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Editorial

Primary Ciliary Dyskinesia: A More Prevalent Disease Than Previously Believed?

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▸ See the article "Clinical Manifestations and Genotype of Primary Ciliary Dyskinesia Diagnosed in Korea: Multicenter Study" in volume 15 on page 757.

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Primary ciliary dyskinesia (PCD) is a rare disease with genetic and clinical heterogeneity. It is caused by genetic mutations in over 40 genes affecting motile cilia, resulting in diseases of the upper and lower airways.[1] Impaired ciliary function leads to unexpected neonatal respiratory distress in term infants at the beginning of life. Then, it continues to have a year-round wet cough, recurrent lung infections, chronic rhinosinusitis, recurrent otitis media with effusion, and bronchiectasis, with or without situs inversus and infertility, whose progress is lifelong but highly variable. PCD affects approximately 1 in 10,000 to 15,000 children in Europe.[2] However, there is a lack of prevalence estimates for PCD outside of Europe, including Korea.

There is no precise test for diagnosing PCD, which requires a combination of nasal nitric oxide concentration, high-speed video microscopy analysis, immunofluorescence, transmission electron microscopy (TEM), and genotyping.[3,4] Recently, PCD can be confirmed by a distinctive ultrastructural defect through TEM or bi-allelic pathogenic mutations, thanks to advancements in new insights into genetics.[1] Of note, there are different clinical phenotypes based on the ciliary ultrastructural defect group and the corresponding genotype. Patients with absent inner dynein arm (IDA), central apparatus defects, and microtubular disorganization in ciliary ultrastructure, or those with *CCDC39* or *CCDC40* mutations, exhibited significantly decreased lung functions and a progressive decline in lung function over time, compared to those with outer dynein arm defect alone or those with *DNAH5* or *DNAH11* mutations.[5,6] These advances facilitate the prediction of bronchiectasis and decline in lung function as well as the earlier identification of rare diseases, leading to personalized medicine.

In this issue of the *Allergy Asthma Immunol Res*, Kim *et al.*[7] showed the clinical characteristics, diagnosis, and genotypes of PCD through the first multicenter study in Korean children. The study was conducted retrospectively and prospectively over a span of 13 years in 15 institutes across the nation. The study included 41 patients with PCD who were diagnosed using TEM (n = 33), pathogenic mutations (n = 12), or a combination of both (n = 4). The mean age at diagnosis was 11.8 years, indicating a delayed diagnosis of PCD in Korean children compared to other countries.[2,4,5] Diagnosing PCD might have been challenging due to the requirement for specialized testing, combined with a lack of general awareness. As a result, clinicians have often failed to identify the typical phenotype. Efforts to enhance understanding of

the clinical characteristics of PCD, led by specialists in the field, can enhance referrals, as demonstrated in the UK.[1] This nationwide multicenter PCD study will mark the beginning, and thus, the age of diagnosis in PCD will drop in Korea by helping clinicians understand the clinical features.

The authors acknowledge several limitations, including a small-sized study that was retrospectively and prospectively designed. This design prevented the investigation of clinical phenotypes based on the ciliary ultrastructural defects and the corresponding mutations. And, when interpreting isolated IDA defects in TEM, caution must be exercised. It was found that more than one-fourth of isolated IDA defects on the first biopsy were normal on repeat biopsy.[8] Furthermore, an IDA defect alone could be a secondary finding caused by inflammation and may not be sufficient to diagnose PCD.

In Korea, PCD is likely more common than cystic fibrosis (CF), an extremely rare disease involving multiple organs, particularly the lungs, caused by exclusive mutations in the *CFTR* gene. CF was also diagnosed at a later age in Korea compared to Western countries due to limited awareness and diagnostic tools.[9] These multicenter surveillances, including the current study by Kim *et al.*,[7] assist Korean physicians in comprehending the clinical features of patients with rare diseases, thereby facilitating early diagnosis and treatment. Especially, PCD could be more prevalent than previously believed because of a lack of awareness, given the advancements in our understanding of ciliopathies and the potential role of genetic testing in future diagnostic procedures. Respiratory management of PCD is guided by evidence from CF, which suggests regular airway clearance and antibiotic treatment for pulmonary exacerbations.[10] Likewise, early diagnosis and treatment strategies are essential in managing PCD, involving multidisciplinary team approaches. A global and collaborative effort is crucial for future research in identifying predictive outcomes, such as bronchiectasis and decline in lung function. Early diagnosis of individuals at a higher risk of developing severe disease could lead to early intervention and potentially improve outcomes.

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