EC PAEDIATRICS EDITOR'S COLUMN - 2019

Primary Ciliary Dyskinesia (PCD): A Consideration in the Evaluation of the Child with Chronic Cough

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COLUMN ARTICLE

Primary Ciliary Dyskinesia (PCD) is an autosomal recessive disorder in which there is abnormal ciliary movement. This finding is caused by absent cilia, abnormal ciliary movement defined as cilia that are immobile or dysfunctional in the removal of debris from the airways and sinuses [1].

The evaluation of chronic cough as defined as a cough lasting four weeks or more, includes the consideration of PCD [2]. The differential diagnosis of chronic suppurative cough includes conditions which lead to chronic pulmonary infections resulting in chronic cough. Patients with chronic cough may be simultaneously evaluated for Cystic Fibrosis and PCD and this is particularly relevant if there is a pattern of recurrent lower respiratory infections. There are certain features of PCD which help to distinguish the disease from other causes of chronic cough such as immune defects, aspiration and CF [3]. The differential of chronic recurrent cough is broad, but there are specific markers of the disease conditions which support the clinical diagnosis of PCD.

Access to the testing is still hindered by insurance coverage, costs, ease of ordering and the site of testing. In the future, it remains a challenge to provide patients with access to the latest diagnostic advances. In one study of cost effectiveness, PCD diagnostic methods were compared. The authors found that the nNO and high speed video microscopy (HSVM) combined was more cost effective than an algorithm with transmission electron microscopy [4].

The history of chronic cough in PCD, unlike in CF, often is associated with chronic otitis infections and congenital abnormalities including structural cardiac defects, heterotaxy and situs inversus [5]. The clinical presentation often includes recurrent infections of the upper and lower respiratory tracts. Most patients with PCD present in childhood with a median age of diagnosis of 5 - 5.5 years. Newborns may have respiratory distress at birth. The otologic complications of PCD are a unique feature in contrast to CF, and the defects in ciliary function lead to poor mucociliary clearance [6].

The presence of situs inversus is a useful sign in establishing the diagnosis of PCD. Approximately 50 percent of patients with PCD have situs inversus [7]. The combination of situs inversus, chronic sinusitis and bronchiectasis is characteristic of Kartagener's syndrome [8]. The incidence of PCD is higher than that of Kartagener's syndrome and has been reported as approximately 1/16,000 - 1/20000 births [9]. Unlike patients with CF, the presence of situs inversus and cardiac structural abnormalities is relatively common.

Patients with PCD also have a 200fold higher incidence of congenital heart disease with heterotaxy [10].

Citation: Amrita Dosanjh. "Primary Ciliary Dyskinesia (PCD): A Consideration in the Evaluation of the Child with Chronic Cough". EC Paediatrics ECO.02 (2019): 23-26.

Thus, the evaluation of chronic suppurative cough should consider associated congenital defects and patterns of infection. In contrast to CF patients, PCD patients tend to have no pancreatic or liver disease.

Diagnostic evaluation

The syndrome of PCD includes a wide range of ciliary function abnormalities including abnormal function, structure of cilia resulting in reduced mucociliary clearance and infection.

The diagnostic work up may include nasal NO measurements with high sensitivity and specificity usually available at PCD centers. In one study, the nasal NO measurement from PCD patients (n = 27) were compared to those with primary immune defects (n = 32). The results showed that the patients with PCD has a significantly lower nasal NO measurement with a median value of 19.7nL/minute compared to 228.9 nL/min in the PID group, $p < 0.0001$ [11].

The use of high speed videomicroscopy (HSVM) demonstrates ciliary movement. Structural defects of the cilia may affect the outer or inner dynein arms of the cilia. Transmission electron microscopy is a traditional method which utilizes sample biopsy from the sinus or respiratory tracts. In comparing methods of diagnosis, logistic and technical challenges may be considered, in addition to cost. HSVM may be used in combination with electron microscopy, but often HSVM alone may establish ciliary function abnormalities, with a sensitivity of 100 percent in one study of 654 patients with possible PCD. The sample should be obtained four to six weeks after infection [12]. Quantitative ciliary beat analysis has been able to discriminate genetic variants of disease, and the most severe reduction in ciliary beat frequency is found among subjects with outer dynein arm defects e.g. DNA H5 [13].

To identify ultrastructural defects of the dynein arms, electron microscopy when performed with technical skill, is useful in demonstrating the actual defect of the cilia. The diagnostic accuracy is high, but approximately 20 percent of PCD patients have a normal study [14].

Genetic testing is available and does not involve an invasive procedure. The testing can identify more than 30 disease causing mutations. The testing may not detect PCD however in all patients, but when used as a screening test, it is a useful in identifying outer and inner dynein arm mutations.

Some genetic variants include DNAH11 which results in normal appearance of the dynein arms but abnormal function [15]. Whole exome sequencing identification of novel DNAH5 mutations has been demonstrated and is used as an adjunctive method when PCD is suspected without presence of situs inversus or heterotaxia [16].

Other methods of diagnostic testing for PCD include immunofluorescence of ciliary proteins and detection of mutations in genes encoding for proteins responsible for ciliary assembly [17].

Thus, a combination of diagnostic methods together with clinical suspicion and work up is often required to establish the diagnosis. The genetic defects are unique and distinct in comparison with the genetic defects associated with CF and immune defects. CF genotyping, the CF sweat test and transepithelial potential differences are useful in detecting CF. Patients with these conditions have overlapping features with PCD patients who have chronic suppurative cough.

Radiographic imaging

Patients with suppurative chronic cough often have similar findings on thoracic imaging. These may include bronchiectasis, mucus plugging, peri bronchial thickening, parenchymal abnormalities and mosaic attenuation. Hyperinflation is usually bilateral and unilateral hyperinflation is unusual in both PCD and CF. While useful in following patients with chronic cough the HRCT findings are not specific for PCD. Routine use of HRCT is typically not used due to concerns regarding radiation exposure. There is a time period prior to the development of bronchiectasis, which is characterized on imaging as reversible airway dilatation and one study comparing findings between CF and PCD suggested the use of thoracic MRI [3,18]. The use of sinus microbiologic sampling is less useful in distinguishing CF from PCD as shown in an extensive systematic review [19].

Pulmonary function testing

Patients with CF tend to have a better correlation between functional abnormalities and structural abnormalities as demonstrated HRCT [20]. In one meta-analysis, spirometric indices showed a decline in FEV1 measurements among adult PCD patients but the variability between study findings may highlight the heterogeneity of the disease [21]. More information is needed to better define phenotype, endotype, and genotype relationships.

CONCLUSIONS

The availability of genetic testing and expansion of genetic testing panels has improved the diagnosis of clinically significant ciliary abnormalities among children with PCD. Nasal NO may be used to establish the diagnosis, but it is a test often only available at major centers. The cost and access of genetic testing for PCD has been improving.

The differential diagnosis of suppurative chronic cough includes aspiration, immune defects and CF. PCD is an important consideration in the evaluation of the pediatric patient with chronic cough. The clinical availability of the testing though should be improved to provide better access and earlier diagnosis and treatment of PCD patients.

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