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Case Series

Primary Ciliary Dyskinesia with Structurally Normal Cilia: An Unusual Diagnosis

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Abstract

Defects in cilia are associated with several human diseases. Chronic rhinosinusitis with nasal polyps is one of those diseases. Ultrastructural ciliary defects diagnosed by transmission electron microscopy are usually seen. Rarely are found patients who have structurally normal cilia with an abnormal ciliary function. We present 2 cases of 15-year-old and 13-year-old female patients with chronic rhinosinusitis with nasal polyps and primary ciliary dyskinesia with structurally normal cilia. Although they had structurally normal cilia at transmission electron microscopy, when analyzed for variation in ciliary beat axis and ciliary deviation, the results were compatible with primary ciliary dyskinesia.

Keywords: Primary Ciliary Dyskinesia; Pediatric Chronic Rhinosinusitis; Transmission Electron Microscopy; Cilia

Introduction

Primary Ciliary Dyskinesia (PCD) is a congenital disease predominantly in an autosomal recessive pattern. It is characterized by abnormal ciliary motion and impaired mucociliary clearance [1,2]. The affected cilia can be found lining the respiratory tract (lower and upper airways, the sinuses, the Eustachian tubes, the middle ears), the fallopian tubes and in the flagella of sperm cells. Therefore, PCD is associated with a wide range of human diseases such as chronic otitis media with effusion, chronic rhinosinusitis, recurrent lower respiratory tract infections, bronchiectasis and subfertility [3]. The estimated incidence of PCD is approximately 1 per 15000 births [3], with no sex predilection reported.

Regarding ciliary defects, PCD is a highly heterogeneous syndrome. Usually includes defects on axonemal structure or the accessory components of cilia. However, cases of ciliary ultrastructure preservation with abnormal function can occur, with reports in the literature up to 21% [4].

Considerable variation exists from patient to patient and the diagnosis is not always easy and requires a high level of suspicion. No gold standard diagnostic test has been estabilished. Diagnostic tests measuring nasal nitric oxide and mucociliary clearance are useful for screening, but generally require confirmation tests of ciliary ultrastructure and function [5]. High speed videomicroscopy (HSVM) and transmission electron microscopy (TEM) are both conventional methods to examine ciliary movement and ultrastructure. When HSVM is not available, TEM can be used to calculate and identify the variation in ciliary beat axis and the ciliary deviation

[6,7]. In addition, genetic testing can identify approximately 60% of phenotypically identified PCD patients [8].

There is no cure for the disease. Since PCD is not a reversible disease, otorhinolaryngologists should focus on monitoring and treating symptoms of chronic rhinosinusitis and hearing loss due to chronic otitis media with effusion. Surgery is an option that can improve quality of life and may reduce lung infections [9-12].

In this report, we present two pediatric cases of PCD with structurally normal cilia.

Case Presentation

Case 1

A fifteen-year-old Caucasian female was referred to ENT department due to daily, year-round nasal obstruction and rhinorrhea. She also had a persistent wet cough but denied other pulmonary symptoms such as dyspnea or wheezing. The past medical history was significant for hypothyroidism since the age of 11. Otherwise she was fit and well. On nasal endoscopy bilateral nasal polyps were visualized.

Sinus CT scan showed changes compatible with chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP). No sinus hypoplasia was seen. Sweat test was normal. Skin prick test was negative. Blood tests including full blood count and quantitative serum immunoglobulin count was also performed with no relevant changes. Nasal cilia were analyzed using nasal brushing and inferior turbinate incisional biopsy. TEM analysis did not show any change in ciliary ultrastructure. Consequently, quantitative analysis of the ciliary beat axis deviation was performed. The authors analyzed 304 axonemes in order to determine the beat axis deviation. That analysis showed a 33,74º of deviation. That results were compatible with PCD.

Despite not having substantial pulmonary symptoms, a thoracic CT scan was also performed but it did not show any changes.

The patient was scheduled for functional endoscopic sinus surgery: bilateral nasal polypectomy, bilateral maxillary sinusotomy, bilateral frontoethmoidectomy and bilateral sphenoidotomy. This procedure lead to significant improvement of her symptoms.

Case 2

A thirteen-year-old Caucasian female, with a mild cognitive deficits and a bad treatment compliance was referred to the ENT department at the age of three due to nasal obstruction, rhinorrhea, wet cough and also recurrent upper airway infections. She was subsequently followed regularly by ENT. In her medical history is important to highlight an adenotonsillectomy plus bilateral myringotomy with ventilation tubes insertion at the age of five. Despite surgery, her nasal symptoms and coughing never disappeared.

Medical treatment of CRS was used until the age of eleven including topical corticosteroids, antibiotics and oral corticosteroid when needed. At that age, nasal endoscopy showed bilateral nasal polyps with abundant mucosal rhinorrhea. She denied pulmonary symptoms such as dyspnea or wheezing.

Sinus CT scan showed changes compatible with CRSwNP. An ear CT scan was also requested and showed bilateral middle ear effusion. Maxillary sinus hypoplasia was seen. Sweat test was normal. Skin prick test was negative. Blood tests including full blood count and quantitative serum immunoglobulin count were normal. It was decided to offer her functional endoscopic sinus surgery plus bilateral myringotomy with ventilation tube insertion. The surgery included bilateral nasal polypectomy, bilateral maxillary antrostomy, bilateral front ethmoidectomy and bilateral sphenoidotomy.

One year after the surgery, despite optimal medical and surgical treatment, the patient presented with recurrence of nasal obstruction and rhinorrhea. A new sinus CT scan showed recurrence of polyps. At this point, due to the refractory symptoms and recurrent polyposis at such a young age, without a known etiology, PCD was suspected. Nasal cilia were analyzed using nasal brushing. TEM analysis did not show any change in ciliary ultrastructure.

Again, quantitative analysis of the ciliary beat axis deviation was performed. The authors analyzed 401 axonemes in order to determine the beat axis deviation. That analysis showed a 31,21º of deviation. That results were compatible with PCD (appendix).

Discussion

Although the clinical diagnosis of CRS in adults is relatively easy, the same doesn't apply to children. Common childhood nasal diseases such as viral upper respiratory tract infections, adenoid hypertrophy/adenoiditis and allergic rhinitis as well as the physical examination and the subjective evaluation by the child's parents make the diagnosis a challenge.

A - Counterclockwise axoneme direction.

B - Clockwise axoneme direction (usual).

The axoneme is composed of nine peripheral microtubule doublets (A-internal and complete; B-external and incomplete) and a central pair of microtubules (C1 and C2).

Microtubule doublets are linked by nexin bridges (blue) through the A microtubule of the doublets, which also presents dynein arms (red), and are linked to the central microtubule pair by the radial spokes (green).

Doublet number one is the one that is in line with a perpendicular line (black) to the central pair. Thereafter, they are numbered in a clockwise manner (following dynein arms).

Cytoplasmic membrane (m) showing its three layer structure.

Chronic adenoiditis plays a significant role in nasal mucosa inflammation and symptoms, both from a bacteriologic and immunologic perspective. However, there is not a clear understanding of its relative contribution to CRS. The role of anatomical abnormalities and changes in bacteriological specimens is also not clear. Other comorbid diseases such as allergic rhinitis, gastroesophageal reflux disease (GERD) and immunodeficiency can also contribute [13].

There are some differences between the cases that should be highlighted. First, the age and the follow-up. In case 1, the patient only presented with sinonasal symptoms at the age of fifteen versus the patient in the second case that not only presented with symptoms of CRS since her third year of life but also otitis media with effusion. Even though PCD is an inherited defect, onset of symptoms is not necessarily in early childhood. However, neonatal respiratory distress is common. The recommended PCD diagnostic criteria are divided by age but in children older than one month, two major clinical criteria are needed for PCD diagnosis plus a genetic or structural or waveform confirmation [14]. In children older than five years old, nasal nitric oxide measuring is a valid screening method. The two major clinical criteria in both cases are daily nasal congestion with pansinusitis on sinus CT and daily wet cough since early childhood. As mentioned before, early presentation doesn't always raise suspicion of an inherited disease since the symptoms are the same of other common childhood diseases. Second, treatment compliance. Poor treatment compliance may divert attention from the correct etiology. This can, sometimes, overextend investigation through many years.

After discard some of the most common etiologies, Cystic fibrosis (CF) and Primary Ciliary Dyskinesia (PCD) should be considered. Normal results in Sweat test make it very unlikely to be CF. However, we acknowledge that although Sweat test is the gold standard, a negative test doesn't completely exclude Cystic Fibrosis.

Although nasal nitric oxide measurement is useful for screening, other respiratory conditions such as cystic fibrosis and acute viral infection may rarely present with low values [15]. In addition, normal values have been described in PCD [16]. PCD diagnosis requires examination of cilia by light and electron microscopy [5]. High speed video microscopy (HSVM) and transmission electron microscopy (TEM) are the most common methods. In our study we didn't use nasal nitric oxide measurement or genetic testing for logistic reasons.

There is not a standardized protocol to diagnose PCD. HSVM is a functional exam that allows the experienced examiner to determine whether cilia have normal coordination, beat frequency and beat pattern [3]. HSVM alone has excellent accuracy with a sensitivity and specificity of 100 and 93 percent, respectively [4]. However, it is not widely available in all centers, including our hospital. TEM analysis is performed when the diagnosis is uncertain after HSVM or HSVM is not available. It allows identification of specific ultrastructure defects and ciliary axis [5,17]. The most commonly described structural abnormality involves lack of outer dynein arms, or a combined lack of both inner and outer dynein arms [18]. However, as seen in the reported cases, not every cases of PCD have morphological changes.

lthough several reports argue in favor of High-speed videomicroscopy for the determination of the ciliary beat frequency, others prefer TEM analysis. These two types of analysis depend on the availability of the facilities. TEM in very experienced hands offer a high level of confidence, especially in association with determination of the variation in ciliary beat axis and ciliary deviation (as in the present case) [7].

When no functional tests are available and no other ultrastructural defects are found, it is mandatory to include ciliary orientation measurement when investigating patients with recurrent respiratory disease [6]. Not all PCD patients have structural changes and not all patients with structural changes have PCD. However, an abnormal variation in ciliary beat axis and ciliary deviation is usually only observed in PCD cases because ciliary beat orientation is determined in early stages of embryogenesis [19,20]. Certainly, the test needs to be supported by a relevant clinical phenotype. Some authors raised the suspicion that ciliary disorientation can arise secondary to respiratory tract infection due to axonemal defects [21]. Although not yet completely understood, if possible, it is important to collect mucosal samples at a time remote from acute nasal or respiratory infection, like we did in our study. Additionally, TEM analysis can also give precious information and help to distinguish between primary or acquired ciliary dyskinesia. In our cases, with TEM morphological analysis we have also excluded the existence of signs of acquired ciliary dyskinesia, such as atypical axoneme findings and/or compound/fused cilia [22].

Although patients with gross ciliary disorientation may have normal or near normal ciliary beat frequency, such patients would still present impaired mucociliary clearance because the direction of beating is not consistent. As De longh R., *et al*. concluded, ciliary orientation in normal subjects was always less than 30º. Patients with ciliary orientation greater than 30° all had recurrent respiratory tract disease [6]. Even in patients with bronchiectasis not due to primary ciliary disease, nasal ciliary orientation did not differ from that of normal subjects. These finding supports that respiratory tract disease did not cause ciliary disorientation [11], making these abnormality, usually, a primary defect.

In both our cases, ciliary orientation was greater than 30º. CRS, recurrent respiratory tract disease, nasal obstruction, wet cough, otitis media with effusion in the second patient and ciliary orientation greater than 30º in both patients supports the diagnosis of PCD. Thus, both patients have probable PCD that warrants genetic investigation. Sensitivity and specificity of this method has not been reported yet. However, we believe it can add a valuable contribution, specially in centers without access to methods like HSVM. Most articles, including those that established the criteria for diagnosis, do not mention the technique of variation in ciliary beat axis and ciliary deviation but only the morphological appearance of the axoneme. Although, in practice, this method is probably equivalent to video microscopy, and we think it should be included in those criteria.

Finally, treatment focus on preventing conductive hearing loss due to persistent otitis media with effusion and controlling symptoms of CRS. Improving quality of life is the main goal. In this paper, we describe a patient with a good outcome and a patient with a bad outcome. Although functional endoscopic sinus surgery was performed in both patients, the results were different. One possible reason may be that endoscopic sinus surgery is not curative but can improve quality of life, reduce disease progression or impact and increase the effects of saline nasal irrigation and topical corticosteroids [10]. In both cases, it was offered due to the symptoms and extension of the nasosinusal disease.

The second patient's outcome was worse compared to the first. Since the surgeon was the same, one reason for this result is probably the better compliance for adjuvant treatment such as saline nasal irrigation and topical corticosteroids; second, a possible more aggressive upper respiratory tract disease in the second case may be possible even if she had a good treatment compliance. Patient number two also had a chronic bilateral otitis media with effusion which required transtympanic ventilation tubes insertion. These differences highlight the importance of an individualized treatment that meets the needs of each patient. Surgical and medical treatment must come "hand-to-hand" to assure the best outcome. Treatment is never curative and close follow-up is important to increase treatment compliance and good management.

Conclusion

Both cases highlight the importance of a high level of suspicion and a complete investigation for an accurate diagnosis. Structural abnormalities are usually found in most PCD cases. However, some patients, only present functional defects. HSVM and nasal oxide

measurement have good sensitivity and specificity but are not widely available. Analysis of the ciliary beat axis deviation helps reducing false negative cases and can be used as an alternative to HSVM when it is not available.

Conflicts of Interest

None.

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