Diagnosing primary ciliary dyskinesia:

A nationally funded diagnostic service should lead to improved outcome

Professor Christopher O'Callaghan – Professor of Paediatrics[1]

Dr Mark Chilvers – Consultant in Paediatric Respiratory Medicine[1]

Dr Claire Hogg – Consultant Paediatric Respiratory Medicine[2]

Professor Andrew Bush – Professor of Paediatric Respirology[2]

Dr Jane Lucas – Clinical Senior Lecturer/Consultant Paediatrician[3]

[1]Leicester Royal Infirmary Children's Hospital, and Institute of Lung Health

Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX

[2]Royal Brompton Hospital, Sydney Street, London, SW3 6NP

[3]Southampton University Hospital NHS Trust, Tremona Road, Southampton, SO16 6YD

Keywords: Primary ciliary dyskinesia; Cilia; Cough; Rhinitis

Word count: 989

Corresponding author:

Professor Chris O'Callaghan

Robert Kilpatrick Clinical Sciences Building

Leicester Royal Infirmary

PO Box 65

Leicester

LE2 7LX

Tel: 0116 252 3269 Fax: 0116 252 3282 E-mail: ajb64@le.ac.uk

The National Specialist Commissioning Advisory Group (NSCAG) has funded three centres to establish and provide a national diagnostic service for England for children and adults suspected of suffering from primary ciliary dyskinesia (PCD). This is welcomed, as state of the art diagnostic testing will be available nationally which will increase the numbers of patients diagnosed with a condition in which early diagnosis has a very significant effect on both short-term and long-term morbidity. Inheritance is autosomal recessive with an incidence of around 1:15,000 in the Caucasian population and, as expected, we have found a much higher incidence in ethnic groups where consanguineous marriages are common. Accurate diagnosis will allow appropriate genetic counselling of families.

PCD is caused by one of a number of different ciliary defects that result in ineffective mucociliary clearance. Although most patients with PCD have symptoms from birth or early infancy [1] the diagnosis is frequently delayed [2] and it is likely that a significant number of patients are never diagnosed.[3] Failure to diagnose PCD leads to progressive and permanent lung destruction owing to obstruction of the airways with secretions and subsequent infection, leading to bronchiectasis. Early diagnosis of PCD is important as deterioration in lung function can largely be prevented by specialist respiratory care.[4] Failure to recognise the condition frequently leads to inappropriate ear, nose and throat (ENT) surgery. Grommet insertion may lead to persistent aural discharge with little improvement in hearing loss. A number of patients with unrecognised PCD present in infertility clinics. Infertility in males, although not inevitable, is due to sperm tails being affected as part of their PCD. There is an increased incidence of ectopic pregnancy due to defective movement of the cilia in the fallopian tube.[5]

As PCD testing is not a front line test for those with respiratory problems, who should be referred? Patients with situs inversus, which occurs in between 40-50% of individuals with PCD, is an obvious indication. Of patients referred to our laboratory with situs inversus, 75% of cases have been confirmed to have PCD. Of patients without situs inversus, those with bronchiectasis and life-long nasal symptoms in whom no other cause has been identified should be considered for referral. A

significant number of patients with PCD will have a history of unexplained neonatal respiratory distress and persistent rhinitis from birth. The real aim, however, is to diagnose children before bronchiectasis develops and before they are subjected to repeated ENT surgery. The investigation of children with host defence problems - including PCD - who are at risk of developing bronchiectasis is frequently delayed. Reasons for the delay include the child's tendency to swallow rather than expectorate sputum, a distinct lack of auscultatory findings and temperature even during acute exacerbations, and the fact that the chest radiograph often appears normal.

So, how do we recognise a young child at risk of developing bronchiectasis? The important sign is that of a persistent "wet" sounding cough. If such a cough persists for more than 8 weeks or improvement is seen with antibiotic treatment but symptoms continue to return when stopped, paediatric review should be arranged. In patients with PCD the cough never goes completely even with treatment and "has always been there". Testing for PCD should be considered if standard first line investigations to exclude cystic fibrosis (CF) and screening for immunological defects are negative and the child has a life-long history of a "wet" sounding cough and has persistent nasal symptoms. A number of patients will have a history of unexplained neonatal respiratory distress. Hearing problems are only seen in half of cases. If the child is from a consanguineous marriage, suspicion should be higher. Nonetheless, symptoms may be mild; in one series, diagnosis was made in 10% as a result of family screening after the diagnosis in an index case.[6]

Diagnosis to date has largely been provided on an ad hoc basis, with lack of standardisation of, and inaccessibility to, diagnostic testing for the majority of patients in the UK. Screening tests for PCD exist, but there are problems associated with them. The saccharin test used to assess mucociliary function is difficult to perform and is unreliable in children. Measurement of nasal nitric oxide, which is very low in patients with PCD, is now accepted as the most sensitive and specific screening test for PCD.[7] Unfortunately this is not widely available and cannot be used in young children. The development of new methodologies over the last few years has allowed improved diagnostic testing for PCD. The traditional measurement of ciliary beat frequency alone has been shown to miss a

proportion of patients with PCD whose ciliary beat frequency is normal, but beat pattern abnormal [8] . Diagnostic assessment following biopsy will now include measurement of ciliary beat frequency, high speed analysis of ciliary beat pattern,[8] detailed electron microscopy of ciliary ultrastructure and, in cases where there are diagnostic uncertainties, cell culture [9] from biopsies. Although the genetics of PCD are slowly being unravelled, owing to the multiple phenotypes of the disease and more than 200 different proteins used to construct the ciliary axoneme, it is likely to be some time before such tests are widely used in the diagnostic examination of patients with PCD.

The diagnostic service is able to accept appropriate referrals from hospital consultants. However, the service does not extend to providing care for patients diagnosed with PCD. As experience of care for patients with PCD is limited, we would suggest a model similar to that for CF where patients should have access to a specialist paediatric respiratory consultant or thoracic physician with an interest in CF or non-CF bronchiectasis and be followed up regularly for life. The diagnostic service, however, will allow a national database of patients with PCD to be established, facilitating clinical trials to help provide an evidence base for management. An active PCD patient and parent support group has been established which we encourage newly diagnosed patients to contact (www.pcdsupport.org.uk).

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