Update on primary ciliary dyskinesia

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Abstract

PCD is a rare autosomal recessive disorder of ciliary function. It is characterised by progressive sino-pulmonary disease, fertility problems and disorders of organ laterality. Clinical phenotype and disease course can vary significantly. A daily chronic wet cough that never goes away is invariably present, with most suffering from persistent and significant rhinosinusitis. Middle ear effusion and hearing difficulty are seen in a proportion of patients. Bronchiectasis is reported in approximately 70% of children.

Diagnosis can be difficult and often requires specialist centre input. In patients with a suggestive clinical phenotype a combination of nasal nitric oxide, high-speed video microscopy analysis for ciliary beat frequency and pattern, and transmission electron microscopy analysis of ciliary ultrastructure are performed as appropriate. In populations studied genetic defects have been identified in approximately 60% of cases, with many genes yet to be discovered.

There is no evidence on which to base guidelines of clinical management and most treatment regimens are extrapolated from those used in Cystic Fibrosis. Specialist care by respiratory and ENT specialists is recommended. Current respiratory management focuses on physiotherapy and exercise to help compensate for defective mucociliary transport together with identification and treatment of infection. Ongoing international collaboration is key in being able to better understand a disease of such heterogeneity and to produce best practice guidance for standardised clinical care.

Keywords bronchiectasis; chronic cough; cilia; Kartagener; PCD; primary ciliary dyskinesia

Defining the disease

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disorder characterized by abnormal ciliary function, leading to progressive sino-pulmonary disease, reduced fertility and disorders of organ laterality. The prevalence of PCD is approximately 1:20,000 live births although this varies significantly between ethnic groups. A prevalence of 1:2,200 has been reported in the UK Asian population.

Large numbers of ciliated cells are present in the respiratory tract, brain ventricles and aqueducts, testicular efferent ducts and fallopian tubes. Ciliated cells are the dominant cell type in human airways (up to 10^9 cilia per cm^2). Normal cilia have nine peripheral microtubular doublets and a central pair arrangement. The key axonemal components are the outer dynein arms and inner dynein arms, motors and radial spokes and the nexin dynein regulatory complex. Each cilium will beat in a coordinated fashion over a million times each day, providing mucociliary clearance and innate lung defence.

In PCD, mucociliary clearance is absent or markedly impaired due to abnormal ciliary movement. Reduced Generation of Multiple Motile Cilia (previously known as Ciliary Aplasia), is a rare disease entity, currently grouped with PCD, in which there are highly reduced numbers of cilia that can either be motile or have motility defects. Patients with this condition appear to present with a more severe clinical course of recurrent and chronic airway infection.

Situs inversus totalis occurs in approximately 45% of confirmed cases of PCD but is not seen in patients with central microtubular defects such as ciliary transposition. Kennedy and

colleagues (2007) reported 6.3% of patients to have heterotaxy (as defined by any thoraco-abdominal asymmetry other than *situs inversus*). In this group, there is a small but significant increase in prevalence of complex congenital heart disease. Rare associations of PCD include hydrocephalus, polycystic kidney disease and retinitis pigmentosa. The sperm tail has a similar structure and motor system to that of cilia. As a result, males with PCD will have marked sub-fertility or infertility. In women, defective ciliary function affecting the reproductive tract may sometimes affect fertility and potentially increase the risk of ectopic pregnancies.

Course of the disease

PCD is a genetically heterogeneous condition with variable clinical phenotypes. Patients invariably present with chronic rhino-sinusitis, a daily wet sounding cough, recurrent pulmonary infections and inflammation of the respiratory tract. Glue ear is very common and can cause significant hearing loss in young children. Studies have reported that up to 91% of children with PCD have a history of neonatal respiratory distress. This is much higher than the UK experience.

Radiological appearances and change over time

Radiologically PCD is characterised by bronchiectasis, with peribronchial thickening, mucous plugging, consolidation and air trapping. Bronchiectasis is more predominant in the middle and lower lobes. CT evidence of bronchiectasis is common occurring in 70% of children on first CT scan (mean age 8.7 years). The true prevalence of structural lung disease in this age group remains unclear as not all children with PCD have CT scans. Expert opinion suggests poor correlation between CT findings and other markers of disease severity such as spirometry.

Lung function abnormalities are common but decline is variable and dependent upon treatment

Abnormal lung function is also common in PCD and is associated with an obstructive pattern with a reduction in both FEV_1 and FEF_{25-75}. Analysis of the published literature through systematic review shows that mean FEV_1 tends to decrease over time and is 58% (range 35–77%) in adults and 78% (range 73–88%) in children. The natural history and disease progression of PCD is poorly defined however with conflicting reports in the literature describing a wide variability in longitudinal change in lung function and disease progression, even from within the same centres. Deterioration in lung function occurs in some individuals before diagnosis and it appears this can be stabilised with appropriate treatment.

In adult patients there is a wide spectrum of lung function impairment and radiological disease severity. Lung clearance index is an alternative and more sensitive marker of airways disease in conditions such as cystic fibrosis. However in PCD, lung clearance index does not appear to correlate with either spirometry or high resolution CT findings. Further work is required to determine its place in assessment.

Effects of chronic infection on phenotype

Pseudomonas aeruginosa colonisation may be a marker of disease severity, rather than a predictor of disease progression. Colonisation correlates with age, impairment in FEV_1 at diagnosis and extent of bronchiectasis but does not correlate with change in lung function over time. These findings differ to those of the clinical course of cystic fibrosis. *P. aeruginosa* colonisation appears much less common in patients with PCD than with cystic fibrosis. A recent review of 107 patients with PCD showed that 39% met the criteria for chronic *P. aeruginosa* infection at least once. In contrast, by adulthood, approximately 80% patients with cystic fibrosis are colonised with *P. aeruginosa*.

Prognosis

The prognosis of PCD varies significantly between affected individuals. Some children develop severe lung disease. Large cohort studies across the age spectrum of 0–73 years have shown that whilst decline in lung function is typically 25–50% less than that reported in cystic fibrosis, 25% of individuals still develop severe disease.

Diagnosis

Unlike cystic fibrosis, newborn screening for PCD is not available. Therefore most presentations are as a result of the recognition of suggestive symptomatology. A diagnosis of PCD is often delayed and diagnosis in adulthood is not uncommon, especially when *situs inversus* is not present. A European survey in 2010 reported the median age at diagnosis to be 5.3 years. It was lower in children with *situs inversus* and in children attending tertiary respiratory centres.

Diagnostic algorithms for PCD vary significantly between countries. There is no “gold-standard” test for PCD. European consensus guidelines recommend a combination of tests including recognition of a clinical phenotype, nasal nitric oxide screening, high-speed video microscopy analysis of ciliary beat frequency and pattern, and transmission electron microscopy analysis of ciliary ultrastructure.

The nationally funded diagnostic services for the UK (Leicester, Royal Brompton and Southampton) have used this approach since 2006. In addition they undertake ciliated cell culture to help in the diagnosis of rare or previously unreported phenotypes. Genetic testing is increasingly used but its availability in diagnostic testing varies significantly between countries.

Clinical phenotype

History

The clinical features of PCD are outlined in Table 1. The single most important clinical feature suggestive of a PCD diagnosis is a wet sounding cough that has ‘always been there’. Typically it is present even when the child is well. Older children and adults often expectorate sputum. Notably cough is present in the neonatal period.

In PCD chronic secretion retention in the upper respiratory tract predisposes to infection in the middle ear, nose and facial sinuses. Chronic otitis media with effusion affects up to 80% of children and is often persistent, with fluctuation through adulthood. Hearing loss is also common and whilst it is usually mild to moderate it can be profound. It does, however, usually spontaneously resolve in teenage years. Most centres do not recommend use of aural ventilation tube insertion (grommets)