Primary Ciliary Dyskinesia: what the radiologist should know

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Learning objectives

- Describe the pathology and the clinical presentation of Primary Ciliary Dyskinesia (PCD)

- Recognise the main screening techniques, confirmatory diagnostic tests and management strategies for PCD patients

- Understand the role of radiology in PCD

- Describe the main imaging findings in PCD
Background

Diagnosis of PCD is often delayed partly because the typical presenting symptoms (e.g. rhinitis, secretory otitis media, cough) are common in children. PCD should be suspected in children with recurrent respiratory disease.

Diagnosis requires specialised testing; radiology forms an important component of diagnosis and assessment.
Genetic testing

PCD is an autosomal recessive disorder with more than 20 PCD-causing genetic mutations described in the literature. Almost half of these have been discovered since 2011 owing to the use of exome sequencing. Multiple further "PCD genes" are currently being studied. With these recent advances it is likely that the sensitivity of genetic testing for PCD will be above 80% in the coming years. Mutations of specific genes have been linked to abnormal ciliary biogenesis whilst other genetic mutations have been shown to cause ciliary dysfunction. Interestingly, genetic studies have confirmed that mutations in genes coding for dyenin (a motor protein) arm components are associated with situs abnormalities. It is anticipated that further novel PCD-causing genes will be discovered in the near future, some of which are likely to be present in patients with a milder phenotype than that encountered in "classic" PCD [1].

Symptoms

PCD patients present with symptoms related to malfunction of mucociliary clearance, which can present at any age. In the antenatal period, some patients are already diagnosed during USS when heterotaxy is noted. 50% of the PCD patients will have a mirror arrangement, and together with bronchiectasis and sinusitis the triad is known as Kartagener syndrome. Neonates commonly present with respiratory distress, together with continuous rhinorrhea. Unfortunately many symptoms are non-specific, especially in children, including secretory otitis media, chronic upper and lower respiratory tract infections. Rhinosinusitis can be particularly severe without remission. Patients may suffer from otitis media with effusion. Patients who are slow to respond to asthmatic mediations with a persistent wet cough, or unexplained bronchiectasis on imaging should alert the clinician to the diagnosis. Adolescents and adults can present similarly, sometimes with the additional findings of infertility.

PCD is also associated with conditions such as congenital heart disease, polycystic kidneys, hydrocephalus, biliary atresia and reflux [6].

Diagnostics

In the UK, the tests for PCD are funded by the National Commissioning Group, hence the tertiary referral centres incur zero financial burden.

nNO

Several studies have shown that the demonstration of low nasal nitric oxide levels (nNO) may be a useful diagnostic test for PCD. In recent years nNO has been used increasingly amongst clinicians in tertiary PCD centres. nNO measurements are obtained
by aspirating air from the opening of one nostril which is then directed into an NO analyser (Fig. 1 on page 9). The test is usually performed with the patient’s soft palate closed to limit contamination with air from the lower respiratory tract. Low nNO levels have been reported in cystic fibrosis and in infective and inflammatory conditions of the respiratory tract. The use of this test for the diagnosis of PCD must therefore be limited to patients without these aforementioned conditions [1].

**Cilia structure**

Fresh airway epithelium biopsies can be obtained from either the bronchi or nasal cavity, more often the latter is obtained via brushings in an out-patient setting, and lasts no more than a few seconds (Fig. 2 on page 9). There are very little complications besides discomfort and minor epistaxis [2]. The samples are then examined by experts under electron microscopy, which is traditionally the gold standard test for PCD. The majority of the patients have an absence or shortening of the outer dyenin arms (ODAs), with or without inner dyenin arm (IDA) defect (Fig. 3 on page 10, Fig. 4 on page 11, Fig. 5 on page 12). Very few patients have an isolated IDA defect. However, there are forms of PCD that have very little defects of the ciliary ultrastructure, beat frequency and waveform. Hence EM is no longer a standalone "gold standard" for diagnosis [1].

**Saccharin clearance**

A microtablet of saccharin is positioned onto the inferior nasal turbinate. The time to tasting saccharin is recorded. It can may take up to 60 minutes, and could be difficult to perform in young children [2]. Saccharin testing has been gradually replaced by more reproducible methods like nNO and electron microscopies.

**Imaging Manifestations**

**Chest radiography**

Plain radiography is usually the initial imaging modality of choice because of availability, relative low radiation dose and specificity. Conventional radiographic abnormalities associated with PCD include peribronchial thickening, atelectasis and airtrapping; these abnormalities eventually lead to bronchiectasis (Fig. 6 on page 13). Radiographic features typically occur in the middle and lower lobes, a distinguishing feature from cystic fibrosis (which has a predominantly upper lobe prominence). Less common pulmonary manifestations include mottled parenchymal shadows and consolidation.

Abnormalities of thoracoabdominal asymmetry occur as a random event in approximately 50% of patients with PCD. PCD is also associated with an increase in the prevalence of situs inversus and heterotaxy with and without congenital heart disease. Approximately 50% of PCD patients have Kartagener’s triad of situs inversus, bronchiectasis, and sinusitis (Fig. 7 on page 14).
High Resolution Computed Tomography (HRCT)

HRCT has a higher sensitivity and specificity than conventional radiography in delineating radiographic features of PCD such as atelectasis, bronchial wall thickening, air trapping and bronchiectasis. HRCT has the additional advantage of detecting early or localized structural changes, crucial in candidates for lobectomy and/or lung transplantation. HRCT has hence become the modality of choice to evaluate chronic lung disease at any age.

The use of HRCT should be considered carefully to avoid excessive radiation. Technical challenges from respiratory related motion artefact in children may lead to non-diagnostic images and care should be taken to avoid this.

Specific HRCT features of PCD include:

**Bronchiectasis** ([Fig. 8 on page 15](#), [Fig. 9 on page 16](#), [Fig. 10 on page 17](#), [Fig. 11 on page 18](#) and [Fig. 12 on page 19](#)): The commonest radiological manifestation of PCD is seen in 100% of adults and approximately 50% of children [5]. The right middle lobe is the most common lobe to manifest bronchiectasis in both adult and paediatric patients. The distribution of bronchiectasis may be either central or diffuse.

**Situs Abnormalities** ([Fig. 13 on page 20](#) and [Fig. 14 on page 21](#)): Situs inversus and heterotaxy are the common situs abnormalities associated with PCD. Heterotaxic subgroups included situs inversus with congenital heart disease, polysplenia with cardiovascular anomalies, polysplenia alone, asplenia with vascular anomalies and abdominal situs inversus with polysplenia.

**Lobectomy**: HRCT may demonstrate evidence of previous lobectomy ([Fig. 15 on page 22](#)). The commonest indication for lobectomy is recurrent pneumonia in a bronchiectatic lobe (usually the right middle or lower lobes) with or without haemoptysis.

**Mucous plugging** ([Fig. 16 on page 23](#)): Occurs more commonly in adults than in children.

Less commonly described HRCT feature of PCD are pectus excavatum ([Fig. 17 on page 24](#)), emphysema and calcium deposition. The distribution of calcium deposition follows that of the involved bronchiectatic airways and may be peribronchial, endobronchial or both.

**Magnetic Resonance Imaging (MRI)**
The primary advantage of chest MRI over HRCT is the avoidance of ionizing radiation. Image acquisitions can hence be repeated (e.g. in case of artefacts) and thus suitable for long-term disease monitoring.

Unlike HRCT, MRI can distinguish between mucous plugging and bronchial wall thickening even in the peripheral airways. This is of relevance because peripheral mucous plugging is a marker of early small airway disease. MRI also enables structural and functional (e.g. perfusion) data to be obtained in a single examination, thereby reducing imaging costs and increasing patient compliance [6].

Drawbacks of MRI are a low signal-to-noise ratio (because of the low proton density of the lung), artefacts from cardiac and breathing motion, long acquisition times and high costs. The spatial resolution of MRI is also lower than that of CT and slight morphological changes such as peripheral bronchiectasis without bronchial wall thickening are not consistently visualized by MRI [6].

The use of MRI for assessing and monitoring PCD has great potential but requires further research which will hopefully lead to lower costs, shorter examination times and higher image resolution.

**Extra-pulmonary features:**

Radiologically evident extra-pulmonary manifestations associated with PCD include hydrocephalus, polycystic kidney disease, liver cysts and biliary atresia.

**Management**

Unfortunately there is no proven PCD therapy, and most of the supportive treatments are extrapolated from patients suffering from cystic fibrosis and bronchiectasis. Treatment is mainly supportive, and the European Respiratory Society Consensus Statement suggests a role for nasal douches, long term antibiotic prophylaxis, anticholingergics and endoscopic sinus surgery.

**Respiratory monitoring**

Patients require regular monitoring of their respiratory functions, airway clearance by physiotherapy or nasal douches (Fig. 18 on page 25). Regular sputum samples (Fig. 19 on page 26) or cough swabs are performed [3]. Patients are routinely immunized against, and any upper or lower respiratory tract infections are aggressively treated.

**Osmotic agents**- Hypertonic saline has some evidence that it may help in airways clearance.
**Anti-inflammatory/antibiotics therapy** - Unlike cystic fibrosis, anti-inflammatories like macrolides are not routinely used, unless patients are proven not to be colonised by non-tuberculous mycobacteria. A range of broad spectrum antibiotics are used to treat acute episodes, but there is no evidence to suggest any benefit from the use of prophylactic antibiotics.

**Surgery** - Lung resections and transplants maybe an option for established bronchiectasis, especially for localized bronchiectasis refractory to normal medical treatment. It should be discussed with specialists, and decision only undertaken after multi-disciplinary meetings. There is some evidence to suggest that there is subjective improvement post resection [4].

**Physiotherapy** - Physiotherapists are actively involved in showing patients the gravity assisted positions and chest percussions (Fig. 20 on page 27). They may also use additional devices including positive expiratory pressure masks (PEP)(Fig. 21 on page 28). Patients are encouraged to exercise to encourage sputum clearance. However, the exact frequency and optimum duration of these therapies are unknown.

**Otolaryngologic disease**
Controversy remains over the best course of action for otitis media with effusion. Some clinicians are fond of tympanostomy tubes, which theoretically improve hearing long term. The tubes may result in otorrhea. The European Respiratory Society Consensus Statement recently recommended against tube placements, as spontaneous resolution may occur as adolescents.

Chronic sinusitis maybe managed conservatively with nasal steroids, lavage, and antibiotics. Surgical treatment involve polypectomy and functional endoscopic sinus surgery, if medical treatment fails.
Fig. 1: Measurement of nasal nitric oxide levels by aspirating air from the opening of one nostril which is then directed into an NO analyser.

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Fig. 2: Fresh airway epithelium biopsies obtained from nasal cavity in an out-patient setting.

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**Fig. 3:** Longitudinal electron microscopy of normal nasal epithelium.

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Fig. 4: High magnification electron microscopy demonstrating the ultrastructure of a normal cilium.

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Fig. 5: High magnification electron microscopy of an abnormal cilium with no dyenin arms.

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Fig. 6: Chest radiograph of a PCD patient demonstrating dextrocardia and bronchiectasis.

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**Fig. 7:** Severe mucosal thickening of the paranasal sinuses. PCD patients commonly suffer from repeated bouts of rhinosinusitis.

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Fig. 8: There is a wide spectrum of the degree of severity bronchiectasis presents on HRCT. On this image there is mild bronchiectasis in the right middle lobe, which is common.

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Fig. 9: Bronchiectasis (with bronchial wall thickening) affecting mainly the right middle lobe and lingula.

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**Fig. 10:** Contrast enhanced CT of a PCD patient demonstrating marked left lower lobe bronchiectasis with volume loss.

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**Fig. 11:** Severe right lower lobe bronchiectasis, with formation of a mycetoma.

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Fig. 12: Florid bronchiectasis, mucous plugging and consolidative changes in a patient with PCD.

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Fig. 13: Contrast enhanced CT of a patient with situs inversus.

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Fig. 14: Coronal MRI image of a patient with dextrocardia and situs inversus.

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Fig. 15: Patient who had a pneumonectomy due to severe bronchiectasis. Inflammatory ground glass changes in the right upper and mid hemithorax lung parenchyma.

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Fig. 16: HRCT of a patient with severe mucous plugging of the lower lobe distal airways.

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Fig. 17: HRCT of a patient with pectus excavatum, and a milder degree of bronchiectasis in the lingula.

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Fig. 18: Patient performing nasal douching, which is also known as nasal irrigation. Chronic mucoid rhinorrhoea maybe treated with saline douches.

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Fig. 19: Thick yellow sputum sample collected from a PCD patient.

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**Fig. 20:** A respiratory physiotherapist uses different positions and gravity to help facilitate secretion drainage from the lungs. Parents and adult patients are taught these techniques, and children are taught to perform these techniques independently as they mature.

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Fig. 21: Different adjunct devices are used to increase efficacy of physiotherapy. For example this patient is using a positive expiratory pressure, which enables air to get in and out of the lungs, increasing efficacy of mucous clearance.

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Conclusion

Earlier recognition of PCD allows supportive care of respiratory tract and ear nose and throat conditions to be instituted, improving quality of life and slowing or preventing deterioration.

The chest radiograph remains the basic investigation but PCD is a multisystem disease.

Radiographs are often insensitive and CT demonstrates bronchiectasis in optimal detail but should be used infrequently in this lifelong condition.
References


