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Mini-symposium: Primary Ciliary Dyskinesia

Congenital Heart Disease and Primary Ciliary Dyskinesia

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EDUCATIONAL AIMS THE READER WILL COME TO UNDERSTAND THE IMPORTANCE:

- Association between PCD and congenital heart disease (CHD), including complex cardiovascular defects.
- Mechanism by which ciliary dysfunction leads to heterotaxic CHD.
- Importance of screening for CHD in patients with PCD, especially those with organ laterality defects.
- Importance of screening for ciliary disorders, including PCD, in patients with CHD, particularly in the context of potential surgical correction of the congenital heart defect.

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SUMMARY

Through the better understanding of the genetics and clinical associations of Primary Ciliary Dyskinesia (PCD), an autosomal recessive disorder of ciliary motility and mucociliary clearance, the association between PCD and heterotaxic congenital heart disease (CHD) has been established. In parallel, research into the cause of CHD has elucidated further the role of ciliary function on the development of normal cardiovascular structure. Increased awareness by clinicians regarding this elevated risk of PCD in patients with CHD will allow for more comprehensive screening and identification of cases in this high-risk group with earlier diagnosis leading to improved health outcomes.

INTRODUCTION

Primary Ciliary Dyskinesia (PCD) is a genetically heterogenous, autosomal recessive disorder of ciliary motility resulting in defective mucociliary clearance. The prevalence of PCD is not well defined but has been estimated to be approximately 1 in 16,000 based on extrapolating the incidence from population-based studies screening chest radiographs for organ laterality defects and bronchiectasis [1,2].

The disorder classically includes neonatal respiratory compromise, chronic sinusitis, recurrent otitis media, male infertility, and recurrent pneumonia with bronchiectasis. The original description of the disorder in 1933 by Kartagener describes a triad of situs inversus totalis, bronchiectasis and sinusitis [3]. While this early description of PCD included situs inversus totalis, it was not until many years later that a connection was established between PCD and other organ laterality defects, including congenital heart disease (CHD) [4,5]. The association between PCD and CHD is supported by studies demonstrating an increased incidence of CHD in murine models of PCD [6]. Increased awareness of this link amongst clinicians, with improved radiology imaging modalities, has resulted in detection of increasing numbers of cases of congenital heart disease amongst patients with ciliary disorders. Recent studies have shown that approximately 50% of patients with PCD have organ laterality defects [4,7,8], with approximately 3.5-6% having cardiovascular malformations [4,8] and at least 2.6% having a complex cardiovascular defect [8]. This review explores a number of aspects of CHD in PCD, including definitions and nomenclature, genetic associations, diagnosis, management, prognosis and potential future directions for these two related conditions.

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DEFINING CHD AND HETEROTAXY IN PCD

Congenital heart disease represents one manifestation of the many organ laterality defects seen in patients with PCD (see Figure 1). The study of these laterality defects, and comparison of previous studies regarding CHD in PCD, is made more difficult by discordance in the published literature regarding the nomenclature and categorisation of the variety of defects that may exist. Previous studies in non-PCD populations have classified patients with organ laterality defects based on the presence of asplenia [9] (failure of L-sided patterning resulting in R-sided isomerism) or polysplenia [10] (failure of R-sided patterning resulting in L-sided isomerism), with both splenic phenotypes associated with particular cardiovascular malformations. However, this categorisation is not universally applicable as the spleen is not always abnormal in terms of its positon and number [11]. In a recent study [8], and its accompanying editorial [12], Shapiro *et al*, provide a useful definition and clear categorisation of the laterality defects associated with PCD. The authors divide the laterality defects seen into 3 broad categories: situs inversus totalis (SI), Situs ambiguus (SA), and heterotaxy. SI, the most common laterality defect, is seen in approximately 40% of patients with PCD and involves total mirror-image arrangement of the organs. Situs ambiguus (SA) is defined as any organ laterality defect other than SI, including non-complex cardiovascular malformations. Heterotaxy is defined as SA with any complex cardiovascular malformation. Throughout this review, where possible, we use these definitions to refer to the laterality defects seen in PCD. The array of cardiovascular malformations seen in patients with PCD and congenital heart disease is summarised in Table 1.

PATHOGENESIS

The prevalence of heterotaxy in the general population has been reported as approximately 1 in 10,000 pregnancies, [14] which represents approximately 3% of all births with CHD [15]. This prevalence is estimated using data extracted from an American population-based registry of congenital malformations including live births, stillbirths at greater than 20 weeks and elective terminations in the second trimester. Spontaneous abortions at less than 20 weeks gestation were not included in this registry; inclusion of these data may have resulted in the discovery of many more cases of heterotaxy that resulted in early spontaneous abortion. The prevalence of heterotaxy (defined as any thoracoabdominal asymmetry that differs from SS or SI) in PCD is much higher, at approximately 1 in 50 patients (which represents a 200-fold increased risk) [4].

To understand the increased prevalence of heterotaxy in PCD, it is important to recall the function of embryonic nodal cilia. There are several types of human cilia, which are usually divided into motile cilia and non-motile, or sensory, cilia. Non-motile cilia, also known as "primary" cilia, play an important role in cellular environment regulation and cell signalling [16]. Dysfunction of non-motile cilia results in a variety of disorders involving multiple organs, including Bardet-Biedl syndrome (BBS), nephronophthisis (NPHP), Senior-Loken syndrome (SNLS), Alstrom syndrome (ALMS), Meckel Gruber syndrome (MKS), Joubert syndrome (JBTS), Oral-facial-digital Type I (OFD 1), Jeune asphyxiating thoracic dystrophy (JATD), Ellis van Creveld (EVC), Leber congenital amaurosis (LCA), and Polycystic kidney diseases (PKD) [16].

Motile cilia are responsible for a number of vital body functions, including mucus clearance from the upper and lower respiratory

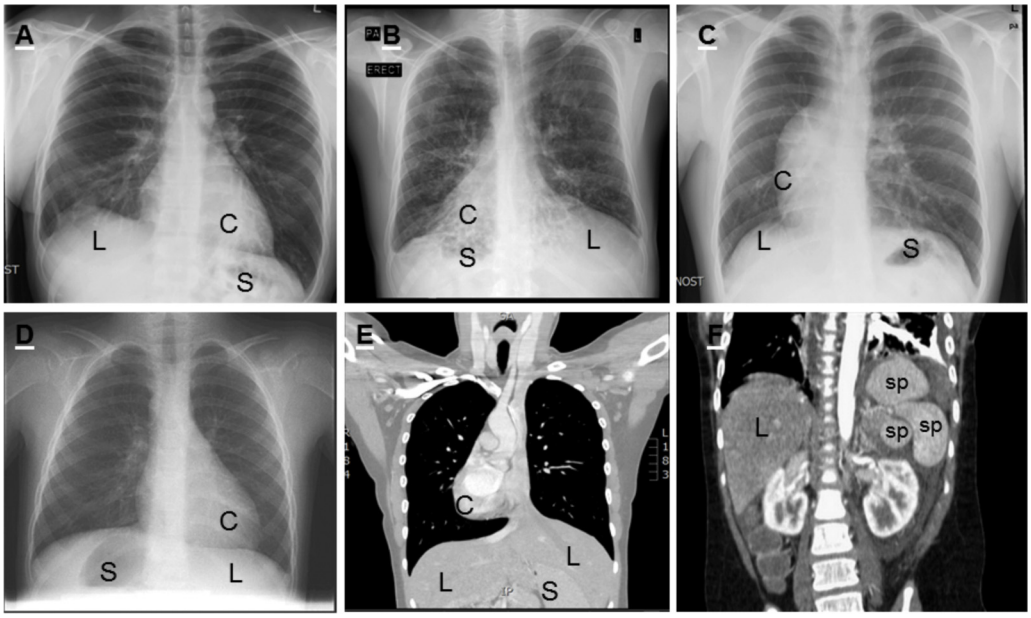

Figure 1. PCD patients with laterality defects on radiological imaging
A: Chest x-ray of a 31 year old male with Situs solitus, or normal organ arrangement, with left cardiac apex, left -sided stomach bubble, and right-sided liver and previous right thoracotomy and right middle lobectomy.
B, Chest x-ray of a 34 year old male with situs inversus totalis, bronchiectasis in left middle lobe and both lower lobes with mirror image organ arrangement, with right-sided cardiac apex, right-sided stomach bubble, and left -sided liver.
C. Chest x-ray of a 31 yr old male with situs ambiguus and isolated dextrocardia.
D. Chest x-ray of a 4 year old girl with situs ambiguus and a left cardiac apex but abdominal situs inversus with polysplenia, interrupted inferior vena cava, and intestinal malrotation.
E. Coronal CT Thorax with contrast image of a 16 yr old female with PCD and situs ambiguus with features of right isomerism with dextrocardia, bilateral trilobed lungs, transverse liver and absent spleen.
F. Coronal CT Abdomen of a 6 year old boy with heterotaxy consisting of levocardia, pulmonary atresia, hypoplastic left ventricle, atrial septal defect, ventricular septal defect, d-Transposition of the great vessels, left sided superior vena cava, and polysplenia.
C=cardiac apex; L= liver; S=stomach, sp=spleen.