Case Report

A rare case of primary ciliary dyskinesia with Kartagener's syndrome - A case report

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Abstract

Primary ciliary dyskinesia (PCD) is an autosomal recessive hereditary disease that includes various forms of ciliary ultrastructural defects. The most serious form is Kartagener syndrome (KS), which accounts for 50% of all cases of PCD. Kartagener's syndrome is a rare disorder and the prevalence is about 1 in 30,000. It is autosomal recessive ciliary disorder comprising the triad of situs inversus totalis, chronic sinusitis, and bronchiectasis. The defective movement of cilia leads to recurrent respiratory infections, and ear/ nose/ throat infections, and infertility. The diagnosis is made clinically and confirmed through electron microscopy, which reveals abnormalities of structural organization of the axoneme in cilia from respiratory epithelia and in spermatozoa. Underlying structural defects include 1) absent inner and/or outer dynein arms, 2) tubular defects, and 3) radial spoke defects. We hereby report a rare case of Kartagener's syndrome, in an infertile male with immotile sperms. The clinician should have a high index of suspicion, so as to make an early diagnosis. An early diagnosis helps in making the options for timely treatment of infertility may be offered and unnecessary evaluation is avoided.

Key words

Primary ciliary dyskinesia, Kartagener's syndrome, Bronchiectasis, Sinusitis, Situs Inversus.

Introduction

In 1933, Kartagener described the triad consisting of dextrocardia, chronic vasomotor rhinitis, and bronchiectasis as a distinct clinicopathological entity. Kartagener emphasized the familial and hereditary character of this syndrome, which now bears his name, Kartagener syndrome (KS) [1-7]. Kartagener's syndrome is an autosomal recessive disorder occurring with frequency of 1:30,000 to 1:40,000. It is characterized by the classic triad of dextrocardia, bronchiectasis and sinusitis [8].

Primary ciliary dyskinesia (PCD)

Primary ciliary dyskinesia (PCD) is the name that has evolved for a group of disorders caused by microtubular defects in cilia and sperm. This group of disorders was previously known as the immotile cilia syndrome until it was discovered that most of the cilia did move, albeit in an uncoordinated or dyskinetic manner [9, 10].

These defects render the cilia in the respiratory tract ineffective in clearing secretions [9, 11], a condition that can lead to sinusitis, repeated pulmonary infections, bronchiectasis, obstruction, and air trapping [12-14]. Primary ciliary dyskinesia is an autosomal recessive disorder thought to affect between 1 in 15,000 and 1 in 30,000 persons [15].

Primary ciliary dyskinesia (PCD), previously known as immotile cilia syndrome, is an autosomal recessive hereditary disease that includes various forms of ciliary ultrastructural defects. The most serious form is Kartagener syndrome (KS), which accounts for 50% of all cases of PCD. PCD causes deficiency or even stasis of the transport of secretions in the respiratory tract. It favors the growth of viruses and bacteria, and results in chronic and recurrent infections. They may be suffering from bronchitis, pneumonia, hemoptysis, sinusitis, and infertility. The irreversible bronchial alterations results in bronchiectasis and other chronic conditions and infections, leading to chronic cor pulmonale. The diagnosis is made clinically and confirmed through electron microscopy. Since there is no specific therapy for PCD, the secondary infections should be treated promptly with antibiotics and prophylactic measures should be undertaken. Situs inversus occurs, randomly, in 50% of the patients with PCD [16].

Primary ciliary dyskinesia (PCD) (MIM 242650) is an autosomal recessive disorder with extensive genetic heterogeneity [17]. Twenty to twenty-five percent of these individuals with complete, mirror-image situs inversus have ciliary dyskinesia and respiratory symptoms (Kartagener syndrome) as associated findings [18].

PCD electron microscopy

In most cases with PCD, electron microscopy reveals abnormalities of structural organization of the axoneme in cilia from respiratory epithelia and in spermatozoa. The other cases have structurally normal but dysmotile or immotile cilia. It is suggested that subtle structural deficiencies of cilia may also be more common [19]. The axoneme is composed of about 250 distinct proteins [20]. Electron microscopy of the ciliary microtubules frequently reveals absence or abnormalities of the outer and/or inner dynein arms [21]. These arms are multisubunit protein complexes with ATPase activity that promote sliding between adjacent microtubules, the basic action resulting in the beating of cilium and flagellum. The axonemal dynein arms are composed of heavy, intermediate, and light dynein chains [22]. A defect in any one of these proteins could lead to an abnormal dynein arm and/or defective beating activity of the axoneme.

Blouin J. L., et al. [23] analyzed in a large number of PCD families that revealed extensive genetic heterogeneity. There was no single genomic region harboring a common PCD locus identified, but several potential chromosomal regions were localized that could harbor genes for PCD [23].

Till date, mutations in two genes are associated with a minority of PCD/ Kartagener syndrome

cases. These are genes coding for the dynein axonemal intermediate chain 1 (DNAI1) [24-26] and the dynein axonemal heavy chain 5 (DNAH5) [27]. Loss of function of the murine DNAH5 dynein gene also causes PCD in the mouse [28]. Other genes coding for axonemal dyneins, such as the heavy chain DNAH9, the intermediate chain DNAI2, and the light chain LC8, were recently excluded as major causes of PCD [29, 30]. Moreover, the FOXJ1 gene, encoding a transcription factor involved in ciliary development, was also excluded as common cause of PCD [7, 31, 32].

PCD in neonates

Clinically it is characterized by onset in the neonatal period of respiratory distress and rhinitis [33], and if untreated, subsequent chronic rhinosinusitis, recurrent respiratory infections and bronchiectasis, and chronic secretory otitis media [7, 34]. 50% of the patients have mirror image organ arrangement [7, 34]. Other features rarely described include oesophageal atresia and gastro-oesophageal reflux [35]; complex congenital heart disease often with [35]; biliary atresia [36]; and hydrocephalus [37, 38].

The diagnosis

The diagnosis is important, to ensure that aggressive airway clearance and appropriate antibiotics are used to prevent the development of bronchiectasis. The unnecessary and inappropriate ear, nose and throat procedures are avoided [7, 39].

The diagnosis is established by

1) **Functional Studies**, usually a direct measurement of ciliary beat frequency on nasal epithelial cells; and

2) From **ciliary ultrastructure** determined by electron microscopy [7].

Underlying structural defects include

a) **absent inner and/or outer dynein arms** [40, 41],

b) **tubular defects** [42], and

c) **radial spoke defects** [43].

Rarely patients with a typical PCD clinical phenotype have normal or near normal ciliary beat frequency (CBF) and normal ciliary ultrastructure, so the cause of their condition is unexplained. Dysfunctional cilia in the middle ear leave patients vulnerable to repeated otitis media, and most suffer some degree of hearing loss [44].

Sperm, which contain an identical microtubular arrangement to cilia in their tails, have been shown to be capable of fertilizing an egg [45] but usually lack sufficient motility to reach one [46, 47]. The microtubular defects of PCD have also been shown to cause motility problems in phagocytic cells where microtubules are involved in directed movement to capture pathogens [48-50].

Case report

A 51-year-old male patient presented with complaints of fever with chills and rigors of 4 days duration, purulent cough associated with left sided non radiating chest pain and exertional shortness of breath of 3 days duration.

History of presenting illness

Patient was apparently asymptomatic 4 days earlier, then he developed fever with chills and rigors, which was relieved on medication, no history of night sweats, no diurnal variation. He developed cough with purulent sputum of 3 days which was insidious in onset, gradually progressive, scanty in amount, blood tinged in color, thick tenacious in consistency, showing diurnal variation occurring more in the morning. No history of wheeze, orthopnea, PND, palpitations, and pedal edema, No history of decreased urinary output. No history of loss of consciousness. No history of weight loss. Patient also had complaints of left sided chest pain which was non radiating, and associated with shortness of breath on exertion.

Past history

History of similar episodes 8-10 times a year in the past. Not a known case of Diabetes mellitus,

hypertension, thyroid disorders, tuberculosis, hypertension, ischemic heart disease. Not a known case of epilepsy/ CVA/ asthma/ COPD. No history of drug allergies.

Family history

Patient is married for 26 years but has no children. Patient was diagnosed with infertility due to immotile sperms.

General Examination

Vitals - Temperature: 99 °F, PR: 70 /min, BP: 90/60 mmHg, RR: 20/min, SPO2: 98% with oxygen support

Systemic Examination:

Upper Respiratory Tract

Nose: No nasal flaring, nasal septum central in position, normal nasal cavities, no polyps, ulcerations. Oral Cavity: Teeth-normal, Gums-normal, tongue-normal, hard and soft palate-normal, uvula-central, Sinus tenderness present at frontal sinus.

Examination of Respiratory system

Inspection: Shape of Chest-normal. Trachea - central in position.

Movements of the chest: equal on both the sides, No usage of accessory muscles, No inter costal indrawing, no engorged veins, no sinuses, no inter costal scars or swellings.

Palpation: All inspectory findings were confirmed. No local rise of temperature and tenderness. No bony swelling or tenderness.

Measurements:

Circumference: Right hemithorax- inspiration: 40.5cm, expiration: 38cms,:

Left hemithorax inspiration: 39.5cm, expiration: 37 cm

AP: Transverse Ratio – 5:7, Transverse diameter-35 cm, Antero-posterior diameter – 25 cm

Vocal fremitus: Increased in left supraclavicular, mammary and inframammary areas.

Percussion: Dull note on left supaclavicular, mammary and inframammary areas.

Auscultation: Bronchial breath sounds in left suprascapular, infrascapular and mammary areas are heard, Adventitious sounds: Lt. Side - coarse leathery crepitations heard at infraaxillary, interscapular and infrascapular. Vocal Resonance: Increased on left supraclavicular, mammary, inframammary areas.Rt. Side- normal bronchovesicular breathing present and there were no advetitios sounds

Cardio vascular system: Apex not felt on left side, Heart sounds -S1, S2 heard distant in 5th left intercostal space, but better heard on Rt. side, no murmurs.

P/A: Soft, with normal bowel sounds

CNS: NAD

Investigations

Viral markers: Hepatitis C Virus Antibody (Anti HCV) - Non reactive, HIV 1 and 2 AG/AB - Non reactive, Hepatitis B Surface Antigen (HBsAg) - Non reactive, Prothrombin Time (PT) with INR - 17.10 sec, Glycated Hemoglobin (HbA_1C) - 5.6%, CBP-Hemoglobin 12.40 gm/dL, Total RBC Count - 4.38 Million/Cu mm, Packed Cell Volume (PCV) - 37.20%, RBC Indices - MCV-84.90 fL, MCH - 28.30 pg, MCHC - 33.3 g/dL, RDW-CV - 13.30%, Platelet Count - 2.6 L/cu mm, Mean Platelet Volume (MPV) - 9.50 fL, Total WBC Count - 17780 cells/cu mm

Differential Count – Neutrophils - 86.8%, Lymphocytes - 7%, Eosinophils - 0.10%, Monocytes - 6%, Basophils - 0.10%; Absolute Counts - Neutrophil 15430 cells/cu mm, Lymphocyte 1250 cells/cu mm, Eosinophil 20 cells/cu mm, Monocyte 1060 cells/cu mm, Basophil 20 cells/cu mm

Peripheral Smear - RBC- Normocytic normochromic, WBC - Neutrophilic leukocytosis, Platelets on Smear-Adequate, Procalcitonin - 0.787 ng/ml., NT PRO BNP - 1107 pg/ml.

Bronchoalveolar Lavage (BAL) Bronchial Washing For AFB -No Acid Fast Bacilli Seen,

Fungal Smear (KOH Mount) for fungal elements-Negative For Fungal Elements

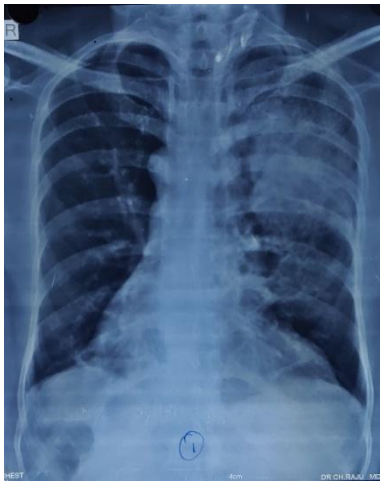
X-PERT MTB/RIF Assay-Not detected, Sputum for C/S - Staph Aureus, Klebsiella grown (vancomycin resistance)

ECG in left sided leads - Normal sinus rhythm, Rate- 76 bpm, Lead 1 - inverted "P" wave, Negative QRS, Inverted "T" wave., Biphasic QRS in aVR with upright "P" and "T"waves, S/O Dextrocardia; ECG in right sided leads:

Normal 'R" wave progression in Right sided precordial leads.

X-ray Chest PA View (**Figure - 1**) shows dextrocardia with consolidation left upper lobe

Figure – 1: X Ray Chest P A View shows dextrocardia with consolidation left upper lobe.



CT Scan Chest (**Figure - 2, 3**)

Situs inversus with dextrocardia and liver on left side. Discrete and confluent foci of consolidation noted in apicoposterior and lingular segment of left upper lobe. Areas of breakdown in consolidation of apicoposterior segment of left upper lobe. Centrilobular nodules with tree in bud appearance noted diffusely in the left upper lobe (**Figure - 2, 3**).

Figure – 2: Shows situs inversus with dextrocardia and liver on left side. Discrete and confluent foci of consolidation noted in apicoposterior and lingular segment of left upper lobe.

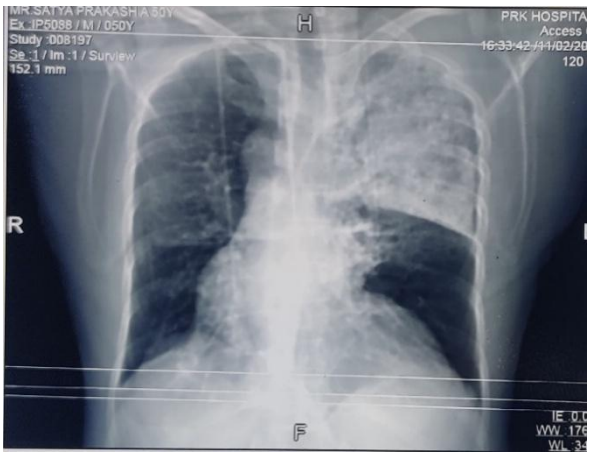
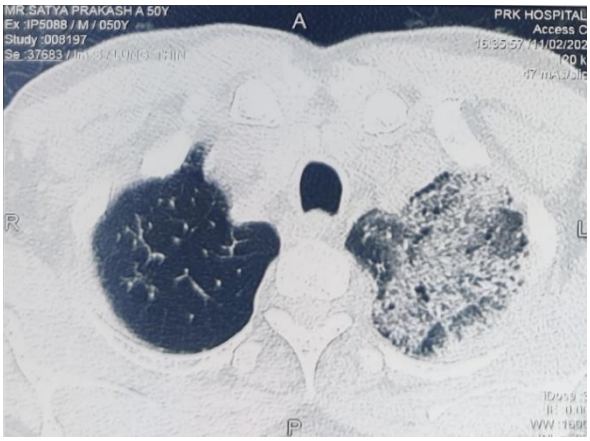
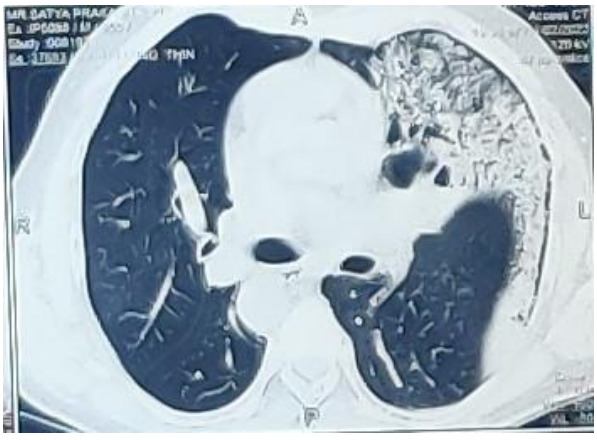


Figure – 3: Shows areas of breakdown in consolidation of apicoposterior segment of left upper lobe. Centrilobular nodules with tree in bud appearance noted diffusely in the left upper lobe.



Varicoid and cystic bronchiectatic changes noted in the lingular segment of the left upper lobe with peribronchial thickening. Mild central bronchiectasis noted in bilateral lower lobes with peribronchial thickening. Small consolidation focus is also noted in the medial basal segment of the right lower lobe. GGOs with interlobular septal thickening noted in the lingular segment of the left upper lobe. Subpleural paraseptal emphysematous changes in the left upper lobe. Left mild pleural effusion of thickness 1.7cm (**Figure - 4**).

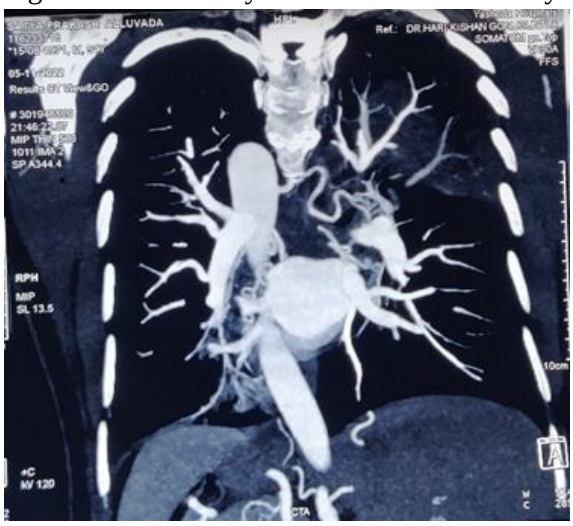
Figure – 4: Shows varicoid and cystic bronchiectatic changes in the lingular segment. Subpleural paraseptal emphysematous changes in the left upper lobe. Left mild pleural effusion of thickness 1.7 cm.



CT Thoracic Angiogram (**Figure - 5, 6**)

Bronchial arteries: Right bronchial artery-origin- D6 vertebral level 12 o'clock position -3.5mm tortuous traceable up to right hilum. Left bronchial artery -origin- D6 vertebral level 3 o'clock position- 3.9mm at ostium, tortuous traceable up to left hilum. Another tortuous bronchial artery arising from an aorta at D7 level measuring 2.8 mm noted traceable to the right hilum (**Figure - 5**).

Figure – 5: Shows origins of Bronchial arteries: Right bronchial artery and Left bronchial artery.



Ascending aorta is on left, and shows normal caliber & enhancement. Arch of aorta is on the right side, and shows normal caliber & enhancement. Brachiocephalic, left subclavian & left common carotid arteries arise from the arch of aorta. Brachiocephalic divides into the right subclavian & right common carotid artery. The both vertebral origins are normal in course and caliber (**Figure - 6**).

2D Echo Doppler study

MVF: EAE/A: 0.6/0.7m/sec

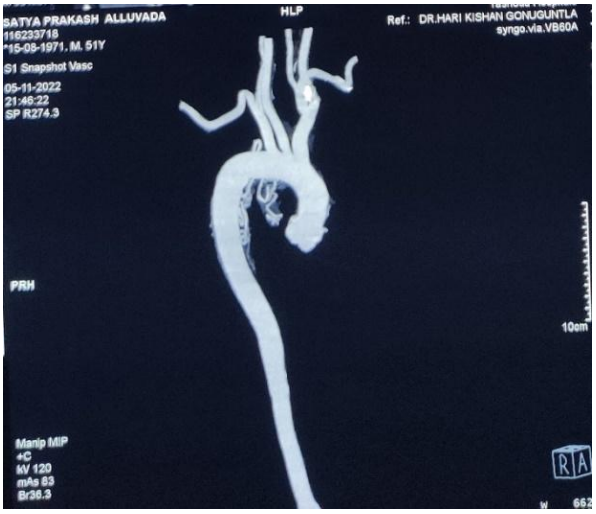
AV: AJV: 1.4 m/sec

PV: PJV: 1.0 m/sec, TRJV 2.4 m/sec, RVSP: 34mmHg

Colour Flow Imaging: Trivial MR/TR.

Conclusion: Dextrocardia, No RWMA of LV, Fair LV Systolic function, Grade 1 LV Diastolic Dysfunction, Trivial MR/TR/NO PAH, No PE/Clot

Figure – 6: shows Ascending aorta is on left. Arch of aorta is on the right side. Brachiocephalic, left subclavian & left common carotid arteries arise from the arch of aorta. Brachiocephalic divides into the right subclavian & right common carotid artery.



CT Scan of Paranasal sinuses (Figure - 7, 8)

Frontal sinus not pneumatized bilaterally.Anterior ethmoid air cells - Mild mucosal thickening bilaterally.Volume reduction in bilateral maxillary sinuses with mild mucosal thickening and bony remodeling of sinus walls suggestive of chronic sinusitis. Sphenoid sinus - mild mucosal thickening bilaterally.Nasal septum -mild deviation of nasal septum towards the left side.

Impression - Bilateral chronic maxillary sinusitis (**Figure - 7, 8**).

Figure – 7: Shows Frontal sinus not pneumatized bilaterally. Bilateral chronic maxillary sinusitis.

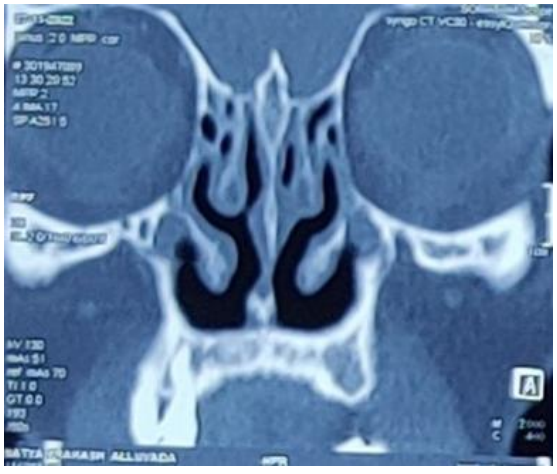
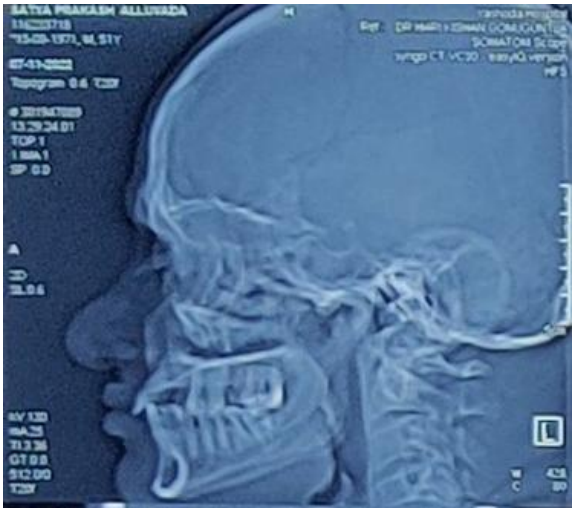


Figure – 8 Shows Frontal sinus not pneumatized bilaterally. Bilateral chronic maxillary sinusitis.



Diagnosis: Kartagener syndrome with Left Upper Lobe consolidation

Treatment given

1. Oxygen
2. IV fluids
3. Tab. MEROPENEM 200 mg twice daily at 8am-8pm for 10 days
4. Tab. LINEZOLID 600 mg twice daily for 10 days
5. Tab. PAN 40 mg once daily - 1⁄2 hour before breakfast
6. Tab. SUPRADYN 1 tablet once daily for 10 days
7. Syp. MUCOLITE 10 ml twice daily for 1 week
8. Nasoclear Saline nasal spray P/N thrice daily

Discussion

Individual clinicians will differ in the order of tests performed. This will also depend on the facilities available. Two points should be stressed:

1) it is important not to be confused by abnormalities that are secondary to an underlying infection and thus might confuse the diagnostic work up [51, 52]and,

2) that more than one abnormality of host defence may co-exist in the same person.

Need for repeated tests

Indications: any suspicion of secondary ciliary dyskinesia; atypical clinical picture; and suspicion of primary orientation defect. If structural studies are diagnostic of PCD and the clinical picture is classical, a repeat sample should be obtained early. Secondary ciliary dysfunction is common in population. Hence, a repeat sample should be obtained several months after the first sample to avoid confusing primary and secondary ciliary dyskinesia. 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 spermatozoal tails are under the control of different genetic loci [53, 54], so semen analysis may not reflect respiratory cilia. Pneumonia with no history of maternal illness or prolonged rupture of the membranes; and for any baby with significant and prolonged nasal discharge.

The saccharin test

Indications: screening for PCD. This test is not suitable for small children who will not sit still for an hour [55]. 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 saccharin taste is observed, a saccharin particle is placed on the tongue to check that the patient can truly taste saccharin.

Presentations of PCD

In view of the high cost and lack of availability of diagnostic tests for PCD, most physicians undertake other screening investigations appropriate to the presenting symptom(s) first. The varying patterns of symptoms have been reviewed [34, 56]. In one series [56], the age at presentation varied between 4 months and 51 yrs, with chronic sputum production and nasal symptoms being the main presenting features. In

a paediatric series [34], cough, sinusitis and otitis were universal. In both the series [34, 56], dextrocardia was present in 50% of the patients. Depending on the presentation, the tests may include sweat testing, immunoglobulins and subclasses, pH probe, etc. The nature of the investigations will depend on the clinical presentation. A diagnosis of PCD should be considered under a number of clinical features; no one feature is an absolute indication, and a combination of clinical features may be more suggestive than one single indication.

Indications for screening for PCD

1) A baby with neonatal respiratory distress: it would seem reasonable to recommend screening for PCD

a) for term babies born by vaginal delivery who become tachypnoeic as to require treatment and who have no conventional risk factors for transient tachypnoea of the newborn;
b) for babies with neonatal pneumonia with no history of maternal illness or prolonged rupture of the membranes; and
c) for any baby with significant and prolonged nasal discharge.

2) Child/adult with bronchiectasis of unknown cause:

a) 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.
b) The anatomical fact of bronchiectasis having been established, investigations to determine the cause should be pursued.

The screening tests

The "first wave" tests

The "first wave" tests are chosen because of the availability and prevalence of the underlying condition. These will include 1. sweat test (often with nasal potentials, and cystic fibrosis genotype),2. immunoglobulins (Ig) including IgE and IgG subclasses, 3.antibody responses, 4.serological evidence of previous adenovirus or mycoplasma infection, 5.autoantibody screen (rheumatoid factor, antinuclear factor) and 6,alpha-1 antitrypsin levels.

The "second wave" tests

If the "first wave" tests are negative, then "second wave" investigations to be considered include 1.fibreoptic bronchoscopy (particularly for disease localized to one lobe), 2.oesophageal pH monitoring; 3.saccharin test in older children and adults, and 4.nasal brushings for ciliary studies; 5.neutrophil function tests; and T-cell subsets. The choice of second wave investigations will depend on any associated features 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 is found.

3) Child with severe or atypical asthma: in this case, it is important to consider whether the diagnosis is correct. Many would like 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 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.

The 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 [57]. An abnormal test must be investigated by ciliary analysis. Ciliary disorientation was recently described as a possible variant of PCD [58, 59]. 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% [60, 61].

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.

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 [62, 63] and bronchiectasis [64],but normal in cystic fibrosis [65,66]. In patients with PCD, nasal [67, 68] and tidally exhaled [68] NO is very low. These findings 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.

Since the underlying defect in PCD cannot be corrected, the mainstay of therapy remains effective bronchial toilet and antibiotic therapy of superinfection as well as such prophylactic measures as vaccination against influenza virus and S. pneumonia [14].

The diagnosis is important, to ensure that aggressive airway clearance and antibiotics are used to prevent the development of bronchiectasis, and that inappropriate ear, nose and throat procedures are avoided [9, 39]. The diagnosis is established firstly, by functional studies, usually a direct measurement of ciliary beat frequency on nasal epithelial cells; and secondly, from ciliary ultrastructure determined by electron microscopy [7]. Underlying structural defects include absent inner and/or outer dynein arms [40, 41], tubular defects [42], and radial spoke defects [43].

Rarely patients with a typical PCD clinical phenotype have normal or near normal ciliary beat frequency (CBF) and normal ciliary ultrastructure, so the cause of their condition is unexplained [69].

1) **In the new-born period**: unexplained tachypnoea or neonatal pneumonia, particularly in a term baby with no risk factor for congenital infection [33]. 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 [35]; oesophageal atresia or other severe defects of esophageal function [35]; biliary atresia [36]; hydrocephalus [37, 38]; 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); severe gastroesophageal reflux; bronchiectasis; rhinosinusitis (very rarely with nasal polyps) [34, 70-72]; chronic and severe secretory otitis media, particularly with continuous discharge from the ears after grommet insertion; and diagnosis in more severely affected sibling [40, 73].

3) **In the adult presentation as** in the older child, but also female subfertility including ectopic pregnancy [1], 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 [74].

Management

Bronchopulmonary toilet is a cornerstone of PCD therapy. Patients with primary ciliary dyskinesia are totally reliant on two mechanisms for secretion removal: coughing, which is almost as effective as the mucociliary elevator in removing secretions [14, 75, 76], and gas-liquid pumping, which involves patients manipulating their secretions by sucking up or down in the back of their throats. Patients can benefit by clearing secretions by these methods every two to three hours while awake. Physiotherapy, such as postural drainage and percussion, may be helpful on an as-needed basis but are not as effective as cough [14].

A relative innovation in chest physiotherapy, the forced expiration technique, may be taught to these patients. Forced expiration, or the "bovine" or "huffing" cough, is done without glottic closure and applies a shearing force to secretions that aids in expectoration [75].

A variety of medications are used to relieve patients' symptoms. Various authors suggest the use of saline aerosols and hypertonic saline solution, methylxanthines, guaifenesin, and bromhexine hydrochloride to improve clearance [13, 14, 44, 75, 77].

Obstruction can be relieved with, Beta-agonists. Decongestant use may relieve sinusitis; mucolytics and adequate hydration may keep secretions from becoming too tenacious to move; and rhinorrhea may be relieved with anticholinergic aerosols. Surgical interventions include trimming the inferior turbinate to relieve sinus obstruction or meatal antrostomies, in which larger exits are drilled into the sinuses for mucus to drain through by gravity [13].

Patients with PCD should have a culture and sensitivity workup and receive antibiotics at the

first sign of infection because the progression of chronic pulmonary infection to bronchiectasis is one of the worst consequences of the disease [13]. Some patients benefit from periodic courses of antibiotics as a preventive measure [14].

Despite the significant morbidity and discomfort associated with PCD, the disease progresses more slowly than cystic fibrosis and can be slowed even more by educating patients and treating infection promptly. Overall, it has a better prognosis than cystic fibrosis [44], and these patients may go on to lead relatively normal lives and remain stable for long periods of time [12, 14].

Most infertile patients with KS have a normal spermatozoid count, but with a structural defect and a complete lack of motility [1]. Arge [78] first reported three male patients with this syndrome having immotile spermatozoa and sterility. Male patients with KS invariably present infertility, while women present reduced fertility [1]. Infertility in male KS patients is due to diminished sperm motility, while in females it is due to defective ovum transport because of dyskinetic motion of oviductal cilia, suggesting that the ciliated endosalpinx is essential for human reproduction [78].

The development of assisted reproductive techniques has allowed rational treatment for these patients. Pregnancies were successful using subzonal insemination (SUZI) and intracytoplasmic sperm injection (ICSI). If there is no sperm motility, ICSI may be the most appropriate treatment and if sperm motility is present, a trial of in vitro fertilization (IVF) should be considered [79].

Conclusion

Primary ciliary dyskinesia (PCD) is the name that has evolved for a group of disorders caused by microtubular defects in cilia and sperm. In most cases with PCD, electron microscopy reveals abnormalities of structural organization of the axoneme in cilia from respiratory epithelia and in spermatozoa. The most serious form of PCD is Kartagener syndrome (KS). PCD causes deficiency or even stasis of the transport of secretions in the respiratory tract. It favors the growth of viruses and bacteria, and results in chronic and recurrent infections. The diagnosis is essentially clinico-radiological, with variation in view of azoospermia and oligospermia. As with all clinical medicine, the key is a high index of suspicion, with the performance of a detailed history and physical examination. In view of the high cost and lack of availability of diagnostic tests for PCD, most physicians undertake other screening investigations appropriate to the presenting symptom(s) first. Since there is no specific therapy for PCD, the secondary infections should be treated promptly with antibiotics and prophylactic measures should be undertaken. Bronchopulmonary toilet is a cornerstone of PCD therapy.

But infertility is also an important aspect which needs to be addressed in evaluation so that they may beget children. An early diagnosis helps in such patients so that the options for timely treatment of infertility may be offered and unnecessary evaluation is avoided. Now the development of assisted reproductive techniques has allowed rational treatment for these patients. Pregnancies were successful using subzonal insemination (SUZI) and intra cytoplasmic sperm injection (ICSI).

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