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Primary ciliary dyskinesia: the patients grow up

Editorial accompanying "A longitudinal study characterising a large adult primary ciliary dyskinesia population"

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The study of Shah and collaborators in this issue of the ERJ presents data from the largest study of adults with primary ciliary dyskinesia (PCD) described up to date[1]. It asks important questions relating to the phenotype and prognosis of this rare disease. The paper describes the practices of a single UK PCD centre, and since the patterns of referral and follow up vary between clinics, is not representative for all adults with PCD. However, the data represent a wealth of clinical experiences and gives us pointers for further studies.

The prevalence of PCD is unclear, because symptoms are nonspecific and a gold standard diagnostic test is lacking[2-4]. Due to limited knowledge about this rare disease patients commonly fail to be referred for diagnostic testing[5]. Furthermore, surveys among physicians[6] and patients[5] show that the procedures used to diagnose PCD vary widely. A survey of a previous PCD taskforce of the European Respiratory Society (ERS) focusing on paediatric services, identified 1192 patients across Europe, the majority aged under 20 years.[7]. Prevalence of diagnosed cases for 0-14-year olds was 1:10,000 to 1:20,000 in some countries, but much lower in others. Median age at diagnosis was 5.3 years, with considerable between-country variation. Many young adults aged 20-30 were still in paediatric care. Diagnostics and management varied between and within countries.[6] Children and adolescents (aged 0-19) account for about 20% of the European population. As life expectancy in PCD is assumed to be near normal, we expect about 4 times as many adult PCD patients as children. This is in stark contrast with the paucity of publications on adults. In a systematic review we searched for all papers reporting clinical characteristics of PCD patients, with a special focus on age-stratified data.[8] We found 17 studies describing paediatric populations, 32 describing populations of mixed age (including few, and mostly young, adults) and only 3 old studies focusing on adults[9-11].

Thus patients with PCD seem to vanish from the research screen when they reach age 20. Are they not transitioned to adult pulmonology? Do they stop having scheduled visits? Do they die young?

Novel data on PCD in adult patients

The paper from Shah et al is timely[1]. It comes from the Royal Brompton Hospital (RBH), one of three designated national diagnostic centres for PCD in England[3,12]. RBH provides a diagnostic service for PCD for the London and South East England, and offers specialist care for both paediatric and adult patients. The group has published widely on its paediatric patients[13-17], but this is the first report on adults. It presents data from 151 patients, who had either been transitioned from the paediatric unit, or had been diagnosed as adults. Median age at diagnosis was 23 (range 0-72) years.

The manuscript provides important insights into the progression of severity of disease in adults with PCD. During the seven years of follow-up 7 persons (4.6%) died, 5 from respiratory causes. Of ninety-three patients who had undergone high resolution computer tomography (HRCT) of the lungs, nearly all (95%) had evidence of bronchiectasis. Forty-five percent of the study population were colonised with Pseudomonas aeruginosa. Lung function decline was estimated as 0.49% FEV_1 percent predicted per year. The authors studied factors associated with disease progression, and reported that older age at diagnosis, microtubular defects, and HRCT scores predicted FEV_1 decline.

The data presented in the paper challenge common notions in PCD, and reflect shortcomings in the available evidence. Several points are worthwhile highlighting:

- In keeping with a previous publication from North America, FEV_1 decline was associated with micro tubular defects; this might help us understand the pathogenesis of PCD and the way the

defect is responsible for the functional abnormalities seen[18] .

- Pseudomonas colonisation was significantly more common in those with reduced lung function, but did not predict subsequent worsening of lung function. As stated in the paper, this might imply that pseudomonas could be a marker of disease severity rather than a cause of disease progression. This fits with current thinking about the airway microbiome and is relevant to understand pulmonary exacerbations not only in PCD but in other airway diseases such as cystic fibrosis (CF), bronchiectasis and COPD[19,20].
- The HRCT score is a sensitive measure of airway damage and decline. However, it's repeated use is limited by the radiation conferred to the lungs. It is hoped that other techniques, such as the MRI, will provide similar information in the near future[21,22].

Transition from paediatric to adult care

As with other chronic diseases that begin in childhood, we need a structured approach to prepare patients for transfer from family-centred paediatric clinics to the adult clinics where patients must make informed decisions about their care. This process of 'transition' should start some time before the transfer to adult services takes place. CF shares many features with PCD including the need for intensive physiotherapy and antibiotics. Life expectancy in CF patients has increased over recent decades and it has changed from a predominantly paediatric disease to an adult one[23]. Models of transitional care for CF might inform PCD care; the need for collaborative working between paediatric and adult clinics is essential to enable longitudinal understanding of the patient, 'from cradle to grave'. The paper from Shah et al, although describing a population which originated from the paediatric service in the same hospital, does not draw on health status in childhood. The earliest information presented in the paper dates from the time of transfer to adult services. Perhaps only patients, and not records were transferred? Intensity of follow-up seems limited in this study. For instance, only 118 of 151 patients (78%) had had at least 1 lung function test done, and only 82 patients (52%) had had 2 or more lung function tests during the 7 years of follow-up. This seems little compared to CF, where three-monthly lung function tests are recommended[24]. Perhaps the model of service delivery at RBH, where the care of some patients is shared with non-specialist pulmonology services has led to paucity of data?

Does early diagnosis improve prognosis?

Can good care after an early diagnosis prevent bronchiectasis and slow the decline of lung function? This question is difficult to answer using observational data, because age at diagnosis is likely to be correlated with disease severity and more severely affected persons might be diagnosed earlier in life. Thus these will seem to have a worse prognosis, despite intensive therapy. Marthin et al, from the Danish National Reference centre for PCD, looked at over 2900 lung function measurements in 74 adult and paediatric PCD patients[25]. During an observation period of 9.5 years, 34% of patients had a decline in lung function, 57% were stable, and 10% improved. There was no evidence that courses of lung function were related to age at diagnosis or initial level of lung function[25]. The current study does not give clearer answers. Figure 2 plots FEV_1 at baseline against age at diagnosis. FEV_1 at baseline was defined as 'the first lung function after diagnosis in patients diagnosed as adults, or the lung function at the time of transition in patients diagnosed during childhood'. This makes interpretation of the results difficult. The fact that FEV_1 was lower in patients diagnosed later might be explained by the fact that those patients were older when their 'baseline' lung function was taken. We cannot deduce how their lung function would be had they been diagnosed earlier.

The question, whether good care can prevent the appearance of bronchiectasis and thereby improve patients' outcomes can only be answered with truly prospective data from childhood onwards, ideally supported with randomised controlled studies, which compare different therapies between groups of randomly allocated patients, who don't differ in aspects other than the treatment in question. The first two RCTS in PCD, testing preventive treatments with azithromycin and hypertonic saline respectively, are currently being conducted and results will be published soon[26].

Is PCD a benign disease?

The mortality data are hard to interpret, as they are not age-standardised. However, nearly 5% of patients dying within 7 years seems high for an average age of 35 years. This challenges the notion that PCD does not affect life expectancy and calls for larger studies with longer and complete follow-up for mortality. In our experience the severity of disease in adults is highly variable, but generally milder than in adults with CF. In Southampton we have patients who were diagnosed late in life but continue to live active and fulfilled lives in their 60s and 70s. Conversely we care for significantly affected young adults because of impaired lung function and other aspects of this multisystem disease. Patients with congenital heart disease face increased risks and there have been case reports of PCD related deaths even in children (personal communications; and conference abstracts)[27]. Noone et al describes severe disease progression in a significant minority of adults with PCD[28]. Large representative data with long-term follow-up, such as the international PCD registry[29], or the international (iPCD) cohort study[30] will provide better mortality data in the future.

Do "older patients" profit from new developments?

Diagnosis of PCD is challenging and has changed over time. There is no single 'gold standard' and the European Consensus guidelines (2009) recommend a combination of tests, including nasal nitric oxide (nNO), high-speed video microscopy (HSVMA) and transmission electron microscopy (TEM)[2]. The three diagnostic reference centres for PCD in England collaborate closely and diagnose PCD using a diagnostic algorithm based on nNO, HSVMA and TEM[3,12]. Inconclusive and positive samples are reanalysed following culture of ciliated cells. Figure 1 in [1] suggests that this algorithm might only have been applied to newly diagnosed patients rather than reviewing diagnostic certainty periodically in the light of new developments in diagnostic testing. This is important given the lack of a gold standard diagnostic test and an evolving understanding of the diversity of the PCD phenotypes. The North American Disorders of Mucociliary Clearance Consortium reported half of the patients initially labelled as "PCD" were de-diagnosed after extensive testing[31]; conversely we are aware of patients whose investigations had previously 'excluded a diagnosis' where that decision has been overturned. In the study described by Shah and collaborators, nNO had been measured in only two thirds of the patients (64%), although it is a non-invasive and affordable test.

What we can learn from this study

The data presented from this adult PCD cohort adds important evidence on severity and long-term course of PCD in older patients. It is one piece of a large puzzle - data from other centres and more countries are highly desirable. We need prospective studies with complete and long-term follow-up from childhood throughout adult life and randomised controlled trials to give clearer answers questions about mortality and progression of function, and how these can be improved. We must be faster in implementing new knowledge into ongoing clinical practice, such as applying new

diagnostic standards to existing patients, or applying transitional care. PCD is no longer a childhood disease and standards of care should be established from birth to late adulthood. There is a need for clinicians to collaborate to improve the experience of transition of patients and empower young adults to participate in decisions about their care. We propose that data 'follow the patients' so that the adult pulmonologists are fully informed about patients' past history and contemporary information from shared-care centres. All this is vital to improve patient care and understand and ameliorate prognosis.

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