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Mini-symposium: Primary Ciliary Dyskinesia

When to suspect primary ciliary dyskinesia in children

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EDUCATIONAL AIMS

The reader will come to suspect the diagnosis of Primary Ciliary Dyskinesia in:

- A term infant with unexplained respiratory distress and migratory collapse on the chest radiograph.
- A toddler with chronic otitis media, purulent otorrhoea and a wet cough.
- A child with laterality defects [situs inversus, dextrocardia, heterotaxy].
- A child with chronic sinusitis and nasal polyposis.
- A child with unexplained bronchiectasis.
- An adult with unexplained bronchiectasis, chronic sinusitis, and infertility.

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SUMMARY

Primary ciliary dyskinesia [PCD] is an uncommon, autosomal recessively inherited condition that is often overlooked and undertreated in childhood. Amidst the myriad of children with coloured nasal secretions, otitis media and a wet cough, there exists a subset with PCD as the underlying unifying diagnosis. In this paper we have highlighted the varying clinical manifestations of PCD, emphasising different presentations between neonates, toddlers, school aged children and adults.

INTRODUCTION

The manifestations of PCD vary with age and involve oto-sino-pulmonary manifestations [1,2]. This may begin antenatally with the detection of situs inversus or complex congenital heart disease on an ultrasound. However, this is seldom raised for discussion and would be an unlikely cause for referral in early post-natal life. In contrast, most children in whom the diagnosis of PCD is made will have a history of neonatal respiratory problems [1–5]. These symptoms may be erroneously attributed to "atypical" transient tachypnoea of the newborn, pneumonia or meconium aspiration [6]. Often the child will recover and the significance of the neonatal problems may be overlooked until later repeated presentations with bouts of cough, tachypnoea and hypoxaemia [1,7,8]. The child may have developed bronchiectasis by the time of presentation, with one series reporting 32% of 84 cases having bronchiectasis at a median age of diagnosis of 6.4 years [1].

Repeated ear infections are frequently noted in many children in the preschool years, but the persistence of symptoms, tympanic membrane perforations and associated conductive hearing loss from chronic middle ear effusions lead to significant morbidity in terms of speech acquisition, developmental progress and the potential for structural damage to the middle ear, tympanic membrane, mastoid bone and surrounding structures [9]. The presence of ear disease may be a clinical pointer to distinguish PCD from conditions leading to suppurative lung disease, such as cystic fibrosis missed on newborn screening.

Nasal congestion is an extremely common feature of PCD, affecting >90% of people with the condition [1,8,10]. It often presents as neonatal rhinitis, which is overlooked at the time but reported to occur increasingly with age [1,4,8,10]. With increasing age, the presence of nasal polyps becomes apparent with chronic sinusitis and an impaired sense of smell [1,8].

Chronic, often wet, cough also occurs on a daily basis in nearly all patients with PCD, and some infants can expectorate

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sputum while coughing. The cough often starts in early infancy. A history of pneumonia or bronchitis can be lacking in young children with PCD, as they are frequently treated with antibiotics for otitis and nasal congestion, thus not allowing opportunity to fully develop clinically obvious lower respiratory tract infections.

These symptoms and signs occur in nearly all subjects in whom the diagnosis of PCD is made. The average age at diagnosis is decreasing with better awareness of the condition and the increasing availability of diagnostic tools, such as nasal nitric oxide [nNO], electron microscopy, video assessment of cilial function, immunofluorescence staining, and expanded genetic testing [8,11]. However, no single diagnostic test, including nNO, light microscopy, electron microscopy, high speed videomicroscopy, cell culture or genetic testing will detect 100% of PCD diagnoses, and often combinations of these investigations will be required in patients with a suggestive history of PCD [11].

Recent reports of the diagnosis of PCD in people with a suggestive history but normal ciliary ultrastructure [8], or the presence of heterotaxy with congenital heart disease [12] have highlighted the need to think critically about the definition of PCD [13]. Electron microscopic assessment alone will miss an estimated 30% of people with PCD [8]. To date around 30 disease-causing genes have been confirmed in patients with PCD, accounting for approximately 60% of phenotypes and providing impetus to examine stronger links for genotype-phenotype correlations [8,11,14]. Much of this is of course is familiar to respiratory paediatricians who care for children with cystic fibrosis, where the status of the "gold standard" test of the sweat chloride and arbitrary values for diagnosis have been blurred with the advent of genotyping and appreciation that sweat chloride values may change significantly over time [15].

In the following text, the presenting features of children with PCD at different ages will be discussed so as to highlight the varied manifestations of PCD.

Antenatal considerations

Prenatal ultrasound is routinely performed at least once in most birthing centres, and PCD is sometimes suspected in babies with situs inversus totalis (SIT - complete mirror image of normal anatomy). Situs inversus totalis on prenatal imaging should provoke a discussion on the possibility of PCD, as approximately 20%-25% of people with SIT also have PCD [7,13,14]. Other situs anomalies, such as situs ambiguus (SA- organ arrangement is abnormal and falls on a spectrum between normal and complete mirror image arrangement) should also raise concern for PCD [7,13,14], yet many of these babies have accompanying severe cardiac malformations, which often overshadow the possibility of a rare respiratory disease [13,14,16].

Prenatal cerebral ventriculomegaly has been reported in babies who are later diagnosed with PCD [17,18]. This finding usually resolves by birth and is presumably linked to PCD via similar dysfunction of motile ependymal cilia, found in the cerebral ventricles and aqueducts of the brain, which are responsible for cerebrospinal fluid flow. While not all cases of cerebral ventriculomegaly are caused by ciliary dysfunction, this finding, together with any organ situs anomaly, should prompt consideration of PCD, accompanied by a detailed family history of respiratory disease and organ laterality defects. As neonatal respiratory distress from PCD can cause severe morbidity and even mortality [19,20] cases with a high prenatal suspicion of PCD may benefit from delivery in a specialized care centre equipped to manage neonatal respiratory distress and to perform proper PCD diagnostic testing.

Neonatal respiratory distress

More than 85% of babies with PCD develop neonatal respiratory distress despite a seemingly normal term birth [21,22]. The cause of the breathing difficulty remains unclear, but some postulate that functioning respiratory cilia are required to sweep amniotic fluid from the lungs to assist in transition from a fluid filled to an air filled lung [23]. Unlike other causes of neonatal respiratory distress (transient tachypnoea of the newborn, neonatal pneumonia, or prematurity related respiratory distress syndrome), where respiratory issues are present immediately from birth, respiratory distress in PCD tends to develop at 12-24 hours of life, after a seemingly normal post-partum transition period [19]. Some children with PCD are discharged home before this distress becomes apparent, and they return to medical attention at a few days to weeks of life with respiratory distress.

Commonly presenting with tachypnoea, retractions, and low oxygen saturation [SpO_2], babies with PCD and neonatal respiratory distress often require days to weeks of supplemental oxygen. [19] Chest radiographs [CXRs] commonly demonstrate upper and middle lobar collapse, which is sometimes diagnosed as neonatal pneumonia. Bedside nurses often report nasal congestion or cough (sometimes even productive) in these children, which is quite unusual for a neonate, but almost pathognomic for an infant with PCD [1,4,7,10,11,19,22,23]. In term newborns with respiratory distress, the presence of lobar collapse, SIT, or a persisting oxygen need for >2 days predicts PCD in an affected neonate with 87% sensitivity and 96% specificity.[6] [19] When neonatal respiratory distress is present in a baby with SIT or SA without cyanotic cardiac defects, there is a very high likelihood of PCD, and proper PCD investigations should be conducted as soon as possible [19]. Thus far, there are no studies on treatment for PCD-related neonatal respiratory distress, and supportive respiratory cares are recommended.

Infants with complex congenital heart disease

Organ laterality defects, including congenital heart malformations, occur in PCD through shared dynein arm anomalies in respiratory cilia and embryonic nodal cilia, the latter of which determines organ symmetry in the developing embryo [24]. Congenital heart disease is found in at least 6% of patients with PCD, and these lesions are often accompanied by other organ laterality defects throughout the body [24]. When cardiologists encounter heart malformations with other laterality defects, the term "heterotaxy" is often ascribed, although some physicians use this term interchangeably with SA. The prevalence of PCD in SA is unknown, but a preliminary study suggests PCD-associated symptoms approach 40% in children with SA and congenital heart disease [25]. The actual prevalence of classic PCD in SA is likely lower than this figure, but remains unclear.

Some children with SA show evidence of respiratory ciliary dysfunction that falls short of a definitive PCD diagnosis. These children have intermediate nasal nitric oxide levels, increased respiratory symptoms, and frequent carrier status of PCD-related gene mutations, yet they do not satisfy the diagnostic criteria for classic PCD (as they have normal electron microscopy and non-diagnostic ciliary waveform anomalies on high speed videomicroscopy) [26]. Children with complex heart lesions commonly associated with heterotaxy or SA seem to have a greater prevalence of respiratory cilial dysfunction and associated respiratory symptoms [27]. Particularly around cardiac surgeries, these children seem to have worse clinical outcomes compared to children with cardiac lesions that are not classically associated with SA [28]. Unfortunately, there are no studies on pulmonary optimization of cardiac patients around their surgical repairs, but