REVIEW PAPER

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PRIMARY CILIARY DYSKINESIA: HOW TO DIAGNOSE, HOW TO TREAT

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Summary
Characteristics of the syndrome. Underlining the diagnostic and therapeutic difficulties. PCD symptoms include ARDS at the age of early – infancy, recurrent lower respiratory tract infections, chronic rhinosinusitis and otitis media, or impaired fertility. PCD requires differentiation with atypical asthma, bronchiectasis and cystic fibrosis. Diagnostic algorithm consist of cascade of tests (brush cytology/bronchoscopic samples, cilia motility evaluation, function and structure assesment with electron microscopy, immunochemical testing, genetic testing) preceded by screening tests (saccharin, measurement nNO). 1. The primary ciliary dyskinesia is rarely taking under consideration in the differential diagnosis of chronic/recurrent upper respiratory tract infections. 2. Available screening tests do not include target group of patients (< 12 y.o.). 3. No recommendations for the type and methods of obtaining material for testing and methods of its transportation. 4. The basic diagnostic limitation is high cost of a conclusive tests. 5. There is necessity to differentiate primary and secondary ciliary dyskinesia. 6. No general algorithm running patients diagnosed with PCD – the mandatory introduction of standard therapy.

Keywords: primary ciliary dyskinesia, PCD, immotile cilia syndrome, Kartagener's syndrome, mucociliary clearance

INTRODUCTION

Primary ciliary dyskinesia (PCD), also known as immotile cilia syndrome is a rare, genetically determined disease (predominantly inherited as an autosomal recessive) mostly interfering with upper and lower respiratory tract. It is associated in 40-50% with visceral situs inversus and other forms of heterotaxy (1). Symptoms of the disease directly result from impaired ciliary clearance.

Unfortunately disorders due to dysmotile cilia have been poorly studied in children. Therapeutic strategies are taken from the algorithms developed for the treatment of cystic fibrosis (CF). Lower requirement for more PCD research is the consequence.

DISCUSSION

CD is determined by a number of different genetic ciliary defects (tab. 1) that result in ineffective mucociliary clearance.

Most patients with PCD have symptoms since their birth or early infancy (2), but the diagnosis is usually postponed (3). Significant number of patients are never diagnosed (4). It seems likely (but stays unproven) that early diagnosis of PCD is important as deterioration in lung function can largely be prevented by specialist respiratory care (5).

How to recognise a young child at risk of developing bronchiectasis? The important sign is that of a persistent "wet" sounding cough. Especially if such a cough persists for more than 8 weeks or symptoms return when antibiotic treatment is stopped. In patients with PCD the cough never goes completely away even with treatment. Likewise, chronic upper airway symptoms, such as constant rhinitis (nasal discharge, episodic facial pain and anosmia). Ear symp-

Table 1. Genes involved in primary ciliary dyskinesia (PCD). Based on (8).

Gene	Locus	Defective structure	Phenotype
NAH5	5p15	ODA	PCD + KS
DNAI1	9p21- p13	ODA	PCD + KS
DNAH11	7p15.3- 21	Normal	PCD + KS
TXNDC3	7p14.1	ODA	KS
DNAI2	17q25.1	ODA	PCD + KS
KTU	14q21.3	ODA+IDA	PCD + KS
RPGR	Xp21.1	Variable	PCD with retinitis pigmentosa
OFD1	Xp22	Not known	PCD with mental retardation
RSPH9	6p21	CP	PCD
RSPH4A	6q22	CP	PCD

ODA – outer dynein arm, IDA – inner dynein arm, CP – central pair, KS – Kartagener's syndrome

toms (recurrent otitis media and glue ear) are a frequent complication (85% of patients) that can require multiple interventions, including repeated courses of antibiotics. Testing for PCD should be considered if standard first line investigations to exclude cystic fibrosis (CF) and screening for immunological defects are negative. A number of patients will have a history of unexplained neonatal respiratory distress. Hearing problems are only seen in half of cases. The clinical aspects of PCD, according to patient's age, are presented in table 2 (3, 6-8).

Diagnosis, due to the lack of standardisation and inaccessibility stays challenging either for the patient or the paediatrician. Screening tests for PCD do exist but they are uncorrelated. There are number of problems and the biggest is that most of the screening tests are unreliable in children. For the moment, the most sensitive and specific screening test for PCD is measurement of nasal nitric oxide (fig. 1) (9-11) but even along special paediatric program it is dedicated for children older than 5 years of age (as well as radioaerosol mucociliary clearance tests). What specialist centres may offer to their patients as diagnostic test? First: obtaining a sample of ciliate cells by nasal brushing or bronchoscopic samples. Then analysis of ciliary function by ciliary beat pattern and frequency analysis, evaluation of the cilia's structure on electron microscopy and even genetic analysis (12). Diagnostic algorithm is presented on figure 2.

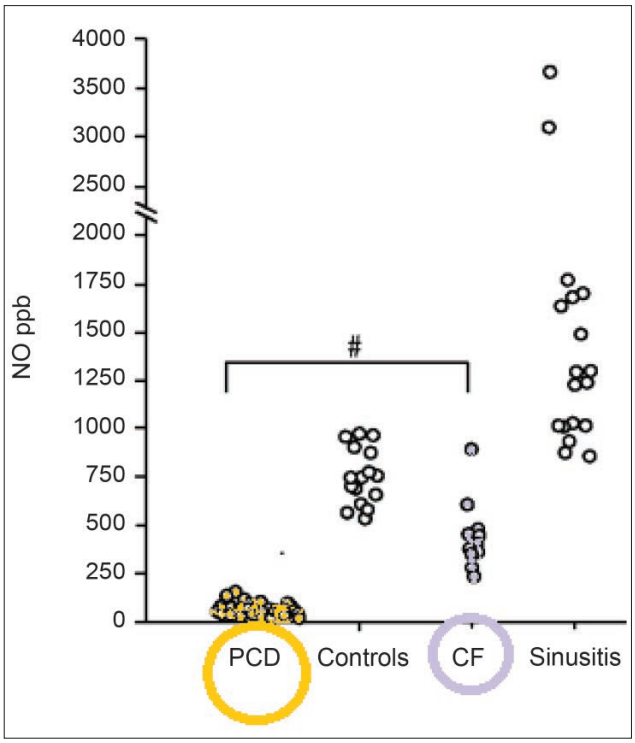

Fig. 1. Nasal nitric oxidemeasurement due to CF and sinusitis test results. Based on (10).

Table 2. PCD symptoms displayed by various age groups. Based on (8).

	Symptoms
Antenatal	*Situs inversustotalis* or heterotaxy on antenatal ultrasoundscanning; 25% of individuals with *situs inversustotalis* have PCD. The prevalence of PCD within the heterotaxic subclass is unknown
	40-50% of PCD patients present with *situs inversustotalis* (Kartagener's syndrome in PCD)
	6% show heterotaxy (*situs ambiguus*)
	Mild fetal cerebral ventriculomegaly
Neonatal	> 75% of full-term neonates with PCD exhibit neonatal respiratory distress requiring supplemental oxygen for days to weeks
	Continuous rhinorrhoea from the first day of life
	Mirror-image organ arrangement and other forms of heterotaxy
	Hydrocephalus may occur in some individuals with PCD, and may reflect dysfunctional ependymal cilia
Childhood	Chronic productive or wet-sounding cough, associated or not with recurrent atelectasis or pneumonia
	Atypical asthma that is nonresponsive to treatment, especially if a wet-sounding cough is present
	Idiopathic bronchiectasis
	Daily rhinitis without remission; nasal polyps are rare at this age
	Severe chronic sinusitis in older children, Otitis media with effusion, Hearing loss
Adolescence and adult life	Same as for childhood
	Bronchiectasis more evident in adulthood (83%)
	Chronic mucopurulent sputum production is common
	Digital clubbing may also be found
	Pulmonary function tests usually show a progressive obstructive or mixed pattern
	Nasal polyposis and halitosis
	Infertility in males (-50%) due to immotility of spermatozoa ectopic pregnancy and subfertility in females

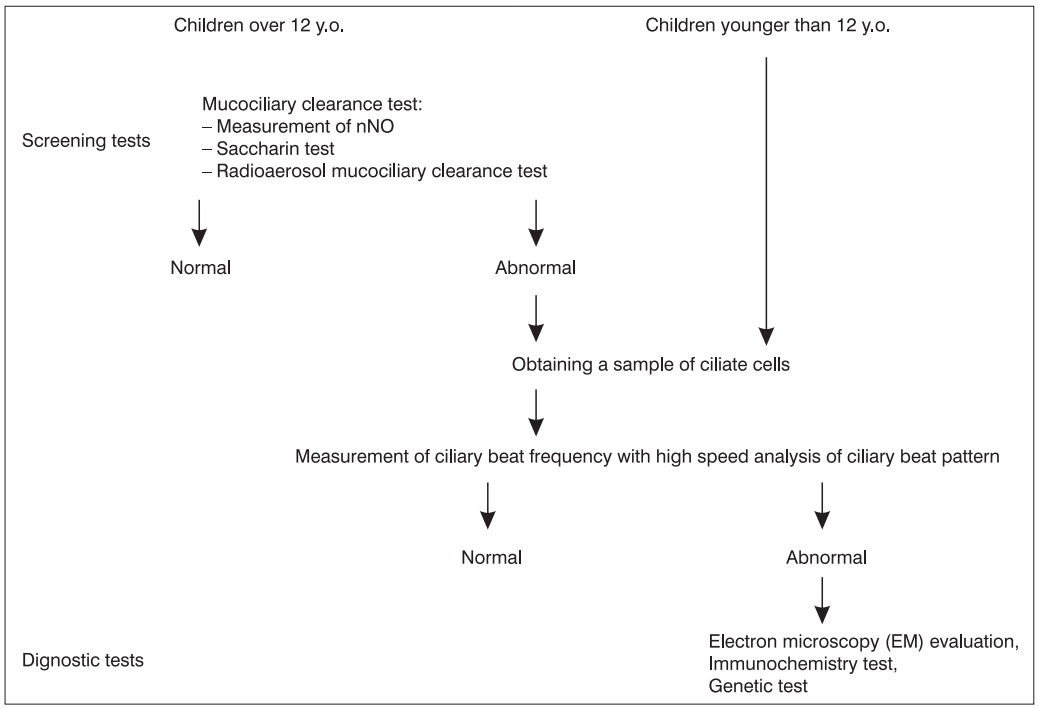

Fig. 2. PCD diagnostic algorithm; a proposition.

Restore or maintain normal lung function is the main aim of therapy for PCD. Unfortunately there are no randomised trials of adequate treatment. Therefore recommendations are based on a very low level evidence. The clinician should abort therapy that is not working. Main, valid guidelines for the therapy are:

- airway clearance by combinations of physiotherapy and physical exercise should be encouraged and regularly prescribed in children with PCD (11, 12),
- high-dose oral antibiotics should be prescribed at the first sign of worsening respiratory symptoms or deterioration in lung function; if persistent respiratory symptoms do not respond to oral antibiotics, then intravenous therapy should be given (8),
- anti-inflammatory strategies, such as alternate-day prednisolone or inhaled corticosteroids, should not be used (12, 13),
- Otitis media with effusion should be managed conservatively, with regular audiological assessment, hearing aids and hearing therapy (14, 15),
- the use of ventilation tubes (grommets) should be avoided where possible (8, 14, 15),
- regular (≥ 3 monthly) sputum or cough-swab cultures should be performed based on clinic and hospital or local colonisation (8).

To deliver best care, patients with PCD should be seen for either full or shared care in a centre specialising in the condition. There is urgent need to publicize information about syndrome itself, about reference centres and diagnostic methods. Further studies are clearly needed to establish general consensus statement.

CONCLUSIONS

1. The primary ciliary dyskinesia is rarely taking under consideration in the differential diagnosis of chronic/recurrent upper respiratory tract infections.
2. Available screening tests do not include target group of patients (< 12 y.o.).
3. No recommendations for the type and methods of obtaining material for testing and methods of its transportation.
4. The basic diagnostic limitation is high cost of a conclusive tests.
5. There is necessity to differentiate primary and secondary ciliary dyskinesia.
6. No general algorithm running patients diagnosed with PCD – the mandatory introduction of standard therapy.

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