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REVIEW

Primary ciliary dyskinesia: diagnosis and standards of care

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Primary ciliary dyskinesia: diagnosis and standards of care. A. Bush, P. Cole, M. Hariri, I. Mackay, G. Phillips, C. O'Callaghan, R. Wilson, J.O. Warner. ©ERS Journals Ltd 1998.
ABSTRACT: Primary ciliary dyskinesia (PCD) is characterized by disease of the upper and lower respiratory tract, in association with visceral mirror image arrangement in 50% of cases, due to abnormal structure and/or function of cilia. The purpose of this paper is to review the clinical features, diagnosis and management of PCD. Presentations include neonatal respiratory distress, recurrent lower respiratory tract infection, chronic rhinosinusitis and male infertility. PCD enters the differential diagnosis of bronchiectasis, atypical asthma, and unusually severe upper airway disease. Diagnosis is by a cascade of investigations, starting with the saccharin test in patients older than 10 yrs; ciliary beat frequency and pattern on light microscopy; and electron microscopy to assess ciliary morphology and orientation. It is important not to confuse primary and secondary ciliary abnormalities. Nasal nitric oxide is low in PCD, and this measurement shows promise as a screening test for PCD. Diagnosis is important, in order to prevent the development of bronchiectasis and to avoid any unnecessary otorhinolaryngological procedures. Regular follow-up is essential, and management should be multidisciplinary, with input from centres with a special interest in PCD, having access to paediatric and adult chest physicians, otolaryngologists and audiological physicians, physiotherapists, counselling services and fertility clinics. The prognosis is good, but morbidity can be considerable if PCD is incorrectly managed.
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Primary ciliary dyskinesia (PCD) is a relatively rare condition mainly inherited as an autosomal recessive [1], but with other inheritance patterns possible [2]. The prevalence is almost certainly underestimated. Late diagnosis is common, as are mild cases picked up by screening siblings of an index case [3]. Even given an incidence of 1 in 15,000, there will be around 70 new cases born per year, and 3,000 cases in the UK in total. By contrast, only around 90 cases are known to the UK PCD support group (personal communication). Even if this group is aware of only one tenth of known cases, the implication is that there are large numbers of undiagnosed patients. This is far from being a matter of mere academic importance, since the diagnosis has implications for many aspects of upper and lower respiratory tract disease, for example, the prevention of bronchiectasis by aggressive use of physiotherapy and antibiotics, avoidance of inappropriate ear nose and throat (ENT) procedures and thoracic surgery, and assessment and treatment of deafness.

The purpose of this paper is to increase the diagnostic awareness of PCD by discussing the indications for referral for diagnostic testing, and to establish acceptable criteria for making the diagnosis once it has been suspected. The authors represent different specialities, all with clinical and research interests in PCD.

Presentations of PCD

In view of the expense and lack of availability of diagnostic testing for PCD (below), most physicians will want to undertake other screening investigations appropriate to the presenting symptom(s) first. The varying patterns of symptoms have been reviewed [4, 5]. In one series [4], the age at presentation varied between 4 months and 51 yrs, with chronic sputum production and nasal symptoms the main presenting features. In a paediatric series [5], cough, sinusitis and otitis were universal. In both series [4, 5], dextrocardia was present in half the patients. Depending on the presentation, these may include sweat testing, immunoglobulins and subclasses, pH probe, *etc*. The nature of the investigations will depend on the clinical situation. A diagnosis of PCD should be considered under a number of circumstances; no one feature is an absolute indication, and a combination of signs and symptoms may be more suggestive than one single indication on its own.

1) In the new-born period: unexplained tachypnoea or neonatal pneumonia, particularly in a term baby with no risk factor for congenital infection [6]. One group found that 13/30 patients with PCD had a history of neonatal respiratory symptoms [5]. Other presentations at this age include the newborn with rhinitis; dextrocardia or complete mirror image arrangement with structurally normal heart; complex congenital heart disease, particularly with disorders of laterality [7]; oesophageal atresia or other severe defects of oesophageal function [7]; biliary atresia [8]; hydrocephalus [9, 10]; and positive family history.

2) In the infant and older child: "asthma" that is atypical or not responsive to treatment; chronic particularly wet cough, and sputum production in the older child who is able to expectorate (these are particularly important symptoms,

whose cause should always actively be pursued in childhood); very severe gastro-oesophageal reflux; bronchiectasis; rhinosinusitis (very rarely with nasal polyps) [5, 11–13]; chronic and severe secretory otitis media, particularly with continuous discharge from the ears after grommet insertion; and diagnosis in more severely affected sibling [14, 15].
3) In the adult presentation as in the older child, but also female subfertility including ectopic pregnancy [16] and male infertility with spermatozoa that are immotile or of reduced motility. It should be noted that infertility in males is by no means invariable [17].

Specific diagnostic situations

Individual clinicians will differ in the order in which tests are performed, and to some extent, this will depend on the facilities available. Two points should be stressed: it is important not to be confused by abnormalities that are secondary to an underlying infection and thus might confuse the diagnostic work up [18, 19]; and secondly, that more than one abnormality of host defence may co-exist in the same person.
1) Baby with neonatal respiratory distress: in the absence of any epidemiological surveys, it would seem reasonable to recommend screening for PCD for term babies born by vaginal delivery who become sufficiently tachypnoeic as to require treatment and who have no conventional risk factors for transient tachypnoea of the newborn; for babies with neonatal pneumonia with no history of maternal illness or prolonged rupture of the membranes; and for any baby with significant and prolonged nasal discharge.
2) Child/adult with bronchiectasis of unknown cause: The first consideration is to demonstrate that bronchiectasis is present; the chest radiograph is notoriously insensitive, and bronchography has been replaced by high-resolution, thin-section computed tomography. This investigation involves irradiation exposure, and should not be undertaken lightly, particularly in children and young females. The anatomical fact of bronchiectasis having been established, investigations to determine the cause should be pursued. The "first wave" tests are chosen because of the availability and prevalence of the underlying condition. These will include a sweat test (often with nasal potentials, and cystic fibrosis genotype), immunoglobulins (Ig) (including IgE) and IgG subclasses, antibody responses, serological evidence of previous adenovirus or mycoplasma infection, autoantibody screen (rheumatoid factor, antinuclear factor) and alpha-1 antitrypsin levels. If these are negative, then "second wave" investigations to be considered include fibreoptic bronchoscopy (particularly for disease localized to one lobe), oesophageal pH monitoring; saccharin test in older children and adults, and nasal brushings for ciliary studies; neutrophil function tests; and T-cell subsets. The choice of second wave investigations will depend on any associated features which may be present. It should be noted that more than one immunological abnormality can exist, and pursuing further investigations should be considered even if one putative abnormality has been found.
3) Child with severe or atypical asthma: in this situation, it is vital to consider whether the diagnosis is correct. Many will want to perform the "first wave" tests above on most children who are not responding to high dose inhaled steroids, and in addition exclude a vascular ring by performing a barium swallow and echocardiogram. Fibreoptic bronchoscopy would also need consideration. PCD also enters the differential diagnosis.
4) Child with upper airway disease: nasal polyps, with or without severe sinusitis, may be the presenting feature of cystic fibrosis, and, in a child mandates a sweat test. If this is negative, then PCD should be excluded. It would be impossible to screen all children with fluid in the middle ear; but the child with persistent serous otitis media, persistent discharge after grommet insertion, or co-existent lower airway infection should be screened for PCD. This has management implications (below).
5) Infertility clinic: all males with spermatozoa that are either immotile or of reduced motility should be considered for screening for PCD even if there are no upper or lower respiratory tract symptoms; and females who are deemed on standard criteria to be infertile or subfertile without an obvious anatomical or hormonal cause, particularly if other features of PCD are present. Fertility does not exclude the diagnosis of PCD in males.
6) Other clinical situations: the upper and lower respiratory tract features of PCD may be inconspicuous or not reported by the patient who has become accustomed to the lifelong symptoms; the possibility of the condition should be considered if there are combinations of suggestive features, including dextrocardia, disorders of laterality, deafness, hydrocephalus, biliary atresia, and congenital heart disease.

Diagnostic criteria

As with all clinical medicine, the key is a high index of suspicion, with the performance of a detailed history and physical examination. Attention must be paid to the timing of onset of symptoms (particularly the onset at birth, compared to within the first few weeks of birth). There are no definitively diagnostic features on history or examination, so diagnosis rests on laboratory testing. This should include an assessment of both structure and function.

There are a number of ways to assess mucociliary clearance, including observation of particle movement and isotope clearance from the lower respiratory tract. Clinically, the most useful is the saccharin test, which is a cheap and easy procedure that can be used to screen older children and adults; a properly performed normal test excludes the diagnosis and obviates the need for more sophisticated testing [20]. An abnormal test must be investigated by cili-ary analysis (below). Figure 1 shows an investigation plan.

The saccharin test

Indications: screening for PCD. This test is not suitable for small children who will not sit still for an hour [21]! A 1–2 mm particle of saccharin is placed on the inferior nasal turbinate 1 cm from the anterior end. The patient sits quietly with the head bent forward, and must not sniff, sneeze, cough, eat or drink for the duration of the test. The time to tasting saccharin is noted and is a measure of nasal mucociliary clearance (NMCC). If after 60 min, no sacc-

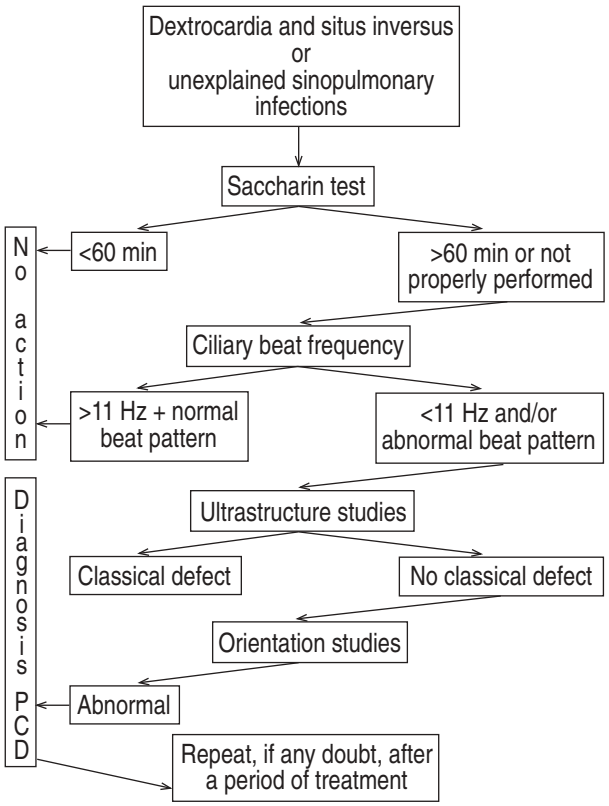

Fig. 1. – Diagnostic algorithm for primary ciliary dyskinesia (PCD). Step 1: saccharin test, result <60 min in a properly performed test, no action. Step 2: ciliary beat frequency, result >11 Hz, low index of suspicion for PCD, normal beat pattern, no action. Step 3: ultrastuctural studies, classical abnormality, no further diagnostic tests. Step 4: orientation studies. Step 5: repeat samples after treatment unless there is absolutely no doubt as to the diagnosis.

harin taste is observed, a saccharin particle is placed on the tongue to check that the patient can truly taste saccharin.

Obtaining cilia

Indications: NMCC >60 min; patient cannot taste saccharin; and patient cannot cooperate with the saccharin test. The subject must have been free from viral upper respiratory tract infection for 4–6 weeks. This may present a problem in a child, and particularly in one with chronic noninfective rhinitis, it may be impossible to determine whether the child has a cold or not. A convenient way of obtaining ciliated cells for study is by brushing the inferior meatus at the lateral aspect of the inferior turbinate, using a sterile or disposable cytology brush [22]. Precise siting of the brush is difficult in the nonanaesthetized child, but adequate brushings can usually be obtained by an experienced operator, regardless of the age of the subject. The brush is agitated in cell culture medium (for example, Medium 199, Minimal Essential Medium) to dislodge strips of epithelium. Normal saline can be used, but ciliary beat frequency (CBF) measurements may be more difficult. In PCD, nasal and bronchial ciliary function is similar [23]. If a bronchoscopy is being performed for other purposes, then we recommend that an endobronchial sample also be taken. It should be noted that some anaesthetic agents, *e.g.* halothane and lignocaine, may reduce the beat frequency markedly [24]. In postpubertal males, semen can be examined, but males with PCD may have motile spermatozoa [17].

Assessment of function

Indications: as above. Cilia should only be studied in centres familiar with the technique. A number of different methods have been used, but there is no published evidence as to which is superior. Whatever technique is to be used, ideally, epithelium should be examined within 2 h. It is possible to transport the samples to centres and still obtain adequate CBF measurements after as long as 24 h. Some centres advocate adding penicillin or streptomycin to the medium in such a case, in order to suppress the growth of any nasal flora in the biopsy sample. If the CBF and beat pattern are normal, then no further investigations are required; however, if they are abnormal in any way, the patient must travel to the centre for further investigation.

Epithelial strips (not single cells) should be examined in a suitable preparation such as a sealed microscope slide-coverslip at a magnification at least ×320, or on a small plastic Petri dish [25, 26]. The extent of ciliation and the amount of debris and bacteria should be noted. At least 10 strips >50 μm in length should be studied. The photometric technique is performed at 37°C by using a warm stage. Other techniques have been used, including the use of a photodiode, with the signal relayed to a computer program for power spectrum analysis [27]. Fifteen minutes should be allowed for CBF to stabilize. It is advised that each laboratory establish its own normal ranges, which may show a slight age variation [28, 29]. The approximate normal range is 11–16 Hz. Some centres use a more sophisticated analysis of beat frequency using Fast Fourier transforms, but these must not be allowed to substitute for direct inspection of the cilia to detect a dyskinetic beat. In addition, the presence of static cilia, and their number as a percentage of the total should be noted, as well as an estimate of beat pattern by an experienced observer. The oscillograph recording will help in the assessment of beat pattern, and ideally, the beating cilia should be videotaped.

Assessment of structure

Indications: CBF <11 Hz; Beat pattern dyskinetic but normal CBF; and NMCC >60 min and strong clinical suspicion of PCD. Electron microscopy is an essential part of diagnostic testing. It can be safely omitted only if the CBF is normal with a normal beat pattern. Even under these circumstances, orientation studies should be performed if clinical suspicion is high [30]. The epithelium should be fixed immediately in cacodylate-buffered 2.5% glutaraldehyde and postfixed in osmium tetroxide, then processed for transmission electron microscopy (TEM). This assessment is more accurate if cilia from different cells are examined, ideally from different strips of epithelium. At least five good cross-sections from each of 10 different non-adjacent cells (*i.e.* a minimum of 50 cilia) should be studied, but more should be examined if differences between cilia are noted. In any case, the numbers of ciliary cross-sections, cells and abnormalities detected should be stated. Abnormalities in up to 10% of cilia may

be seen in a normal sample [28, 31, 32]; if in doubt, a repeat sample should be taken (see below). There do not appear to be any significant ultrastructural differences between bronchial and nasal cilia [33], or age-related changes [34].

Ciliary disorientation was recently described as a possible variant of PCD [35, 36]. Patients typically have cilia with normal structure and normal or near-normal beat frequency, but their cilia lack efficacy because their beat direction is disoriented. It has been suggested that this is a genetically conferred abnormality of the basal bodies or possibly of the anchoring mechanism, preventing normal orientation of cilia. This has to be measured by electron microscopy from cross-sections of ciliary shafts or basal feet. Lines are drawn through the central pairs, or to transect the midpoint of base and apex of the basal feet, of a number of cilia arising from a single cell. These lines should normally all be roughly parallel with each other, and thus make a similar angle with a second line drawn vertically. The standard deviation (SD) of these angles should, therefore, be small. An SD can be calculated for a number of cells in the sample and a mean SD computed. Disorientation results in a larger SD. Typical normal values are SD 10–15% and for PCD with disorientation, 20–25% [30, 37]. However, ciliary disorientation can be transient, secondary to infection, so a second sample is taken after treatment to reduce inflammation and eradicate infection before a diagnosis of PCD secondary to disorientation is made. Table 1 gives the ultrastrutural abnormalities which may be encountered in PCD.

Need for repeated tests

Indications: any suspicion of secondary ciliary dyskinesia; atypical clinical picture; and suspicion of primary orientation defect. Since secondary ciliary dysfunction is common, unless structural studies show a clear-cut abnormality diagnostic of PCD and the clinical picture is classical, a repeat sample should be obtained several months after the first sample to avoid confusing primary and secondary problems. Intensive and prolonged treatment of any inflammation and infection should be undertaken before the second sample is taken. If possible, a further sample should be taken from another part of the respiratory tract, *e.g.* at bronchoscopy. There is some evidence that spermatazoal tails are under the control of different genetic loci [46, 47], so semen analysis may not reflect respiratory cilia.

Despite detailed investigation, diagnostic doubt may remain. Under these circumstances, the patient should be treated energetically as if the patient had PCD, along the lines set out below. Failure to do this may result in permanent lung damage.

Table 1. – Ciliary abnormalities in primary ciliary dyskinesia

Abnormality	Detail	Reference
Dynein arm defects	Absence or reduced number of inner and/or outer arms	[13, 38]
Tubular defects	Transposition, extra microtubules	[39]
	Commonly secondary	[17, 18, 27]
Radial spoke defects	Absence	[40]
Ciliary disorientation	Suspect if mean standard deviation of angles >20°, not reducing after treatment and present in two sites (nose, bronchus)	[34, 35, 41]
Abnormal basal apparatus		[42]
Ciliary aplasia		[43]
Abnormally long cilia		[44]
No abnormality	Repeat test and do orientation studies	[27, 45]

Measurements of nasal and exhaled nitric oxide

Nitric oxide (NO) is produced from the upper and lower respiratory tract. Exhaled NO is increased in uncontrolled asthma [48, 49] and bronchiectasis [50], but normal in cystic fibrosis [51, 52]. In patients with PCD, nasal [53, 54] and tidally exhaled [54] NO is very low. These observations are currently unexplained. It would be premature to suggest that measurement of NO can be used to diagnose or exclude PCD, or even as a screening test. However, if NO is found to be unexpectedly low in a patient thought to have uncontrolled asthma or bronchiectasis of unknown cause, then the diagnosis of PCD should be actively excluded. Further research is needed, but currently, we cannot recommend a definite clinical role for NO measurements in the diagnosis of PCD.

Standards of care

There are very few clinical trials in this area, partly due to the rarity of the condition. The views presented here, except where otherwise referenced, are our current consensus on best practice.

Care from general practitioners

The general practitioner (GP) will carry out all routine care and monitoring as with any child with a chronic illness. This includes ensuring full routine immunization; bacille Calmette-Guérin (BCG) in line with local policy; and yearly influenza immunization. There should be a willingness to see the child/adult with PCD urgently at the request of the patient/family, recognizing the need to prevent lung damage by aggressive treatment of infection. The GP will co-ordinate the community services where appropriate. The GP is a pivotal figure who should emphasize the need for daily home physiotherapy (with parental/carer assistance or self-administered, sometimes with the support of a community physiotherapist), which is the bedrock of treatment, and the aggressive use of antibio-tics. The aim of treatment should be prevention of chronic lung damage and bronchiectasis.

The hospital(s) in turn will liaise closely with the GP, recognizing that PCD is a rare condition, and that education, information and sharing of protocols is essential if the GP is to provide good care. It should be recognized that the requirements of care of a patient with PCD are

such that referral to a paediatrician with an interest in respiratory disease (for a child) or respiratory physician (for an adult) is mandatory.

Hospital care

The local paediatrician/chest physician will undertake most of the rest of the care of patients with PCD, including regular review, in order to obviate the need for repeated long journeys to special centres. It is anticipated that regular visits will take place every 2–3 months in children and six monthly or annually in adults. The local centre will provide general medical/paediatric care, including regular growth assessment during childhood. The patient with PCD has the right to the following services in the local hospital. If, as is likely, some cannot be provided, then referral to an appropriate special centre is mandated.

Respiratory monitoring. This should include regular pulse oximetry and spirometry. In our view, looking after a patient without routine access to these measurements in the clinic is no more justified than doing a hypertension clinic without measuring the blood pressure. Isotope ventilation scans can be used to give additional information in children too young to perform lung function [55], but the role of this investigation in PCD is still under investigation. Chest radiography and regular sputum culture are performed when appropriate. Regular assessment by a physiotherapist with expertise in respiratory medicine is essential. Access to a respiratory nurse or other qualified professional to check techniques with drug delivery devices, provide education about the condition, and give advice about smoking and allergen avoidance in the home environment should also be part of routine care.

The twin pillars of respiratory treatment are antibiotic treatment and chest physiotherapy. Prolonged, high-dose oral antibiotics should be given at the first sign of any increase in respiratory symptoms or deterioration in lung function. The main infecting organism is *Haemophilus influenza*, but *Staphyloccocus aureus* and *Streptococcus pneumoniae* have also been reported [2, 56–58]. Intravenous treatment should be used if symptoms do not respond. In adults, *Pseudomonas aeruginosa* colonization is not rare [5, 57] and may require the more aggressive use of intravenous therapy and consideration of long-term nebulized antibiotics.

Daily physiotherapy is essential for augmenting airway clearance in order to delay the onset and progression of obstructive airway disease. This should be administered by the parents for young children and self-administered with appropriate support by older children and adults. In conjunction with the active cycle of breathing techniques (ACBT) gravity-assisted positioning is advised to aid secretion drainage from the dependent parts of the lungs. ACBT consists of "breathing control" which is relaxed breathing using the lower chest, "thoracic expansion exercises", where four deep breaths, with an emphasis on inspiration, are performed with chest clapping if found more effective and then the "forced expiration technique" or huff is performed [59]. A minimum of 10 min in any one position and two positions per treatment are recommended. In addition to the lower lobes, the middle and lingula must not be forgotten. Twenty minutes of physiotherapy twice a day is recommended when well, increasing during respiratory exacerbations. Bronchodilator therapy may be beneficial, but formal reversibility studies should be carried out. Exercise may be a better bronchodilator than β-2 agonists in PCD [60] and encourages sputum clearance. The importance of exercise should be emphasized to parents and adults.

Hearing and ENT monitoring. This includes hearing assessments, using age-appropriate techniques (behavioural testing and pure tone audiometry). Traditionally, grommets are inserted if secretory otitis media affects hearing to a degree as to impair speech, language and educational development [61]. However, the use of hearing aids may be preferable to grommet insertion to avoid the almost inevitable discharge from the ear after this procedure in PCD patients [62]. Hearing aids often can be discarded in later childhood, as the condition spontaneously improves, and the end result for hearing deficit does not appear to be related to previous treatment, including grommet insertion [63]. Alternatively, unilateral grommet insertion, if successful, will restore hearing. Should this result in prolonged, the other ear can be fitted with a hearing aid. The discharging ear may respond to gentamicin with hydrocortisone ear drops; if this fails, the grommet should be removed and topical antibiotics continued until the ear is dry. Concerns have been expressed regarding the use of ear drops containing aminoglycosides and polymixins [64], but these may dramatically improve many cases of chronic otorrhoea which, if left untreated, may be prone to serious complications, including sensorineural deafness. The risk of ototoxicity appears to be very small [65] and MERFIELD *et al.* [66] could find no evidence of sensori-neural hearing loss in 70 ears treated with drops containing potentially ototoxic drugs. The use of antibiotic drops combined with hydrocortisone is significantly more effective [67].

For most patients, ENT symptoms will be regarded as a minor annoyance rather than disabling. Patients can expect to have a degree of serous otitis media lifelong, although their hearing loss is usually minimal and no intervention is required. A "sniffly" nose can be expected, along with a degree of nasal block, this too will continue, but is usually regarded as of little consequence as it has been a life-long symptom. Tonsillectomy and adenoidectomy may be indicated if there are specific symptoms but will have no effect on the underlying situation. Sinus surgery is occasionally justified if patients who develop secondary sinusitis, in which case functional endoscopic sinus surgery (FESS) does play a useful role in improving drainage, aeration and access for medication [68], though mucus will still not be propelled, and alkaline nasal douche, topical corticosteroids and systemic antibiotics will still be required when indicated.

Fertility clinic. Although infertility is not inevitable, many patients with PCD will need access to techniques of assisted conception.

Psychosocial. This should include help applying for benefits; and counselling, particularly about possible subfertility or infertility, and assessment by an educational psychologist when appropriate. Patients may need help in coping with deafness. Liaison with schools so that teach-

ers are aware of the child's potential problems is also essential.

Care from Centres with a special interest in PCD

Because of the rarity of the condition, it seems likely that patients would benefit from periodic review in a special centre with expertise in the care of patients with respiratory disorders. The frequency of review would depend on the expertise available at the referring centre and the severity of the disorder. Such a centre would offer additional testing facilities such as bronchial challenge (histamine, methacholine, or exercise), detailed lung function, sleep studies and fitness to fly testing. Detailed testing would be carried out at yearly intervals unless mandated earlier by a change in clinical status. Good communication, with agreed protocols and contact numbers for advice will be a key to success. Good liaison with care workers locally is essential. Older patients will wish for access to fertility services such as artificial insemination, and *in vitro* fertilization.

In addition, if any worthwhile research is to be carried out on this condition, patients will need to be grouped in, or known to, special centres in order that they can be offered the opportunity to participate in research studies.

Outcome for patients with PCD

The prognosis is generally considered to be good, with usually a normal life expectancy [2, 57, 58]. Occasional neonatal deaths have been recorded [59]. However, unless PCD is managed appropriately, morbidity can be considerable, from recurrent infections and iatrogenic complications, to harmful surgical procedures which must also be avoided.

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