Primary ciliary dyskinesia: when clinical suspicion meets genetics - a pediatric case report

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ABSTRACT

Background: Primary ciliary dyskinesia (PCD) is a rare genetic disorder characterized by structural and/or functional abnormalities of motile cilia. It typically presents with neonatal respiratory distress, recurrent respiratory infections, and sometimes laterality defects, which define Kartagener syndrome. Diagnosis is often delayed due to nonspecific symptoms.

Case Presentation: A 10-year-old female was referred to pediatric allergy consultation for chronic nasal obstruction and impaired growth. Her history included neonatal respiratory distress with hypoxemia, hydrocephalus requiring ventriculostomy, *situs inversus totalis*, recurrent otitis media with confirmed hearing impairment, and chronic rhinosinusitis. Genetic testing by whole-exome sequencing revealed a previously undescribed heterozygous frameshift variant in *FOXJ1* (c.929_932del p.Asp310Glyfs*22), a gene crucial for motile cilia function and associated with autosomal dominant PCD. Chest computed tomography showed extensive bronchiectasis. She started multidisciplinary treatment, including airway clearance, additional immunizations, and prophylactic azithromycin.

Conclusion: This case reinforces the importance of clinical suspicion for PCD when faced with characteristic symptoms to achieve early diagnosis and intervention. Identification of a novel FOXJ1 variant expands the genotypic spectrum of PCD and highlights the role of genetic testing in diagnosis and counseling. Early diagnosis and comprehensive management are essential to prevent disease progression and improve quality of life.

Keywords: Case report, primary ciliary dyskinesia, Kartagener's syndrome, *Situs inversus totalis*, Bronchiectasis, Rhinosinusitis.

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Introduction

Primary ciliary dyskinesia (PCD) is a rare genetic disorder characterized by a spectrum of structural and/or functional ciliary abnormalities [1,2]. Autosomal recessive inheritance is the most frequent, although autosomal dominant and X-linked patterns have been identified [3]. Clinically, it presents with neonatal respiratory distress, recurrent upper and/or lower respiratory tract infections, and subfertility [2]. Laterality defects are present in approximately half of patients [1,2,3], constituting a subtype known as Kartagener syndrome, which is characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis [1,4,5,6]. The estimated prevalence ranges from 1 in 7,500 – 50,000 live births [1,2,3,4,6]. The diagnosis is challenging, and the average age at diagnosis varies widely across studies, with cases occasionally diagnosed in adulthood [1,2,6].

Case Presentation

A 10-year-old female was referred to the pediatric allergy consultation, presenting with chronic nasal obstruction associated with rhinorrhea and poor growth. Her medical history included respiratory distress with hypoxemia at 8 days of life, followed by acute hydrocephalus due to aqueductal stenosis at 2 months of age, which required ventriculostomy. At 2 years old, *situs inversus totalis* (Figure 1) was identified, although structural and functional cardiac assessment was normal. At the age of 7, she began follow-up in otolaryngology due to recurrent otitis media, speech delay, and suspected hearing impairment, which was confirmed, leading to hearing aid placement. She was diagnosed with serous otitis media and chronic rhinosinusitis and underwent bilateral myringotomy.

The parents are non-consanguineous, and there is no significant family medical history.

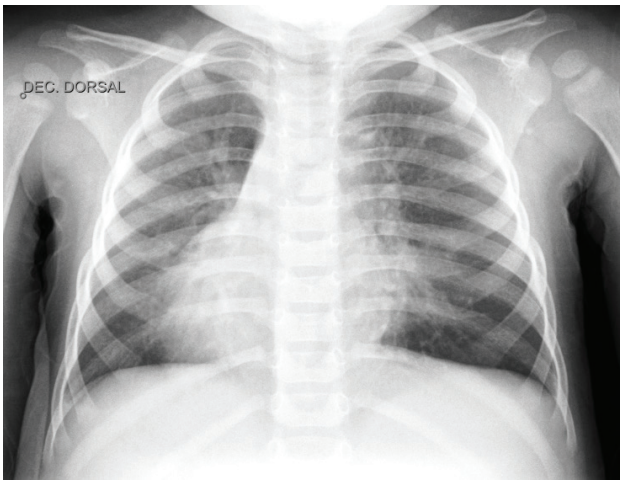

Figure 1. *Chest radiograph at 2 years of age showing dextrocardia, with the cardiac apex oriented toward the right hemithorax.*

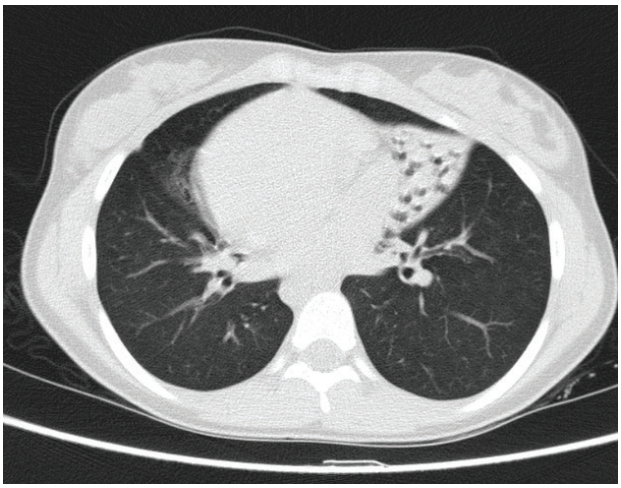

Figure 2. *Axial chest CT scan showing mirror-image arrangement of thoracic organs (situs inversus), widespread cylindrical and varicose bronchiectasis, and total collapse of the middle lobe consistent with lobar atelectasis.*

Impaired growth was confirmed, with the patient's stature falling short of the expected familial target height.

Investigations at the pediatric allergy consultation included a complete blood count, blood glucose, renal and liver function tests, serum electrolytes, total proteins and albumin, iron studies, inflammatory markers, venous blood gas analysis, coeliac disease serology, immunoglobulin levels, and a sweat test, all within normal limits. Bone age radiograph consistent with chronological age. Karyotype analysis revealed 46, XX.

Given the high clinical suspicion of PCD, genetic testing was performed using whole-exome sequencing with CNV analysis. This revealed a heterozygous variant, c.929_932del p.(Asp310Glyfs*22), in the *FOXJ1* gene, which encodes a transcription factor essential for the formation of motile cilia. This variant introduces a premature stop codon, leading to the production of a truncated protein. Notably, this variant has not been previously described in the literature or genetic databases. Referral was made to a medical genetics consultation for family study and genetic counseling.

The patient subsequently developed lower respiratory tract symptoms that were poorly responsive to standard treatment. A chest computed tomography scan revealed extensive bronchiectasis (Figure 2). Microbiological analysis of respiratory secretions showed no abnormalities. Pediatric pulmonology follow-up was started at a tertiary care center following this result.

Pediatric ophthalmologic assessment excluded retinitis pigmentosa.

In addition to routine childhood vaccinations, the patient received the 23-valent pneumococcal vaccine and is vaccinated annually against influenza. She is currently undergoing respiratory physiotherapy, nebulization with hypertonic saline, inhaled therapy with a combination of long-acting bronchodilator and corticosteroid, as well as azithromycin prophylaxis, with good adherence and tolerability, resulting in satisfactory control of major symptoms.

Discussion

In the present case, the patient's history of neonatal respiratory distress, hydrocephalus, recurrent otitis media, chronic rhinosinusitis, and associated hearing impairment raised a strong clinical suspicion for PCD. Additionally, the presence of *situs inversus totalis* should have further prompted earlier diagnostic consideration. Several studies have emphasized that the combination of neonatal respiratory distress and situs abnormalities in a term infant without congenital heart disease is highly suggestive of PCD and warrants further investigation [3]. Neonatal respiratory distress, as observed in our patient, occurs in over 80% of PCD cases [5]. However, it is a common and non-specific finding in neonates and, in isolation, does not justify immediate investigation for PCD. Similarly, symptoms such as recurrent otitis media and chronic rhinitis are frequent in childhood and non-specific, often contributing to diagnostic delays and missed diagnoses [2]. Still, a comprehensive clinical assessment that integrates the patient's full medical history and clinical findings can help assemble the diagnostic puzzle and overcome barriers leading to delayed or missed recognition. In fact, delayed clinical suspicion is a common issue, with reports indicating that up to 70% of patients are evaluated numerous times before a diagnosis is established [4].

Early diagnosis enables prompt initiation of symptomatic treatment and prevention of complications such as recurrent respiratory infections, thereby helping to limit the development of bronchiectasis, a major determinant of long-term prognosis. Although no disease-specific therapy exists, current management is extrapolated from treatment strategies for bronchiectasis of other etiologies, including cystic fibrosis [1,2].

In this case, the patient exhibited impaired growth despite directed etiological investigation, raising the hypothesis that it resulted from long-standing, untreated chronic illness. Both the hearing impairment requiring hearing aids and the development of bronchiectasis likely reflect disease progression in the absence of early diagnosis and intervention. These factors have had a significant impact on the patient's quality of life and contributed to her learning difficulties.

Given the patient's complete immunization coverage according to the National Immunization Program, only supplementary immunization with the 23-valent pneumococcal vaccine and annual influenza vaccine was required. Immunization is a key preventive strategy against viral and bacterial infections in the management of PCD [2].

Kartagener syndrome was diagnosed based on a strong clinical phenotype and the identification of a variant with functional impact in a gene known to be associated with the condition. While PCD is most inherited in an autosomal recessive pattern, pathogenic variants in the *FOXJ1* gene follow an autosomal dominant inheritance [2].

Recent advances in genetic testing not only facilitate etiological diagnosis but also enable genetic counseling for patients and their families. Moreover, genotype-phenotype correlations may support future developments in the diagnosis and clinical management of PCD. In this context, it is worth noting the presence of hydrocephalus, as reported in other cases of PCD associated with FOXJ1 mutations [7,8,9].

Conclusion

This case reinforces the importance of clinical suspicion across different medical specialties when faced with a constellation of symptoms highly suggestive of Kartagener syndrome, in order to achieve an early diagnosis and treatment. Late recognition of PCD may lead to progressive respiratory deterioration, including bronchiectasis, as well as systemic complications such as impaired growth, likely reflecting chronic inflammation and prolonged disease activity in the absence of early intervention. A comprehensive approach, including routine airway clearance, immunization strategies, and prophylactic antibiotic therapy such as azithromycin, is essential to improving quality of life, reducing infectious exacerbations, and preserving long-term pulmonary function in patients with PCD. A previously undescribed heterozygous variant in *FOXJ1* was identified, supporting the diagnosis of PCD with an autosomal dominant inheritance pattern, which contrasts with the typically recessive nature of most PCD cases.

What is new?

The authors describe a pediatric case of Kartagener syndrome caused by a previously undescribed heterozygous FOXJ1 variant with autosomal dominant inheritance, a less common pattern in PCD.

The presence of hydrocephalus further supports the association between FOXJ1 mutations and this finding, as described in other cases. This case reinforces the value of genotype-phenotype correlations in guiding early diagnosis, anticipating comorbidities, and tailoring clinical management in PCD.

List of Abbreviations

CNV Copy number variation
PCD Primary ciliary dyskinesia

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Informed consent was obtained from the patient's mother (as the patient is a minor), and patient anonymity was ensured.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	Patient (gender, age)	10 years, female
2	Final diagnosis	Primary Ciliary Dyskinesia, subtype Kartagener Syndrome
3	Symptoms	Recurrent otitis media, chronic rhinosinusitis, hearing impairment, situs inversus totalis, impaired growth.
4	Medications	Airway clearance, additional immunizations and prophylactic azithromycin
5	Clinical procedure	None
6	Specialty	Pediatrics