Primary Ciliary Dyskinesia (PCD)

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PCD is a rare disease that begins in childhood and continues into adulthood and can be very debilitating.

The diagnosis in children is often delayed.
• No gold standard diagnostic test; various methods in use
• No evidence-based data (RCT’s) on effect of different treatments
• No representative data on current diagnostic and treatment practices in Europe

➤ Creation of ERS taskforce on PCD in children (2006)
1. To write a consensus statement on diagnosis and treatment of PCD in Children

Angelo Barbato, Claudia Kuehni, Thomas Frischer

2. To collect representative European data on the epidemiology and management of PCD in children:

Thomas Frischer, Claudia Kuehni, Angelo Barbato
Countries & paediatric centres of Task Force

25 countries
214 centres
185 with cases
1103 patients
945 <20 yrs
Healthy Cilia

- Cilia are situated on the surface of upper and lower airways (nose, middle ears, sinuses & bronchi)
- Beating movements transport mucus (and trapped particles and pathogens)
- Role in airway cleaning and host defense
- Cilia are also involved in:
  - Development of laterality
  - Sperm motility, transport of eggs
  - Ependyma of brain
Healthy Cilia

1.- Axonema
2.- Cell membrane
3.- Intraflagellar transport
4.- Basal Body
5.- Cross section of flagella
6.- Triplet of microtubules of basal body
HC = Heavy chain
LC = Light chain
IC = Intermediate chain

- The ependymal cells lining the ventricles of the brain carry motile cilia with a 9+2 ultrastructure.

- The endothelium covering the back of the cornea carries monocilia; photoreceptor cells are polarized sensory neurons consisting of a photosensitive outer segment and an inner segment bridged by a connecting cilium (9+0).

- Ventral surface of the embryonal node is covered with monocilia that rotate in a clockwise direction generating a leftward flow or ‘nodal flow’.

- Respiratory cells have cilia 9+2.

- In the kidney, glomerulus cells and tubular cells carry monocilia 9+0 resembling nodal cilia.

- Spermatozoa/fallopian tube have cilia.

- The ependymal cells lining the ventricles of the brain carry motile cilia with a 9+2 ultrastructure.
Primary Ciliary Dyskinesia

- Primary ciliary dyskinesia (PCD), formerly called immotile cilia syndrome, is a recessively inherited disorder of ciliary structure and/or function resulting in impaired mucociliary clearance.
Sick Cilia (PCD)

Congenital defect (usually autosomal-recessive)
Defective structure or function of cilia, resulting in disturbed mucus clearance, with
• Lower respiratory infections, wet cough
• Upper respiratory infections (ears & sinus)
• Permanent lung damage (bronchiectasis)

Other symptoms
• Situs inversus or heterotaxy
• Male (rarely female) subfertility
• Hydrocephalus
Sick Cilia (PCD)

The lack of mucociliary clearance is caused by:

- **Dynein arm defects:**
  total or a partial absence of inner or both outer dynein arms or both. Sometimes, shortened dynein arms are the only defect.

- **Radial spoke defects:**
  a total absence of radial spokes or an absence of radial spoke heads.

- **Microtubular transposition defects:**
  absence of the central pair of tubules with transposition of the outer doublet to the center.
Absence of nexina

Normal orientation

Absent IDA e ODA and more central microtubules
**TABLE 3. FREQUENCY OF CILIARY STRUCTURAL DEFECTS IN CLASSIC PRIMARY CILIARY DYSKINESIA (n = 76*)**

<table>
<thead>
<tr>
<th>Structural Ciliary Defect</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODA alone</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>IDA alone</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Both ODA and IDA</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Central apparatus†</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: IDA = inner dynein arm; ODA = outer dynein arm; PCD = primary ciliary dyskinesia.

* n = 2 others with complete “classic” PCD phenotype/mutations in a gene associated with PCD (DNAH1) declined nasal scrape samples for analysis.

† Defects of the central pair, radial spokes, or nexin links.

Noone PG et al, Am J Respir Crit Care Med 2004; 169: 459-467
Figure 2. Ciliary activity scores for subjects with PCD (by ciliary structural defect), as compared with healthy control subjects. Significant differences (analysis of variance, followed by unpaired t test) were seen between all subjects with PCD and normal subjects ($p = 0.001$). ODA = outer dynein arm defect; IDA = inner dynein arm defect; ODA/IDA = both dynein arms defective.
Epidemiology

- Rare disease
- Estimated prevalence: 1/20,000 to 1/60,000 children
- Clinical data and prognosis only available from case series (<100 cases)
- Some evidence that early diagnosis and treatment might improve long-term outcome
Age at diagnosis

- Diagnosis relatively late in childhood
- Especially in children without situs inversus
Clinics

Children with PCD often have a clinical history of lower airway disease, manifested by a persistent “wet” sounding cough and occasionally wheeze or shortness of breath.

In addition, virtually all subjects have evidence of chronic upper airway symptoms such as chronic rhinitis (nasal discharge, episodic facial pain, and anosmia).
Clinics

Antenatal presentation

• *Situs inversus totalis* or *situs ambiguous*

• Mild fetal cerebral ventriculomegaly can be a prenatal sonographic marker of PCD.
Clinics

Presentation in the newborn period

• Unexpected neonatal respiratory distress or an intensive care admission for neonatal pneumonia;
• Continuous rhinorrhea from the first day of life;
• Mirror image organ arrangement and other forms of heterotaxy;
• Hydrocephalus (uncommon);
• Neonatal screening (positive family history).
Clinics

Presentation in childhood

- Chronic productive or “wet” sounding cough; associated with recurrent atelectasis or pneumonia.
- Atypical “asthma”, non-responsive to treatment, especially if a wet-sounding cough is present.
- “Idiopathic” bronchiectasis.
- Rhinosinusitis; nasal polyps (rare).
- Otitis media with effusion; hearing loss.
- Positive family history of PCD.
Clinics

Presentation in adolescence and adult life

- As above, for childhood
- Bronchiectasis
- Chronic mucopurulent sputum production
- Digital clubbing
- Nasal polyposis and halitosis
- Male infertility and ectopic pregnancy and subfertility in women
### TABLE 1. “CLASSIC” PRIMARY CILIARY DYSKINESIA

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>(% predicted)</th>
<th>(nl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 18 yr; r = 47 [31 females]; median age, 36 yr; range, 19–73 yr)</td>
<td>47 (100%)</td>
<td>46 (98)</td>
<td>22 (47)</td>
<td>43 (92)</td>
<td>30 (65)</td>
<td>22 (46)</td>
<td>60 ± 4</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>Pediatric subjects (&lt; 18 yr; n = 31 [11 females]; median age, 8 yr; range, 1–17 yr)</td>
<td>31 (100%)</td>
<td>19 (61)</td>
<td>20 (65)</td>
<td>31 (100)</td>
<td>27 (87)</td>
<td>21 (68)</td>
<td>85 ± 3</td>
<td>16 ± 4</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** NO = nitric oxide; NRS = a syndrome of neonatal respiratory symptoms.

n = 78 (42 females); age (years): mean = 27; median = 29; range 1–73.

Continuous data ± SD are presented.

* All subjects reported chronic cough. See text for definitions of bronchiectasis (excess purulent sputum and/or radiographic evidence) and NRS.

† All 78 subjects had a history of chronic upper airway symptoms/chronic rhinitis; see text for definition of sinusitis—i.e., prior surgery, computed tomography/sinus radiographs showing evidence of chronic sinusitis. 100% of those who had computed tomography scans had evidence of chronic sinusitis.
Middle lobe bronchiectasis in a PCD patient
PCD as an associated diagnosis

- Complex congenital heart disease
- Asplenia (right isomerism) or polysplenia (left isomerism)
- Polycystic kidney or liver disease
- Hydrocephalus
- Biliary atresia
- Severe oesophageal disease
- Retinal degeneration, including *retinitis pigmentosa*
- Oral-facial-digital syndrome type 1
Diagnostic & Treatment

• No gold standard diagnostic test; various methods in use
• No evidence-based data (RCT’s) on effect of different treatments
• No representative data on current diagnostic and treatment practices in Europe

➢ Creation of ERS taskforce on PCD in children (2006)
Diagnosis

Screening tests

Nasal nitric oxide measurement

- Noone et al. Am J Respir Crit Care Med 2004;169;459-467

Nasal Saccharin Test


Nasal Radioaerosol mucociliary clearance test:

Sample for PCD testing:

Nasal brushing

Bronchial brushing and biopsy
I.- Non ciliated columnar cell, covered by microvilli of uniform length

II.- Globet cell packet with mucigen granules

III.- Basal Cells

IV.- Ciliated columnar cell covered by cilia and microvilli of uniform length
normal
Bronchial epithelial cells

II.- Globet cell packet with mucigen granules

III.- Basal Cells

IV.- Ciliated columnar cell covered by cilia and microvilli of uniform length
normal
Diagnosis

• Ciliary beat pattern
• Frequency analysis:
  - normal pattern: movement like a lasch
  - normal frequency: > 10 Hz

✓ Immotility
✓ Low-frequency beat
✓ Abnormal beat pattern
✓ Normal beat pattern with cilia disorientation
Diagnosis

Ciliary beat frequency measurement:
- beat frequency is low, suspicion of PCD is high.
  Patients with defects of the central microtubular pairs and some patients with an inner dynein arm defect will have a beat frequency within the normal range.

Cell culture:
- improves diagnostic certainty of PCD.
  It is mostly used to reduce the false positive diagnoses in patients with secondary ciliary dysfunction, and to confirm less common phenotypes such as ciliary disorientation, ciliary aplasia, central microtubular agenesis and inner dynein arm defects.
Diagnosis

Electron microscopy:

a) absence of ODA and IDA; b) absence of ODA; c) absence of IDA

Inner dynein arm defects are difficult to determine, because they are less electron dense and less frequent along the ciliary axoneme.
Diagnosis

Other techniques

- Analysis of dynein protein localisation:
  by immunofluorescent microscopy
  - this method is not altered by secondary ciliary abnormalities

- Genetic analysis:
  So far, mutations in four genes (DNAI1, DNAH5, DNAH11 and RPGR) that encode for dynein proteins have been linked to the disease.
  - There are known PCD-causing mutations on two genes linked to the production of outer dynein arm (ODA) protein: DNAI1 and DNAH5. Together, the mutations on these two genes account for approximately 38% of all cases of PCD and close to 63% of ODA related PCD.
# Diagnosis

## Genetic analysis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Defective structure</th>
<th>Exon Hot spot</th>
<th>Founder mutation</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNAH5</td>
<td>5p15</td>
<td>ODA</td>
<td>79+1Exons 34, 50, 63, 76, 77</td>
<td>c.10815delT</td>
<td>PCD+KS</td>
</tr>
<tr>
<td>DNAI1</td>
<td>9p21-p13</td>
<td>ODA</td>
<td>20</td>
<td>Exons 13, 16, 17</td>
<td>PCD+KS</td>
</tr>
<tr>
<td>DNAH115</td>
<td>17p15.3-21</td>
<td>Normal</td>
<td>82</td>
<td>Not known Not known</td>
<td>PCD+KS</td>
</tr>
<tr>
<td>TXNDC3</td>
<td>7p14.1</td>
<td>ODA</td>
<td>18</td>
<td>Not known Not known</td>
<td>KS</td>
</tr>
<tr>
<td>DNAI2</td>
<td>17q25.1</td>
<td>ODA</td>
<td>14</td>
<td>Not known Not known</td>
<td>PCD+KS</td>
</tr>
<tr>
<td>KTU</td>
<td>14q21.3</td>
<td>ODA+IDA</td>
<td>3</td>
<td>Not known Not known</td>
<td>PCD+KS</td>
</tr>
<tr>
<td>RPGR</td>
<td>Xp21.1</td>
<td>Variable</td>
<td>~25</td>
<td>Not known Not known</td>
<td>PCD with retinitis pigmentosa</td>
</tr>
<tr>
<td>OFD1</td>
<td>Xp22</td>
<td>Not known</td>
<td>23</td>
<td>Not known Not known</td>
<td>PCD with mental retardation</td>
</tr>
<tr>
<td>RSPH9</td>
<td>6p21</td>
<td>CP</td>
<td>5</td>
<td>Exon 5 c.801_803delGAAPCD</td>
<td>PCD</td>
</tr>
<tr>
<td>RSPH4A</td>
<td>6q22</td>
<td>CP</td>
<td>6</td>
<td>Not known Not known</td>
<td>PCD</td>
</tr>
</tbody>
</table>

## Description of more frequent genes involved in PCD.

Respiratory treatment:

involves aggressive treatment of upper and lower airways infections and airway clearance by combinations of physiotherapy and physical exercise. As with CF patients, it is likely that the best results will be obtained if treatment is in a centre with experience of the disease caring for a sufficient number of patients.
**Treatment**

**Antibiotics**

- Airway infection with *Haemophilus influenza*, *Staphylococcus aureus* and *Streptococcus pneumoniae* frequently occur, but *Pseudomonas aeruginosa* and non-tuberculous *Mycobacteria* have also been reported, usually in adults.  
  
  Noone et al. *Am J Respir Crit Care Med* 2004; 169: 459-467

- There is no evidence to recommend the use of prophylactic oral antibiotics in all patients.

- High-dose oral antibiotics are recommended at the first sign of worsening respiratory symptoms or deterioration in lung function. (on the basis of sputum or cough swab culture).

- If *Pseudomonas aeruginosa* is isolated, most clinicians would prescribe an eradication regime similar to those used in CF.
Treatment

Inhaled therapy

There is even less evidence for other therapies.

- **Regular bronchodilators** do not lead to worsening airway reactivity, but they are not particularly effective.
- The role of *nebulised rhDNase* in PCD patients remains unproven, but can be usefull.
- Use of *nebulised normal or hypertonic saline* may theoretically be effective in increasing mucus clearance, but unlike in CF, there are no randomised controlled trials.
- **N-acetyl-cysteine** has been shown not to be useful.
- **Anti-inflammatory strategies** such as alternate day prednisolone; no data in PCD patients.
- **Inhaled corticosteroids**; no data available.
Treatment

Airway clearance therapy

- **Airway clearance techniques** are prescribed widely in PCD patients, but there is no evidence for the efficacy of any one particular technique. The physiotherapy options should be tailored to the age of the individual and the changing clinical state and might vary according to the local expertise and availability of resources across countries.

- **The effect of physical exercise on airway clearance in PCD has not been fully investigated but may help sputum clearance.** Exercise is encouraged at all ages to promote general health and wellbeing.
Treatment
Prevention

- **Environmental exposures**
  - avoidance of active and passive smoking;
  - minimisation of exposure to respiratory pathogens; and minimisation of exposure to indoor and environmental pollutants. Cough suppressant medications must be avoided.

- **Immunizations**
  - PCD patients should receive all childhood immunizations, and also pneumococcal and influenza A immunization.
Treatment

Surgical procedures

- ENT surgery
- Complications of bronchiectasis and chronic lung disease become more prominent with age.
- The role of lobectomy in advanced bronchiectasis is similar to that in other aetiologies, and can rarely be recommended.
- There are reports of PCD patients going on to lung transplantation, both living related and cadaveric.

Important to treat children aggressively to retard later deterioration.
Follow-up

- Regular access to respiratory paediatricians, audiology, ENT surgeons and respiratory physiotherapists.
- **Regular visits to a tertiary centre** to check growth, lung function (incl pulse oximetry) and hearing.
- **Regular sputum or cough swab cultures** should be performed.
- **Chest radiographs** are probably relatively insensitive.
- **HR-CT scan** of the lungs is used to define the extent of bronchiectasis, and can be used to monitor the progression of the disease.