*; moist sounding cough, unusual but suggestive; complex congenital heart disease; esophageal and biliary atresia; hydrocephalus; positive family history of PCD.
Infant and older children	Chronic cough with sputum production; rhinosinusitis; chronic secretory otitis media with prolonged otorrhea after tympanostomy; pneumonia; bronchiectasis; repeated courses of antibiotics for chest infections; atypical asthma refractory to treatment.

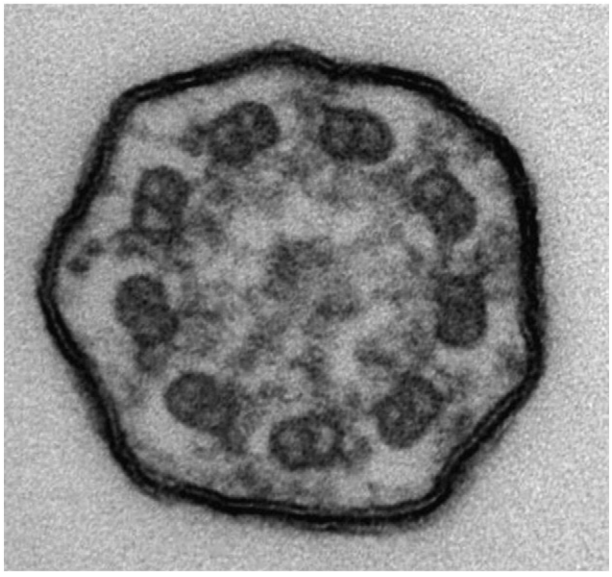

Fig. 3. Transmission electron micrograph of ciliary ultrastructure showing axonemal ultrastructure in PCD with lack of central pair (magnification × 110.000).