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Clinical case
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Primary ciliary dyskinesia. Cause of recurrent respiratory infections: series of three cases

Discinesia ciliar primaria. Causa de infecciones respiratorias recurrentes: serie de tres casos

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ABSTRACT. Primary ciliary dyskinesia is a rare autosomal recessive genetic disease affecting ciliary movement. The clinical manifestations of the disease can present from birth with respiratory distress syndrome or during childhood with chronic productive cough and non-seasonal rhinosinusitis, recurrent respiratory infections that even require in-hospital management, so it should be considered as part of the approach to study recurrent infections in the pediatric patient. **Clinical cases:** we investigated the evolution and relevant history of three patients entitled to the Secretary of the Navy with recent diagnosis of primary ciliary dyskinesia by electron microscopy and genetic panel who presented recurrent infections in childhood, which required in-hospital management on several occasions. The aim of this article is to keep in mind the disease as a cause of recurrent respiratory tract infections in order to perform an adequate approach, avoiding sequelae in our patients secondary to a late diagnosis.

Keywords: ciliary dyskinesia, respiratory infections, chronic cough.

RESUMEN. La discinesia ciliar primaria es una enfermedad genética poco frecuente, autosómica recesiva, que afecta el movimiento ciliar. Las manifestaciones clínicas de la enfermedad pueden presentarse desde el nacimiento con un síndrome de dificultad respiratoria o durante la infancia con tos crónica productiva y rinosinusitis no estacional, infecciones respiratorias recurrentes que incluso requieran manejo intrahospitalario, por lo que se deberá considerar como parte del abordaje de estudio de infecciones recurrentes en el paciente pediátrico. **Casos clínicos:** se investigó la evolución y antecedentes de importancia de tres pacientes derechohabientes de la Secretaría de Marina con reciente diagnóstico de discinesia ciliar primaria por microscopia electrónica y panel genético; presentaron cuadros de infecciones recurrentes en la infancia, los cuales requirieron manejo intrahospitalario en varias ocasiones. El objetivo del presente artículo es tener presente la enfermedad como una causa de infecciones recurrentes de vías respiratorias para realizar un adecuado abordaje, evitando secuelas en nuestros pacientes secundario a un diagnóstico tardío.

Palabras clave: discinesia ciliar, infecciones respiratorias, tos crónica.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare genetic disease, usually presenting with an autosomal recessive inheritance pattern affecting cilia movement, mainly affecting the DNAH5 and DNAI1 genes.[1] It is considered an early-onset disease with no gender, ethnic and/or racial predilection, with a frequency of 1 in 10,000-20,000 live newborns, with an increased prevalence of up to 5% in patients with recurrent respiratory tract infections in European countries.[2]

Cilia are organelles found on the cell surface. There are two types of cilia: immotile and motile; each cilium is composed of a cytoskeleton, called axoneme, composed of nine longitudinal microtubule doublets that surround a central pair, forming the 9 + 2. Each peripheral microtubule doublet has an outer arm and an inner arm of dynein, which contains the motile protein of the cilium.[3] Seventy percent

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of patients with PCD have a pathogenic variant in a gene related to cilia function, causing structural and functional changes. In the case of PCD, the condition is found in motile cilia responsible for the sweeping action, mobilizing fluids and debris unilaterally. When a defect in this movement is found, the patient will present an abnormal mucociliary clearance, which is clinically manifested in the patient, presenting symptoms such as repeated respiratory tract infections in children, cases of infertility in men and women by affecting the movement of spermatozoa and ciliary movement of the uterine tubes, respectively.[4-6] Likewise, cases have been reported with clinical presentation from the neonatal period with atelectasis and recurrent respiratory infections, accompanied in 50% by *situs inversus*.

Pathologies such as cystic fibrosis, immunodeficiencies, pulmonary aspiration, asthma and recurrent respiratory tract infections (sinusitis, otitis, rhinopharyngitis, pneumonias, among others) are part of the differential diagnosis; however, four key features have been identified for the diagnosis of PCD: 1) productive (wet) cough throughout the year; 2) non-seasonal daily rhinosinusitis with early onset; 3) 80% history of respiratory distress syndrome at birth; and 4) laterality defects.[7]

Three cases of patients diagnosed with FCD by electron microscopy are presented below.

PRESENTATION OF CASES

Case 1: eight-year-old female with a history of recurrent respiratory tract infections since birth, three events of pneumonia, two of influenza and three cases of otitis. A diagnosis of asthma was made by spirometry with mild obstruction with positive response to bronchodilator, persisting with productive wet cough despite high doses of asthma control treatment. Recurrent wheezing and coarse ralescence. High resolution chest tomography (HRCT) was performed with the presence of cylindrical bronchiectasis *(Figure 1A)*, pathologies such as cystic fibrosis, immunodeficiencies, gastroesophageal reflux and bronchopulmonary aspergillosis were ruled out. Flexible bronchoscopy was performed for cilia biopsy (endobronchial), which was reported with endobronchial epithelium with ultrastructural and membrane alterations compatible with ciliary dyskinesia (processed by electron microscopy), with absence of dynein arms that corresponds to type I FCD according to the classification of Barlocco and collaborators[8] *(Figure 1B)*. The genetics service performed a molecular panel study of 538 genes by next-generation sequencing for ciliopathy, which reported that the patient is compound heterozygous for two variants in the DNAH5 gene, the variant c.2578-2A>T is previously reported as pathogenic; the variant c.1981C>A (p.Arg661Ser) is classified as of uncertain significance *(Figure 1C)*. Diagnosis of PCD was established and, with it, inhaler dose reduction until withdrawal; pulmonary rehabilitation therapy and multidisciplinary management with otorhinolaryngology, audiology and pediatric cardiology services was initiated. *Situs inversus* was ruled out.

Case 2: 16-year-old female, with repeated respiratory infections since she was three years old, previously treated for difficult to control asthma, all her spirometries showed mild obstruction with no response to bronchodilator; she was approached due to persistent respiratory symptoms (productive cough, abundant secretions in the airway and recurrent wheezing). CT scan showed the presence of cylindrical bronchiectasis *(Figure 2A)*. Flexible bronchoscopy was performed with endobronchial biopsy for electron microscopy, in which changes compatible with type V PCD of the Barlocco and collaborators classification,[8] corresponding to ciliary fusion, were reported *(Figure 2B)*. A ciliopathy genetic panel was requested, which showed heterozygous deletion of chromosome 16p12.2 pathogenic

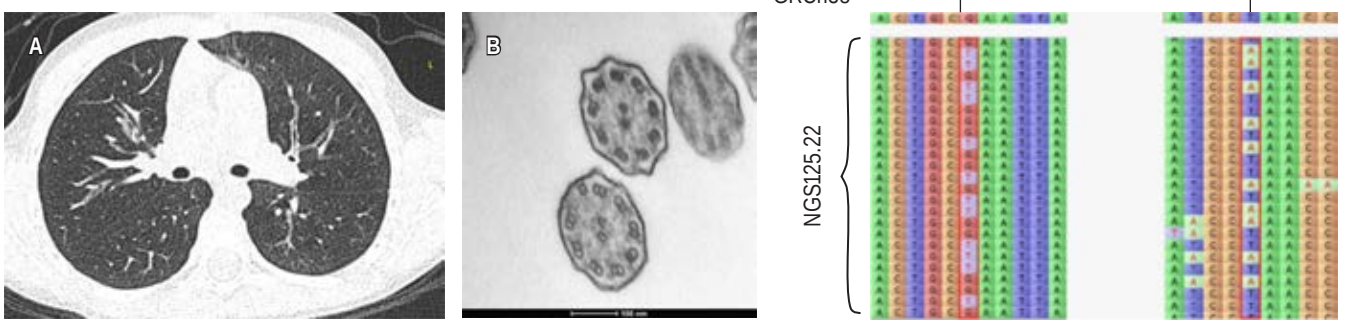

Figure 1: A) Axial section of high-resolution pulmonary computed tomography, showing cylindrical bronchiectasis in the right hemithorax; electron microscopy **(B)** shows absence of dynein arms. Primary ciliary dyskinesia type I according to the modified classification of ciliary alterations by Barlocco et al.[8] The genetic study **(C)** reported two variants in the DNAH5 gene, the variant c.2578-2A>T and the variant c.1981C>A (p.Arg661Ser).

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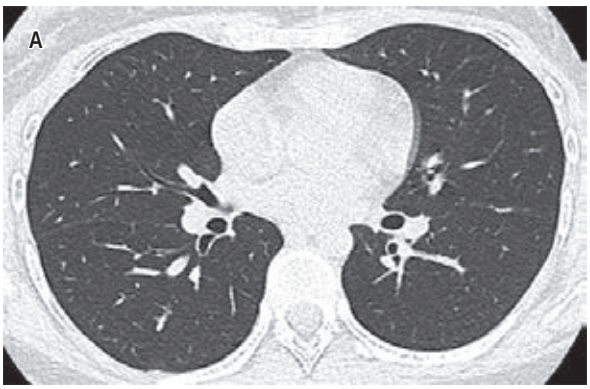
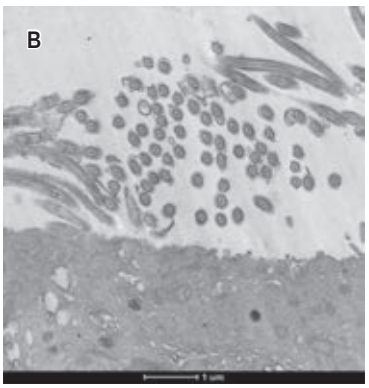
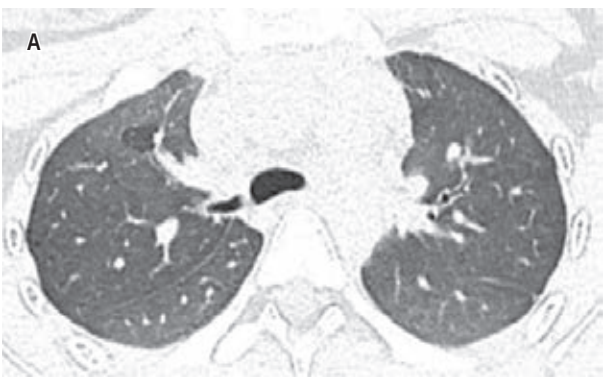




C

Detected change	Chromosomic location	Genomic coordinates	Genes located in the region	CNV Type
Heterozygous deletion	16p12.2	Chr16:21477979- 21808586	IGSF6, METTL9, OTOA	Pathogenic variant

Figure 2: A) Axial section of high-resolution computed tomography showing cylindrical bronchiectasis in the right lung and peribronchial thickening in the left lung; electron microscopy **(B)**, showing changes compatible with primary ciliary dyskinesia type V of the Barlocco *et al* classification,[8] corresponding to ciliary fusion; genetic panel **(C)** of ciliopathies with heterozygous deletion of chromosome 16p12.2 pathogenic variant.
CNV = copy number variation.



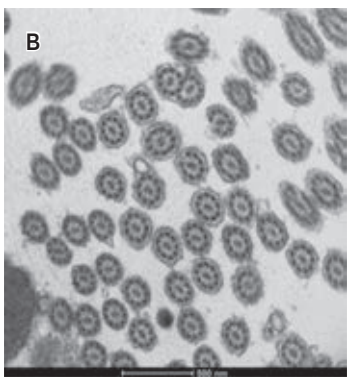


Figure 3:

A) Axial section of high-resolution computed tomography of the chest, showing peribronchial thickening at the hilar level in both lung fields; electron microscopy **(B)** shows absence of peripheral doublets and fusion in some of the cilia membranes, corresponding to primary ciliary dyskinesia type III of the Barlocco *et al* classification.[8]

variant *(Figure 2C)*. Pulmonary rehabilitation therapy was started, inhaler doses were reduced until withdrawal, with improvement of respiratory symptoms. Currently, she is only undergoing pulmonary physiotherapy. Multidisciplinary management was initiated through genetics, cardiology and otorhinolaryngology services. *Situs inversus* was ruled out.

Case 3: 14-year-old female with a diagnosis of chronic cough and suppurative syndrome. At birth she presented airway infection. During her childhood with recurrent infections of pharyngotonsillitis, repeated otitis media, surgical treatment of tonsillectomy and placement of ventilation tubes; thrive failure. She presented recurrent events of bronchospasm, productive cough, without requiring hospitalization. CAT scan was requested, with presence of bronchiectasis and peribronchial thickening *(Figure 3A)*, spirometry with normal bronchodilator without reversibility, esophagogastroduodenal series with grade I reflux. Bronchoscopy was performed with endobronchial biopsy for electron microscopy; it reports alterations compatible with PCD, with alteration in the microtubules, absence of peripheral doublets *(Figure 3B)*, PCD type III of the Barlocco and collaborators classification.[8] Genetic panel is requested.

DISCUSSION

Most patients with SCD present with clinical manifestations at an early age; however, diagnosis is delayed until an average age of four to six years secondary to the low index of suspicion.[9] In order to make a diagnosis at an earlier age, this pathology should be suspected in patients with recurrent or chronic respiratory symptoms such as wet

cough, rhinorrhea, sinusitis, otitis media and/or presence of bronchiectasis, with a history of term newborn with admission to the Neonatal Intensive Care Unit due to pulmonary pathology, congenital heart disease or alterations of laterality.[10] In our case series, we observed that all three patients presented recurrent respiratory tract infections, initially treated as difficult-to-control asthma. Likewise, 100% presented radiological alterations such as peribronchial thickening and bronchiectasis; CATAR was used in all cases.

There is no single diagnostic test for the diagnosis of PCD; therefore, predictive scales such as PICADAR, used in combination with different study methods, have been proposed. In our institution we have flexible bronchoscopy, so it was decided to perform the diagnosis by this method; the interpretation by electron microscopy was subrogated to the National Institute of Medical Sciences and Nutrition «Salvador Subirán», since there are few centers that have this resource. Our institution has a genetics service, so a molecular study for ciliopathies was requested. At present, other methods exist in specialized centers, such as the exhaled nitric oxide fraction; however, in our center, we do not have this resource, which is a limitation for this study.

Among the complementary studies to measure pulmonary function, spirometry with bronchodilator was requested, which may be normal during early childhood, reaching, according to the evolution of the condition, a certain degree of airflow obstruction.

At present, there is no treatment to correct ciliary dysfunction. Consistent treatment is pulmonary physiotherapy to improve mucociliary clearance and avoid bacterial superinfection, so early initiation of antibiotic therapy is recommended for respiratory tract infection.[11] Multidisciplinary management is important.

CONCLUSIONS

Patients with PCD present a variable clinical picture, with mild to moderate manifestations, usually with early onset and late diagnosis, affecting the patient's quality of life. As it is an autosomal recessive pathology, genetic counseling is required for the parents, since there is no definitive treatment to recover the movement of the affected cilia. In our study it was observed that we still have limitations to achieve an early diagnosis due to the heterogeneity of the symptoms and the lack of resources, such as electron microscopy and exhaled nitric oxide fraction, but it is extremely important to apply scales of diagnostic suspicion and to start early the approach to rule out other pathologies. We plan to apply the study and prospectively follow up to these patients in order to have a better knowledge of prognosis and quality of life.

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