Review Article

Primary Ciliary Dyskinesia (PCD)- A Disease in Disguise: Latest Situation Analysis in Bangladesh

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Abstract

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive genetic condition due to dysfunction of cilia, the microscopic organelles in child's respiratory system. This results in defective functioning of cilia, leading to chronic sinu-pulmonary infection, situs inversus, dextrocardia, and congenital heart abnormalities, ultimately leading to subfertility and infertility.

Alike other low-income countries, lack of awareness on PCD remains one of the existing challenges associated with PCD diagnosis, in Bangladesh (BD), particularly in its primary care-phase, since it's non-specific symptoms mimic other conditions. Basically, absence of a single, "gold standard" genetic-based diagnostic test is fatefully missing in BD. The test in itself remain highly expensive and requires certain sophisticated steps, hi-fi equipment and a highly-trained professional team to run and maintain those appropriately.

Although management predominantly remains supportive it is not based on high-level evidences, *per se*. This updated review aims to discourse the importance of early, accurate and available diagnosis of PCD and its management particularly in countries like BD where it is prevalent but often remains under-cover.

Introduction

PCD is a rare autosomal recessive, genetic disorder resulting from mutations in genes coding for ciliary protein "dynein" which is involved in the ultrastructure, transport and function of cilia. Mutation leads to abnormalities in ciliary motility (dyskinesia), cilia function and impaired mucociliary clearance and chronic sino-pulmonary infection, bronchiectasis and infertility. Kartagener's syndrome (KS) is a subset of primary ciliary dyskinesias (PCDs) comprising a triad of situs inversus, bronchiectasis and sinusitis.[1] The term "primary" means it is an integral problem of cilia and not a 'secondary' problem caused by inflammation and infection.

Similar to many low-income countries, Bangladesh faces the challenge of limited awareness about Primary Ciliary Dyskinesia (PCD), especially during its initial phases of diagnosis. This is primarily due to the fact that the symptoms of PCD are nonspecific and can be easily mistaken for other medical conditions. In Bangladesh, there is a notable absence of a single definitive, "gold standard" genetic-based diagnostic test for PCD. Furthermore, the available tests for PCD are costly and require sophisticated equipment and a highly skilled professional team to administer and maintain properly.

While the management of PCD primarily focuses on supportive care, it lacks a strong foundation of high-level evidence. This updated review seeks to emphasize the importance of early, accurate, and accessible diagnosis of PCD, especially in countries like Bangladesh where the condition is prevalent but often goes undetected

The aim of the updated review is to provide a latest scenario- a '*status-quo*' on the clinico-epidemiological characteristics in Bangladesh, it's currently available diagnostic modalities and the latest management capabilities of childhood-PCD in BD.

This would facilitate our clinicians' in adding values towards:

- Increasing broader understanding of our clinicians/ pediatricians on PCI in Bangladesh
- Building boarder awareness to address this life-threatening yet manageable genetic disorder

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- Getting optimistic in characterizing & early-diagnosing such serious lie threatening cases
- Thus, to add values in child's life with better prognostic approaches and higher survival rates through increased detection and outcome in Bangladesh.

Clinico-Epidemiological Characteristics:

A large international survey on pediatric PCD, including 1,192 children by Kuehni et al. concluded that the prevalence of PCD ranged from 1:10,000 to 1:20,000.[2] However, the actual prevalence is thought to be much higher since PCD is often underdiagnosed due to poor knowledge of the disease, symptoms resembling other respiratory conditions and the lack of diagnostic facilities.[3]

The mode of inheritance is autosomal recessive, making it more common in populations with high prevalence of consanguineous marriages such as those reported in British Asian population.[4,5]

Etiological and patho-physiological features:

PCD is inherited in an autosomal recessive manner, however some cases of autosomal dominant and X-linked recessive inheritance has also been reported.[5,6]

Pathogenesis and pathognomonic characteristics:

Normally the respiratory epithelium is lined by ciliated columnar cells. The axoneme of motile cilia is composed of nine peripheral doublet microtubules with attached inner and outer dynein arms (IDA and ODA, respectively) and radial spokes, surrounding a central pair complex (CC) consisting of two central microtubules surrounded by the central sheath(so called 9 + 2 structure).[6]

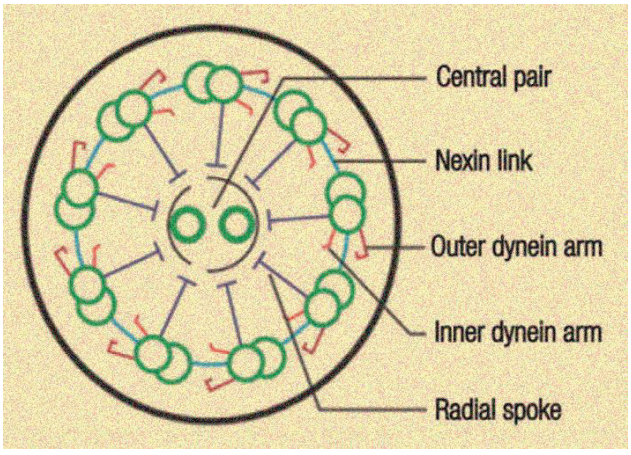

Fig: *Ciliary Ultrastructure*[2]

Cilia beat in a coordinated fashion, at 10–15 Hz, transporting mucus, trapped particles and pathogens towards the nasopharynx and out of body, (muco-ciliary clearance).[7] In PCD, mutation of gene coding for ciliary ultrastructure leads to abnormalities in ciliary structure, (loss of ODA or IDA), ciliary motility (dyskinesia) and impaired muco-ciliary clearance. As a result, there is buildup of respiratory secretion and the affected child suffers from lifelong chronic airway infection, recurrent pneumonia, chronic rhino sinusitis, glue ear and subsequently bronchiectasis.

In addition, subfertility or infertility is seen in male PCD patients caused by sperm dysmotility. Moreover, dyskinesia of cilia results in situs inversus as motile nodal cilia are crucial for normal situs development during embryogenesis.[8,9]

Clinico-epidemiological Features

Early warning features of PCD that should make clinicians suspect this disorder are-

Neonatal period:

- Unexplained neonatal respiratory distress in an otherwise healthy full-term baby and requiring long term O_2 therapy[10]
- Early onset persistent and recurrent rhino sinusitis and wet sounding cough

Infants and children:

- a persistent, daily "wet sounding cough" that has always been there, never completely clears even with treatment
- chronic and persistent rhino sinusitis is the most common feature.6,11
- chronic or recurrent otitis media with effusion, with hearing and speech impairment
- situs abnormalities (around 50% of cases).[6,12]
- Recurrent pneumonia and infective exacerbations
- Bronchiectasis and respiratory failure.[6,12]

Adults

- Subfertility /infertile due to dyskinetic sperm.[8,9]

Examination findings may include-

- Dextrocardia and situs inversus, asplenia, nasal polyps, rhinitis and conductive deafness.
- Features consistent with chronic lung disease and bronchiectasis, bilateral wheeze and crackles.
- Extremities may exhibit digital clubbing.[6,9,11]

Indications of referral for diagnostic testing

- Neonatal respiratory distress requiring prolonged oxygen of unknown cause.[10]

- History of consanguinity and sibling with PCD, particularly if symptomatic
- Situs inversus plus respiratory or sinu-nasal symptoms
- Recurrent sinu-pulmonary infection, serous otitis media in association with lower and upper airway symptoms.[6,9,12]
- Daily lifelong "wet cough that does not seem to go away"
- If considering testing for cystic fibrosis (CF), also consider testing for PCD particularly if rhinitis, sinusitis or glue ear with dextrocardia are present
- Unexplained bronchiectasis.[13]

Required Investigations and Accurate Diagnosis:

The diagnosis of PCD remains challenging due to a lack of awareness by general practitioners and pediatricians, symptoms overlapping other respiratory conditions and a lack of a gold standard investigation.[13,14]

Diagnosis is usually made by conducting a combination of five PCD-specific tests [3, 13] where laboratory setup is available *e.g.*

- Measurement of nasal nitric oxide (nNO) concentration: It involves breathing in nitric oxide and then measuring the level during exhalation through the mouth or nose with a chemiluminescent analyzer. It is found to be low in patients with PCD (10–15% of normal values) due to reduced ciliary clearance in the para nasal sinuses.[15] It used to be a moderately accurate and immediate screening tool for patients >5 years of age. However, the ERS guidelines argue that nNO should not be used as a screening test, since low levels are found in nasal obstruction and CF.[15] and there are no age-related cut-off values.
- High-speed video microscopy (HSVM): Ciliary function is assessed by ciliary beat pattern (CBP) and ciliary beat frequency (CBF) less than 10 Hz/second. It can be quantified by highly magnified and high-resolution video images of cilia recorded by a digital camera attached to a microscope.[16]
- Immunofluorescent (IF) antibody staining of ciliary proteins: Involves visualization of fluorescence- labeled antibodies specific for cilia proteins in epithelial cells.[17]
- Transmission electron microscopy (TEM): TEM is used to visualize respiratory cilia ultrastructure defect in electron microscope at high magnification (>60 000×).[18]
- Genetics: Genetic mutation analysis to detect genes associated with PCD.[19]

Other required investigational approach

- Saccharine test: Saccharin is placed in the nose and the speed of transport to the nasopharynx is measured. However, it is technically difficult to perform in young children & thus no longer used.[6,9,20]
- X-ray chest: Show dextrocardia, lung over-inflation, bronchial wall thickening, peri-bronchial infiltrates and atelectasis.3,6,9,11,21
- HRCT scan: Bronchiectasis and involvement of paranasal sinuses (poorly aerated mastoids ± absence of frontal sinuses.3,6,12,21
- Pulmonary function tests: Spirometry reveals an obstructive picture with a reduction in the FEV1/FVC, FEV1 and a reduction in respiratory flow of 25-75%.[22]

Diagnosis:

Based on the above clinical features and investigation findings.

In the UK, diagnosis is based on consistent clinical history plus at least two abnormal tests (TEM, HSVM and low nNO; repeating nNO and HSVM if TEM is normal) [23] whilst in North America, genetic testing is given more importance.[24,25]

According to European Respiratory Society (ERS) guidelines, diagnosis of PCD include.[2,3]

➢ **Definitive PCD**
- Patients with a supportive history of PCD with
- Non ambiguous bi-allelic mutation OR
- Hallmark ciliary ultrastructure defect

➢ **Highly likely PCD**
- Compatible history, And
- Very low nasal nitric oxide (nNO), And
- Either highly abnormal ciliary beat pattern on high-speed video microscopy on 3 occasions OR
- Highly abnormal ciliary beat pattern on high-speed video microscopy analysis on cell culture

➢ **Extremely unlikely PCD**
- Modest on non-suggestive history And
- Normal or high nNO And
- Normal ciliary ultrastructure

In countries with limited resources, Neonatologists, Pediatricians and ENT specialists should keep a high index of suspicion for PCD as clinical diagnosis. **PICADAR** (Primary Ciliary DyskinesiA Rule) is a recent validated predictive tool based on clinical characteristics that can help identifying patients with PCD to refer for further testing.[26]

The score is based on analysis of 7 clinical questions of a patient who has been suffering from a daily wet cough, started since early childhood. However, PICADAR is not designed for patients without a wet cough.[26]

Was the patient born pre-term or full term?	Term	2
Did the patient experience chest symptoms in the neonatal period (e. g. tachypnea, cough, pneumonia)?	Yes	2
Was the patient admitted to a neonatal unit?	Yes	2
Does the patient have situs abnormality (situs inversus or heterotaxy)?	Yes	4
Does the patient have a congenital heart defect?	Yes	2
Does the patient have persistent perennial rhinitis?	Yes	1
Does the patient experience chronic ear or hearing symptoms (e. g. glue ear, serous otitis media, hearing loss or ear perforation)?	Yes	1

The score demonstrates good sensitivity and specificity. Patients with a PICADAR score ≥10 have more than 90% probability of testing positive for PCD, while a score ≥5 indicates more than 11% chances of being diagnosed as PCD. In countries with no diagnostic testing, PICADAR could potentially be used to estimate the diagnostic likelihood of patients.[26]

In addition, centers where TEM is not available should consider collaborating with a PCD service with electron microscopy capacity. An advantage of TEM is that samples in fixative blocks may be sent by land or air to specialist centers.[18]

Differential diagnosis:

PCD may be confused with the following condition-[2,3,6]

- Allergic rhinitis
- Conditions linked to bronchiectasis e. g.
    - Acquired obstruction- foreign body aspiration
    - Tuberculosis
    - Congenital obstruction - bronchomalacia, pulmonary sequestration
    - Immunodeficiency
- Cystic Fibrosis
- Miscellaneous disorders e. g. alpha-1 antitrypsin deficiency, Interstitial lung diseases

PCD situation in Bangladesh

There is very little awareness as regards to PCD in children of Bangladesh. Moreover, the confirmation of diagnosis is very difficult. The facilities for the investigation are lacking here including the provision for measurement of nasal nitric oxide concentration, high speed video microscopy (HSMV), immune-fluorescent antibody, transmission electron microscopy to visualize respiratory cilia ultrastructure defect in electron microscope at high magnification. There is documentation of cases of PCD with presentation since early infancy with chronic wet-sounding cough, massive and long standing productive sputum, sinusitis and bilateral bronchiectasis [6,9,21] but the cases were diagnosed clinically and could not be subjected to genetic test.

Management

PCD is difficult to diagnose, thus are often labeled as difficult-to-treat asthma/ Cystic Fibrosis/ immunodeficiency [25] and is treated accordingly. Although sometimes patients respond to such treatment "by chance", the daily wet cough and rhino sinusitis never completely clears. Such a label often delays the diagnosis, it is thus very important to correctly label the disease and treat it specifically to improve outcome. Evidence-based medicine protocols for PCD is very limited and management protocols have largely been deduced from treatment programs for CF bronchiectasis.[27]

Management should be undertaken by multidisciplinary team and families should be counseled about the genetic basis of disease. The mainstay of treatment for PCD involves-

Airway mucus clearance

- Mucolytic therapies (first line): Nebulized inhalation of hypertonic saline /N-acetyl cysteine. It moistens and dilutes viscous airway secretions, and thereby facilitates muco-clearance techniques.[28]
- Muco-clearance techniques (second line): Manual chest physiotherapy, postural drainage, active cycle breathing, and manual devices like positive expiratory pressure (PEP) valves, and mouthpiece or chest wall oscillating devices.[28]

Infection control and prevention:

- Systemic antibiotics (indicated for respiratory exacerbation marked by changes in cough quality, sputum production, increased respiratory rate, and work of breathing, or a decline in FEV_1%). Duration of treatment is 14–21 days.[29] The commonest pathogen found in sputum of patients with PCD is H influenza.[30] Others include S pneumoniae, S aureus, M catarrhalis and P aeruginosa.[30] The selection of antibiotics should be based on most recent sputum culture results and colonization history of individual patient. Macrolides is a good choice. Regular inhaled or oral antibiotics *e. g.* Azithromycin should be considered in patients where eradication strategies fail. Inhaled Tobramycin should be reserved for P. aeruginosa infection.[30]
- Vaccinations against pneumococcus & Influenza are recommended on an annual basis.[29]

Other supportive treatment

- ENT disease including recurrent otitis media with effusion may require tympanostomy tube placement and endoscopic sinus surgery.[27]
- Elimination of exposure to inflammatory triggers and passive smoke
- **Pulmonary surgical resection** (i.e., segmentectomy or lobectomy) in diffuse lung disease and severe hemoptysis despite medical management of bronchiectasis.[27]
- Lung transplant.[27]

Follow up

- Routine clinical visits (2-4 visits per year) for spirometry monitoring, respiratory culture surveillance through sputum or oropharyngeal cultures [27] and chest radiography reserved for acute episodes

Complications

Bronchiectasis, pneumonia, empyema, conductive deafness, infertility and communicating hydrocephalus.[3]

Prognosis:

There is no reliable estimate of life expectancy for children with PCD. It is a life altering, life shortening, multi-system condition, with progressive decline in lung function progressing to develop bronchiectasis during childhood, reducing quality of life. Careful and routine follow-up to monitor symptoms and manage chronic lung disease and bronchiectasis can help improve patient outcomes

Summary

Primary Ciliary Dyskinesia, although common, are seldom diagnosed in children especially in countries with limited resources due to a lack of awareness and confirmatory tests. In such cases, high index of clinical suspicion, scoring systems e.g. PICADAR and cost-effective alternatives should be considered. Features that might increase suspicion of PCD include consanguinity, recurrent and chronic upper & lower respiratory symptoms along with sinusitis, middle ear infection and dextrocardia or situs inversus. Investigations are costly, time consuming and requires technical expertise and countries like Bangladesh fall short of such resources. However, it is important to setup international networks and collaborations with neighboring countries to widen the accessibility of diagnostic tests and develop standardized protocols to correctly label and manage the disease.

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