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MINIREVIEWS

Clinical spectrum of primary ciliary dyskinesia in childhood

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Abstract

Although the triad of bronchiectasis, sinusitis and situs inversus was first described by Kartagener in 1933, the clinical spectrum of primary ciliary dyskinesia is still under investigation. Heterotaxy defects as well as upper and lower respiratory tract symptoms are the main manifestations in childhood. It is now recognized that situs inversus is encountered in only half of patients. The first lower respiratory symptoms may be present from infancy as neonatal respiratory distress. The most common lower airway manifestations are chronic wet cough, recurrent pneumonia and therapy resistant wheezing. Patients are at risk of developing bronchiectasis which may even be the presenting finding due to delayed diagnosis. Upper respiratory tract infections such as nasal congestion, nasal drainage and recurrent sinusitis as well as otologic manifestations such as otitis media or otorrhea with conductive hearing loss are also often encountered. It seems that the type of ciliary ultrastructure defects and the involved mutated genes are associated to some extent to the clinical profile. The disease, even in nowadays, is not recognized at an early age and the primary care clinician should have knowledge of its clinical spectrum in order to select appropriately the children who need further investigation for the diagnosis of this disorder.

Key words: Primary ciliary dyskinesia; Kartagener's syndrome; Immotile cilia; Heterotaxy; Respiratory tract

Core tip: The clinical spectrum of primary ciliary dyskinesia (PCD) has been recently better understood through the evolution of electron microscopy techniques, molecular genetics and imaging of the respiratory tract. Herein, we highlight the clinical profile of the disease from infancy to adolescence, focusing on clinical studies of children with a laboratory confirmed diagnosis of PCD. Additionally, the currently recognized associations of the type of ciliary ultrastructure defects and involved mutated genes with the clinical spectrum of the disease are presented. This information is of interest for the paediatrician in order to conduct a timely investigation of children with symptoms suggestive of PCD.

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INTRODUCTION AND HISTORICAL REVIEW

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder characterized by cilia dysfunction. It is a rather rare disorder with a prevalence which ranged from 1.3 to 111 diagnosed cases per million inhabitants aged 5-14 years in different European countries[1].

A case of PCD was first reported in 1904 as an association of bronchiectasis and situs inversus by Siewert[2]. Later in 1933, Kartagener described the classic triad of bronchiectasis, sinusitis and situs inversus in a group of patients[3]. Today it is well known that situs inversus is present in only half of PCD cases and therefore it is not a necessary prerequisite for the characterization of the disease. In 1976, Afzelius[4] studied mucocilia motion in subjects with PCD who produced immotile sperm while electron microscopy indicated absence of dynein arms of cilia from the relevant cells.

The aim of this review was to describe the clinical spectrum of PCD in childhood an entity which is recently better recognized thanks to the availability of modern screening techniques and the genetic identification of this disorder. Heterotaxy defects, upper and lower respiratory tract features are the main manifestations of PCD in childhood which are herein presented. Infertility which may affect males and females with PCD in adulthood is beyond the scope of the current review.

CILIA STRUCTURE AND FUNCTION

A basic knowledge of cilia structure and related function is a prerequisite for the understanding of the clinical features of PCD. Cilia are long protuberances extending from the cell body of certain eukaryotic cells. They are categorized as motile and non-motile (sensory) cilia. Herein the structure and function of motile cilia are described as only this type of cilia is involved in the pathogenesis of PCD.

The axoneme is the core of a motile cilium. The axonemal cytoskeleton consists of a "9 + 2" arrangement of microtubules. Nine peripheral microtubules surround a central inner pair[5]. Nexin links connect the nine peripheral doublets which are connected to the central pair by radial spokes. Outer and inner dynein arms are motor proteins that are attached to the outer microtubules providing energy for ciliary movement. Each cilium is anchored to the cell by the basal body. Each ciliated epithelium cell has approximately 200 cilia which beat in a coordinated fashion and contribute through this function to the respiratory epithelial defence mechanisms.

There is also a specific type of cilia with a "9 + 0" arrangement which has nine peripheral doublets and dynein arms but lacks the central pair of microtubules[6]. Cells of the ventral node have a single motile cilium of this type per cell. The rotary pattern of the beating of the nodal cilia may confer to organ laterality during embryogenesis[7].

HETEROTAXY DEFECTS

Situs inversus totalis is encountered in approximately half of patients with PCD as it is corroborated by many studies[8-10]. Heterotaxy defects are attributed to the loss of function of nodal cilia during embryogenesis[7]. There is a case report[11] of monozygotic female twins with PCD, one with situs solitus and the other with situs inversus totalis. This observation suggests that situs inversus is a random event in the foetal development of patients with PCD. However, with the advances in genetics it has been shown that subjects with central apparatus defects and RSPH1 mutated genes do not have laterality defects which is in line with the recognition that the "9 + 0" embryologic nodal cilium does not contain radial spokes and is unaffected by central apparatus defects[12]. Boon *et al*[13] also found that situs inversus was significantly less frequent in subjects with PCD and normal ultrastructure and in those with central pair abnormalities, compared to those with dynein deficiency.

Patients with normal ultrastructure, as the researchers suggested, may represent a combined group of patients with authentic normal ultrastructure and patients with unrecognizable subtle central pair abnormalities. The latter group was not expected to have situs inversus and therefore the proportion of situs inversus occurrence in the whole group of patients with presumably normal ultrastructure would have been expected to be lower.

In addition to situs inversus, other heterotaxy defects have been encountered in patients with PCD. Situs solitus and situs inversus totalis were identified in 46% and 47.7% of patients respectively in a retrospective review of 337 patients with PCD[10], whereas 6.3% of patients had other heterotaxy defects (situs ambiguous). It is of interest that approximately half of patients with heterotaxy defects also had cardiac and/or vascular malformations, a prevalence much higher than in the general population. In another series of patients with PCD[14], situs ambiguous prevalence was nearly twice (12.1%) than that reported by Kennedy *et al*[10]. However, in accordance with Kennedy's study results[10] cardiovascular malformations were also identified in nearly half of patients with PCD and situs ambiguous.

It should be mentioned that the presence of situs inversus contributes to the earlier diagnosis of PCD as median age at diagnosis of PCD in Europe was 3.5 years for subjects with situs inversus compared with 5.8 years for those with situs totalis[1].

LOWER RESPIRATORY TRACT MANIFESTATIONS

Features in neonatal period

The first lower respiratory symptoms of PCD may be present from infancy as neonatal respiratory distress.

However, even in the presence of early symptoms the diagnosis may be delayed until late childhood[15]. Transient tachypnoea of the newborn characterized by tachypnoea starting soon after birth and resolving by the 5th day of life is a well known cause of respiratory distress in term and near term neonates[16]. It is speculated that it is associated with the delayed absorption of foetal lung fluid. It seems that ciliary motility contributes to the foetal lung fluid clearance and as a consequence fluid is not cleared rapidly in neonates with PCD and respiratory symptoms present often shortly after birth. In different series of patients with PCD, neonatal respiratory distress frequency range from 43% to 74% and this percentage may be rather an underestimation due to recall bias, which is usually anticipated in retrospective studies[8,9,17-19]. In a case control study[15], the most common diagnosis in the PCD cases with neonatal respiratory distress was neonatal pneumonia, whereas the most common diagnosis in the control subjects of that study was transient tachypnoea. Furthermore the administration of oxygen treatment was more frequent in the PCD cases as well as the length of treatment in days. The combination of situs inversus, oxygen therapy for longer than 2 d and/or lobar collapse on chest X-ray (CXR) has a sensitivity of 87% for detecting PCD, whereas the combination of oxygen therapy for longer than two days and/or lobar collapse on CXR has a sensitivity of 83% for predicting PCD. Approximately half of the PCD cases (48%) had situs inversus. The median age of diagnosis in this subgroup was 0.83 years compared with a median age of 5 years at diagnosis for the subgroup without situs inversus.

Features from infancy to adulthood

The most common clinical manifestations of lower airways involvement are chronic wet cough, recurrent pneumonia and therapy-resistant wheezing. Recurrent cough and lower respiratory tract infections were among the presenting clinical history features in more than 60% of children in a series of children with PCD from Australia[9], in 83% in another series from the United Kingdom[17], whereas all children with PCD had a clinical history of a productive cough in another study from the United States[18]. Patients with PCD are at risk of developing bronchiectasis which may even be the presenting finding due to delayed diagnosis. In the series of patients from Australia[9] bronchiectasis was the presenting history in 32% of children. A diagnosis of PCD was established as the underlying cause of bronchiectasis in 1%-17% of children with imaging evidence of non-cystic fibrosis (CF) bronchiectasis who attended paediatric chest clinics[20-23]. Although development of bronchiectasis increases with age[18], it has even been described in toddlers with PCD[24].

As is now well recognized, high resolution computed tomography (HRCT) is a highly sensitive imaging modality for diagnosing bronchiectasis[22,25]. Using this non invasive technique in children with PCD and indications of severe lung involvement, based on clinical and/or radiological parameters, bronchiectasis was found in 73% of them in a series of 26 children with PCD who also had available a HRCT[8]. Bronchiectasis were detected in all of the adults and in 56% of children with PCD in another series of patients with PCD reported by Kennedy *et al*[26]. Other findings of HRCT imaging were mucus plugging, peribronchial thickening, consolidation, ground glass opacification, air trapping, atelectasis[8,26]. The most frequently affected lobes were the right middle lobe and lingula followed by the lower lobes[8,26-28] in contrast to what is observed in CF patients[28]. Using a modified Brody composite HRCT scan scoring system, Santamaria *et al*[28] showed that the total HRCT score was significantly higher in CF patients compared to PCD patients. In that study the total HRCT scan score as well as the bronchiectasis subscore was significantly negatively related to FEV1 and FVC indices. Nevertheless spirometry was less accurate than HRCT for the evaluation of the progression of lung disease in PCD patients, as it was shown by Maglione *et al*[27]. It was of note that in that retrospective study[27], patients underwent lung function tests and HRCT at least twice and no relationship was found between the change of a total HRCT scan score and FEV1. In contrast it was observed that lung function remained stable or even improved despite the deterioration of total HRCT scan score at the second evaluation. It is also of interest that, although at both evaluations the total HRCT scan score as well as bronchiectasis subscore were significantly negatively related to FEV1 and FVC, there were patients with normal spirometry and substantial lung imaging abnormalities at the baseline HRCT. The abovementioned data suggest that spirometric indices are not accurate enough to detect patients with structural lung changes. Most recently it was shown by Boon *et al*[29] that lung clearance index (LCI) was a more sensitive functional marker of lung structural abnormalities compared with FEV1 in patients with PCD.

The microbiology of lower airways infections in PCD patients was investigated in a cohort of children and adults with PCD[18] revealing that the most common culprit was *Haemophilus influenzae* followed by *Staphylococcus aureus, non-mucoid* and *mucoid Pseudomonas aeruginosa,* and nontuberculous mycobacteria. However, in this cohort *mucoid Pseudomonas aeruginosa* was isolated mainly in subjects older than 30 years of age. In another cohort[30] of children and adolescents with PCD, *Streptococcus pneumonia* and *Moraxella catarrhalis* were also isolated, whereas *mucoid Pseudomonas aeruginosa* was recovered in 5% of children.

UPPER RESPIRATORY TRACT MANIFESTATIONS

Nasal congestion and nasal drainage typically present from the neonatal period are among the characteristic symptoms that occur in 76%-100% of children in different cohorts of patients with PCD[17,18]. Acute and/or

chronic rhinosinusitis are also common in older children and it was seen among the symptoms that were present at the time of diagnosis in 11% of children in the series described by Coren *et al*[17] and in 71% of children in the series presented by Hosie *et al*[9]. Sommer *et al*[31] found that 59% of children who attended a PCD clinic documented recurrent problems of rhinosinusitis with 32% of them having needed antibiotics more than 30 times. Frontal and/or sphenoidal aplasia or hypoplasia also seem to be common in children with PCD as Pifferi *et al*[32] disclosed these findings in 73% of children with PCD (aged 8-17 years) who underwent a computed tomography (CT) scan of paranasal sinuses. Nasal polyps were identified in about one-third of patients in the cohort of Boon *et al*[13] during the follow up when the median age of the total group was 17.7 years. In contrast Rollin *et al*[33] did not find any polyps in a group of 30 children with PCD. However, the patient age of the latter group ranged from 1-14 years, with a mean age for the Kartagener's syndrome patients being 6 years and the mean age of the PCD patients being 9 years. The differences therefore between the findings from these two studies may simply imply that nasal polyposis tends to occur in patients with PCD at an older age.

Otologic manifestations, such as chronic otitis media with effusion, recurrent acute otitis media and chronic or recurrent otorrhea with conductive hearing loss[2] are also encountered very often among children with PCD. Serous otitis media was present at the time of diagnosis in 28/55 patients in the series presented by Coren *et al*[17] while hearing loss was found in 14/55 patients in this study. Similarly recurrent otitis media was among the presenting symptoms in 49% of children with PCD in another cohort[9]. It is of note that 38% of patients with PCD were diagnosed by their ENT doctor as found by Sommer *et al*[31] but at an older age compared to patients diagnosed by other specialists.

The prevalence of otologic manifestations is even higher than the abovementioned proportions during the course of the disease. In the survey by Sommer *et al*[31] it was shown that 81% of children with PCD had a history of recurrent otitis media and as much as 38% of the patients needed more than 30 antibiotic treatments in their life. However, it seems that recurrent acute otitis media decreases with age and is not present in patients older than 18 years of age[34] while otitis media with effusion is still frequent even in subjects over 18. In the same study[34], it was shown that the occurrence of chronic otitis media increased until the age of 18 and the majority of these patients experienced otorrhea. Retraction pocket, cholesteatoma and tympanic perforation were among the otologic complications observed in this group of patients.

It should also be mentioned that the majority of patients with recurring otitis media received ventilation tubes and about one-third of them needed more than three tympanostomies according to the findings of Sommer *et al*[31] The role of tube placement in children with PCD and recurrent ear problems is controversial but it is beyond the aim of this review to present and evaluate the management options for recurrent ear problems in this population. Although data from different studies differ regarding the frequency of auditory impairment[31,34,35], it seems that its prevalence progressively decrease with age.

UPPER AND LOWER RESPIRATORY TRACT MORBIDITY AND ULTRASTRUCTURE

Recent advances in PCD genetics have allowed the investigation of the relationship between specific ciliary ultrastructure defects and disease associated mutated genes with the clinical profile and progression of PCD. It was found that children with outer dynein defects (ODA) and ODA plus inner dynein defects (IDA) do not differ significantly to children with IDA and central apparatus defect with microtubular disorganization (IDA/CA/MTD) with respect to clinical respiratory features and respiratory pathogens[30]. In another genetic study, Knowles *et al*[12] showed that subjects with PCD and biallelic mutations in RSPH1 differed from those with classic PCD and dynein arm defects, showing a lower prevalence of neonatal respiratory distress and later onset of recurrent wet cough. In accordance to this observation, FEV1 was higher in RSPH1 cases compared to those with classic PCD.

Boon *et al*[13] evaluated PCD patients with normal and abnormal ultrastructure and they did not find any difference regarding lung function parameters, imaging findings and lower respiratory tract features. The type of ciliary ultrastructure did not seem to have any association with the prevalence of upper respiratory tract manifestations in children with PCD[13,30,36].

RARE FEATURES

Hydrocephalus has been described in association with PCD in a small number of patients[37] and is attributed to the impaired beating of cilia which is necessary for cerebrospinal fluid circulation.

Recently it was recognized that a number of clinical phenotypes exist that are associated with the dysfunction of non motile cilia[6]. These diseases are known as ciliopathies. However, it is beyond the scope of this review to present all human ciliopathies.

PSYCHOSOCIAL IMPACT OF THE DISEASE

As is evident by the abovementioned features, PCD would be expected to have a significant impact on health which could possibly affect the quality of life of affected children and their families. It was found that quality of life was worse in patients who had severe disease which required more aggressive treatment[38].

It was also recently shown[39] that children with PCD had higher scores compared to the control group

regarding internalizing problems such as withdrawn, somatic complaints and anxiety/depression. Therefore the psychosocial impact of the disease should also be taken into consideration by the physicians who take care of children with PCD. However, it is beyond the scope of this review to present the treatment options[40] for children with PCD, such as regular respiratory monitoring, physiotherapy, antibiotic treatment and maybe psychological support

CONCLUSION

The clinical features of PCD are nowadays well recognized but clinical suspicion of the disease in absence of heterotaxy remains rather low, although first manifestations may be present from infancy. The primary care clinician should have knowledge of the clinical spectrum of this condition in order to select appropriately the children who need further investigation for the diagnosis of PCD.

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