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HEALTH-RELATED QUALITY OF LIFE AND UNMET NEEDS IN PATIENTS WITH PRIMARY CILIARY DYSKINESIA

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ABSTRACT

Background: Few studies have evaluated the quality of life of patients with primary ciliary dyskinesia (PCD).

Objective: We sought to determine the health impact of the disease as well as the unmet needs in a large group of patients.

Methods: Questionnaires were either posted or e-mailed to known patients with PCD and published on the website www.dcp-pisa.it. Questionnaires included the St. George's Respiratory Questionnaire (SGRQ), the Medical Outcomes Study Short Form-36 (MOS SF-36), and a questionnaire that we produced to obtain information on age of diagnosis, symptoms and likely PCD-specific problems of these patients.

Results: 78 subjects (96% of those invited) answered all the questionnaires. Patients were diagnosed at a mean age of 9.4 years. Progressive worsening of the disease was observed, and adherence to physiotherapy was found to be poor, particularly in adolescents and adults. Patients with the highest treatment burden had a worse quality of life. With time patients become progressively less interested in treating their disease, and adherence to treatment modalities decreases.

Conclusions: PCD is associated with a progressive and continuous impact on physical and mental health of the patients. Earlier identification of the patients and better strategies aimed at improving compliance with care are urgently needed.

KEY WORDS: Medical Outcomes Study Short Form-36, Primary Ciliary Dyskinesia, Quality of Life, St. George's Respiratory Questionnaire, Unmet Needs.

Abbreviations' list

BP = Bodily Pain

GH = General Health

HRQL = Health Related Quality of Life

MCS = Mental Component Summary

MH = Mental Health

MOS SF-36 = Medical Outcomes Study Short Form-36

PCD = Primary Ciliary Dyskinesia

PCS = Physical Component Summary

PF = Physical Functioning

QoL = Quality of Life

RE = Role Emotional

RP = Role Physical

SF = Social Functioning

SGRQ = St. George's Respiratory Questionnaire

SI = situs inversus

SS = situs solitus

VT = Vitality

Introduction

Primary Ciliary Dyskinesia (PCD) is an uncommon and difficult-to-diagnose disease which is a phenotypically and genetically heterogeneous disorder due to congenital abnormalities in structure and function of respiratory cilia [1,2]. Typically, impairment of mucociliary clearance leads to recurrent infections of the upper and lower respiratory tract with chronic symptoms including a daily productive cough. Since the diagnosis of PCD is frequently delayed, lung damage and bronchiectasis may occur before treatment is instituted [3], and eventually a significant deterioration in respiratory function may occur. Therefore, early diagnosis is desirable so appropriate treatment may be instituted (physiotherapy, antibiotics). This would be hoped to prevent the most serious long-term consequences. Indeed, PCD patients diagnosed late appear to have by worse lung function [4,5].

Much research on PCD focuses on the genetics and pathophysiology of the disease [6], and there is only one study evaluating the effects of illness on the overall health status of PCD patients [7]. In particular, this study assessed the pattern of symptoms, describing their variability and their development over the life-span, and measured the impact of the disease on the life-style and on mental health of those patients living in the UK. Disease-specific studies are important, because in PCD patients there is prominent involvement of both upper and lower airways. Specifically, and unlike in most people who have chronic suppurative lung disease, PCD patients have the early onset of significant chronic rhinitis, otitis media and chronic rhinosinusitis. This is important, since upper airway disease causes significant morbidity [8,9]. Furthermore, since prognosis is better in PCD patients compared to that observed in subjects with Cystic Fibrosis (CF), PCD is in danger of being trivialised.

The aim of our study was to assess the impact of PCD on Health Related Quality of Life (HRQL) in Italian patients. Moreover, since a delay in recognizing the disease and/or an its inappropriate management may lead to adverse consequences for patients with PCD, the second aim of the study was to identify the unmet needs of the patients and the potential diagnostic and therapeutic pitfalls.

Materials and Methods

Beginning in December 2007 questionnaires were posted or e-mailed to patients with a diagnosis of PCD, made either in the Department of Pediatrics, University Hospital of Pisa, or in the Cystic Fibrosis Center, Hospital of Verona, in the Department of Pediatrics, University of Verona, or to the patients who contacted us after the publication of the HRQL survey project on our website: www.dcp-pisa.it. The questionnaires were returned before May 30th 2008, when the survey was concluded. All the patients seen at tertiary centres were diagnosed with electron microscopic evaluation of ciliary structure and orientation. Any patient not previously attending a specialist centre were seen in Pisa to confirm the diagnosis. Ciliary beat frequency measurements and ciliary beat pattern analysis were done in all the patients followed in Pisa.

There is no validated, disease specific instrument to assess QoL in PCD. However, the St. George's Respiratory Questionnaire (SGRQ), has previously been validated in patients with bronchiectasis [10], and is available in a validated Italian translation [11]. For these reasons we applied the SGRQ, together with an Italian version of the Medical Outcomes Study Short Form-36 (MOS SF-36) [12]. Furthermore, we devised a questionnaire, "Questionnaire on PCD/Kartagener Syndrome", on the clinical course of the disease, investigation, and management, which includes a question on the patient's perception of quality of life after receiving the diagnosis (available on-line at http://erj.ersjournals.com/). As previously suggested [7], separate versions of the questionnaires with minor wording changes were provided for adults, cooperative older children, and for younger, non cooperative children. We attached a letter suggesting the parents helped their children in answering the questions, or answered themselves when children were too young to collaborate. We asked parents to report if the questionnaire was completed by the patient alone, if the child was helped by the parents or if only the parents answered the questions.

The SGRQ is a self-administered HRQL measure containing 50 items and 76 weighted responses divided into three components: Symptoms, Activity, and Impacts [13]. The Symptoms component comprises 8 items concerned with the level of symptoms, including frequency of cough, sputum

production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The Activity component (16 items) is concerned with physical activities that either cause or are limited by breathlessness. The Impacts component (26 items) covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarizes the responses to all items. A zero score indicates no impairment of quality of life. Approximately 10 minutes are needed to complete the questionnaire.

The SF-36 questionnaire is a self administered questionnaire containing 36 items which provide 8 scales, 4 of them related to *physical health*: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), and the remaining 4 related to *mental health*: Vitality (VT), Social Functioning (SF), Role Emotional (RE), Mental Health (MH). Each scale is scored from 0 to 100. In PF, RP, BP, SF and RE 100 indicates absence of limitations or disability, while in GH, MH and VT the best health corresponds to the score of 50. These 8 scales provide 2 summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS), which normal score is 50 ± 10. The normal value is 50 and diminishing scores indicate worsening conditions. Only 5 minutes are needed to fill in the questionnaire. Separate age and sex-related norms for the SF-36 questionnaire reported by Apolone et al. in Italians aged > 18 years [12,14], and reference values that we obtained in 30 healthy age and gender matched (15 male and 15 females, aged 8,6 ± 4,4 years) children have been used for comparison.

We used a study-specific questionnaire on PCD/Kartagener Syndrome, composed of 15 questions related to diagnosis, clinical features, follow-up, therapy and the presence of other PCD patients within the family (see Appendix in online depository). The questionnaire can be completed within 5 minutes.

Informed consent for the survey was obtained from adult patients or from parents of children with PCD and the Hospital Ethical Committee approved the study protocol.

Statistical analyses

Baseline variables are described as group mean ± SD. Differences between means and distributions were evaluated by the 2-tailed Student's t test. Chi-square test was used to evaluate the association between the presence of mirror image arrangement and diagnosis of PCD.

The statistical significance of correlations between each component of SGRQ and SF-36 questionnaire (including the total score, which summarizes the responses to all items), and other variables, such as the age and the features of the patients gathered by the questionnaire on PCD/Kartagener Syndrome were examined using Pearson correlation test and Spearman rank signed. Multiple linear regression analyses were conducted to evaluate the associations between the dependent variables SGRQ-Symptoms, SGRQ-Activity, SGRQ-Impact, SF-36: PCS, SF-36: MCS and Age, Age at Diagnosis, and Time since Diagnosis (calculated as current age minus age at diagnosis), as independent variables. A p-value < 0.05 was considered statistically significant.

Since the SGRQ and SF-36 are questionnaires designed for adults sub analyses were performed; age $\geq$ 18 years vs. $<$ 18 years; and either including or excluding children requiring any assistance in completing the SGRQ and SF-36 questionnaires.

All statistical calculations were performed using SPSS version 14.0 software for Windows (SPSS, Inc, Chicago, IL) for personal computers.

RESULTS

Participants in the survey

The questionnaires and the covering letter were sent to 81 addresses. Seventy-eight subjects completed all the three questionnaires (response rate 96%). Fifty-eight patients were followed in the tertiary centres of Pisa (n = 45) and Verona (n = 13) and twenty were recruited through the website. These last were members of the Italian Association Kartagener/PCD and I.A.D. (Italian Association Dyskinesia)-Kartagener ONLUS. All the patients followed by tertiary centres were invited to participate irrespective of age and severity of the disease. The age of the participants (34 male, 44 female) ranged between 1.7 and 48.5 years (mean ± SD: 21.4 ± 12.9 years). Female respondents were slightly, although not significantly (p = 0.08), older (mean ± SD: 23.6 ± 13.1 years) than males (mean ± SD: 18.5 ± 12.3 years). There were 35 children age less than 18 years (mean age ± SD = 9.04 ± 3.4 years). Parents reported helping their children in answering questions in three subjects (aged respectively 5.5, 5.9, and 6.5 years) and being the sole respondent in the four youngest patients (1.7, 2.4, 3.9, 4.9 year-old). All the remaining 28 children (12 male, mean age ± SD = 10.2 ± 2.6, range 7.2-18 years), were reported as filling in the questionnaires unassisted and were included separately in the sub-analysis. The 43 adult patients were aged (mean ± SD) 31.4 ± 8.2 years

St. George's Respiratory Questionnaire

The three sub-scales of the St. George's Respiratory Questionnaire all correlated highly with one another (Symptoms with Activity, $r = 0.600$, $p < 0.001$; Symptoms with Impacts, $r = 0.624$, $p < 0.001$; and Activity with Impacts, $r = 0.705$, $p < 0.001$) and this remained true for the subgroups aged ≥ 18 years (n=43) and in the younger subjects whether or not the 7 children who were unable to complete the instruments themselves were considered**.** Considering the whole study population, all the three subscales correlated significantly with age: Symptoms sub-scale ($r = 0.285$, $p = 0.01$),

the Activity sub-scale ($r = 0.295$, $p = 0.009$), and the Impacts subscale ($r = 0.539$, $p < 0.001$), while no correlation was found with the age of the patients in any subgroup.

Cough, on almost all days per week in the last 12 months, was the most frequently reported symptom (48.7% of patients) regardless of age, together with excessive phlegm (57.7% of patients) significantly increasing with age ($p < 0.001$). This was true also in the adult subgroup for cough ($p=0.028$) but not for phlegm. In those aged less than eighteen years (excluding the 7 subjects who needed assistance in filling in the questionnaire), the increase in cough and phlegm with age was still significant, ($p=0.05$ for both). Furthermore, in the whole study population, a significant correlation was found between time since diagnosis and Impacts sub-scale (Spearman $p<0.0001$ $r=0.403$) (Pearson $p=0.01$ $r=0.31$) and for the Activity sub-scale (Spearman $p=0.001$ $r=0.368$) (Pearson $p<0.0001$ $r=0.37$), while no significant correlation was found for Symptoms sub-scale. In both the adult and the less than 18 subgroups, (excluding the 7 children who needed assistance) there was no significant correlation between time since diagnosis and any of the three sub-scales.

Breathlessness, which was mostly an issue at the time of respiratory infections (37.2%), worsened with age in the whole study population ($p < 0.001$). The correlation with age is lost if the patients age less than eighteen years are excluded. However, the scores for Symptoms, Impacts, and Activity were significantly worse in adults (≥18 years) compared with younger patients (< 18 years); respectively (mean ± SD) 47.2±23.1 *vs* 36.01±16.5 $p=0.009$, 30.5±20.3 *vs* 12.8±9.8 $p=0.00001$, and 29.1± 24.5 *vs* 16.7±18.7 $p=0.008$. This was true even if the seven children who required assistance were excluded, (mean ± SD respectively 47.2±23.1 *vs* 37.1±16.7 $p=0.025$, 30.5±20.3 *vs* 14.5±10.3 $p=0.0001$, and 29.1± 24.5 *vs* 18.4±16.6 $p=0.02$). This suggests that deterioration of symptoms may initially be progressive, but that subsequently there is a stabilization and an adaptation or a reduced perception of worsening by the patients. There were no significant gender differences in scores.

The SF-36 measures of Health Status

We observed a decline of PCS and MCS scores (and also in each subscale) in relation to age in the PCD patients. However, the negative correlation was significant only for MCS ($p< 0.0001$ r: -0.447). For both scores the decline was significantly greater than that reported with normal ageing in the healthy Italian population (12,14) [respectively: PCS $p< 0.001$ and MCS $p=0.02$ for age 0-18 years whether the seven children who required assistance were included or not (without the 7, PCS $p< 0.001$, MCS $p= 0.001$), PCS $p=0.001$ and MCS p=ns for the age range 18-24 years, PCS $p<0.001$ and MCS $p=0.04$ for the age range 25-34 years, PCS $p=0.02$ and MCS p=ns for the age range 35-44 years, PCS p=ns and MCS $p=0.003$ for the age range 45-54 years]. Again, no gender differences were found among PCD patients. There was no correlation between PCS and MCS and age in adults ≥ 18 year-old, or in younger subjects, excluding the seven children who required assistance with the questionnaire**.**

Questionnaire on PCD/Kartagener Syndrome

Mean age at diagnosis was 9.4 years (range: newborns to 44 years; SD: 10.4 years, median 7.7 years); there was a trend for earlier diagnosis ($p = 0.08$) for PCD with mirror image arrangement (situs inversus: SI) (mean ± SD: 7.9 ± 9.7 years, median 5.0 years) than in PCD with usual organ arrangement (situs solitus: SS) (mean ± SD: 12.4 ± 11.3 years, median 8.0 years). Hence the presence of situs inversus may result in earlier diagnosis. Situs solitus is significantly correlated with late diagnosis in the subgroup of adult patients ($p=0.013$). The scatter in both groups was however very large, indicating that in part the older patients had only been diagnosed relatively recently (twelve patients were diagnosed when older than twenty years (mean ± SD = 29.6 ± 8.0,). There was a non-significant ($p = 0.1$) trend for later diagnosis in females (mean ± SD: 11.1 ± 11.8 years, versus 7.4 ± 7.9 years,) in males.

Age at diagnosis in relation to symptom scores was correlated with the responses acquired with SGRQ and SF-36. Table 1 shows the regression of scores upon age, age at diagnosis, and then time since diagnosis for the whole study population. Age at diagnosis was significantly positively

correlated with SGRQ-Symptoms, Activity, and Impact suggesting that older age at diagnosis results in worse effects on symptoms, activity and impacts, and also that mental health is worse. Furthermore, the significant positive correlation between time since diagnosis and SGRQ-Symptoms and Impacts scores suggest that treatment is only partially effective or that adherence to treatment is progressively poorer, or both. Other than for symptoms, this remained true even when the seven children who required assistance completing the questionnaire were excluded (table on line).

Reduced compliance with treatment is also suggested by the negative correlations between SF-36 MCS and both age at diagnosis and time since diagnosis. A reduction in SF-36 MCS over time is a marker of progressive deterioration of the mental component of the patients. It may be that with time, patients give-up and become fatalistic about the disease. This is suggested also by the fact that in the older group there is a significant correlation only with Activity sub-scale ($p=0.04$), but more work is needed to confirm this. Moreover, in the whole study population, both age and age at diagnosis correlated with either the presence of sinusitis ($p<0.001$, $p=0.006$, respectively) and bronchiectasis ($p<0.001$, $p=0.003$, respectively), the latter suggesting that these clinical presentations are important diagnostic clues. In the sub-group of the twenty eight children who filled in the questionnaire without assistance, the presence of sinusitis correlated both with time since diagnosis ($p=0.008$) and with age at diagnosis ($p=0.001$). Furthermore, in the adult population the prevalence of sinusitis correlated with time since diagnosis ($p=0.033$). In this group there is no correlation between bronchiectasis and age at diagnosis and time since diagnosis, suggesting that bronchiectasis may be an early event in this disease. This is further confirmed by the lack of any correlation when the twenty eight children who filled in the questionnaire are considered separately. In addition, in the whole study population, age and age at diagnosis positively correlated with breathlessness ($p< 0.001$, $p<0.001$, respectively), seen also for age at diagnosis in the adults ($p=0.004$), but not in the twenty-eight children who filled in the questionnaire unassisted. This suggests that breathlessness is a late event.

Presence of mirror image arrangement

Fifty respondents (64.1%) reported mirror image arrangement, one subject (1.3%) self-reported isolated dextrocardia, and the remaining 27 (34.6%) patients usual organ arrangement. There was no gender difference in the prevalence of mirror image arrangement (males and females, 64.7% and 63.6%, respectively). There were no significant differences in respiratory symptoms and health status between PCD patients with and without mirror image arrangement. Hovewer, it was interesting that there were significantly more patients with SI than SS (chi-square = 6.87, $p < 0.05$) suggesting that there is a pool of undiagnosed patients with SS.

Other clinical findings

The prevalences of different clinical features are depicted in Fig.1. Three patients (two with mirror image arrangement) had congenital heart disease (ventricular septal defect, or right-sided partial anomalous pulmonary venous drainage with atrial septal defect).

Diagnostic procedures and follow-up

A variable pattern of diagnostic procedures have been used (Fig.2). In particular, two patients, who answered the questionnaires through the web site, had a final diagnosis based only on clinical features (mirror image arrangement plus bronchiectasis and chronic sinusitis). These two patients were subsequently evaluated by us with TEM and CMA, confirming the presence of PCD (both patients had absent dynein arms). Moreover, it is noteworthy that non-invasive procedures such as audiometry and lung function evaluation were only irregularly performed during follow-up (Tab. 2).

Genetic counselling and family education

PCD was present in other family members of seventeen respondents (21.8%). One male adult (1.3%) was a current smoker (ten cigarettes per day), and 18 patients (23.1%) were exposed to passive smoke in their home.

Treatments

Treatment modalities are reported in Table 3. Most patients were currently using physiotherapy and breathing exercises/techniques, as well as were taking regular antibiotics and bronchodilators. In

general there was no relationship between time since diagnosis and any treatment except for daily physiotherapy which was less frequently performed by patients who had been diagnosed longer ago ($p = 0.04$) and this held true in the adults considered separately ($p=0.037$), but not in subjects younger than eighteen years whether the seven youngest patients were included or not. Furthermore**,** patients performing daily physiotherapy as well as those on antibiotic therapy had significantly worse scores both for SGRQ and SF-36 than those not following those regimens (significant differences between patients on and patients without physiotherapy for Activity $p = 0.002$, and for PCS $p = 0.01$; between patients on and patients without antibiotic treatment for Symptoms $p = 0.003$, for Impact $p = 0.003$, for Activity $p = 0.002$, and for PCS $p=0.002$). Moreover, in the older group there is a progressive reduction in the regular use of antibiotics ($p=0.040$) and bronchodilators ($p=0.035$).

The interpretation of these results is difficult. Longitudinal data are needed to assess whether patients consider treatment as a preventive strategy or only reactive. From this cross-sectional study, we are not able to say whether these are the sickest patients and this is why they are prescribed a considerable number of treatments, or whether it is the burden of treatment rather than the disease that leads to a poor quality of life.

Surgical procedures performed are reported in Table 4.

Quality of life after diagnosis of PCD

A clear majority of patients (71.8%) considered their quality of life significantly or slightly improved after diagnosis (38.5% and 33.3%, respectively), while only three, recently diagnosed, subjects (3.7%) perceived a worsening in their quality of life. After scoring the answers to the "Quality of life after diagnosis" question (from 1 for greatly worsened to 5 for greatly improved), there was a statistically significant positive correlation between time since diagnosis and improvement in perceived quality of life ($p = 0.02$), but this was not correlated with age or age at diagnosis.

DISCUSSION

We report for the first time that delay in diagnosis of PCD is associated with a poorer subsequent quality of life. This finding is counter-intuitive, since it would be expected that milder cases would be diagnosed late, and have a better QoL. However, it is also possible that children and parents who had been given the diagnosis in early childhood may have adapted better than those diagnosed late. Furthermore, for the majority, QoL improved after diagnosis; a similar finding has been reported in cystic fibrosis. This adds weight to the evidence that early diagnosis of PCD is beneficial.

It could be argued that the study would have been stronger if disease-specific questionnaire for PCD patients had been used, and certainly the development of such an instrument is worth further work. However, the use of current instruments allows comparison with previous work. Only one study evaluated quality of life in CF patients with SGRQ [16], and reported that SGRQ scores were higher (indicating poorer quality of life) among patients with CF than in general population or among patients with chronic obstructive pulmonary disease. Furthermore, the score for age, symptoms, activity and impact were no different from those we observed in our patients with PCD. Another study used the SF-36 [17] to document that pulmonary exacerbations affect physical HRQOL more than psychosocial HRQOL with baseline scores being significantly worse ($p=0.03$) than those observed in our patients but with a mental score ($p=0.332$) similar to those observed in our study population.

In our study, as in other chronic lung conditions, respiratory symptoms were assessed by the St. George's Respiratory Questionnaire (SGRQ) [10,11], while the impact of the disease on a patient's daily life was measured by version 2 of the SF-36 questionnaire, which is a widely used generic instrument for assessing mental and physical functioning [12,14]. Neither the St George's Respiratory nor SF-36 questionnaires are validated in children, but they have been previously used in children over 6-12 years [18,19, 20]. SGRQ and SF-36 are complex instruments and are definitely valid if completed by the individual under study and without the help of others and for this reason subgroup analyses with and without the children who needed help completing the

questionnaire were performed. Most in fact completed the questionnaire unassisted. When we only looked at data from adults, the group in which SGRQ and SF-36 are validated, some correlations are lost, in particular those related to the age of the patients and the time since diagnosis. We cannot determine on the present dataset whether this is due to loss of power because the numbers are smaller, or because the childrens' data was less reliable because the instruments are not valid; we believe the first to be more likely. It is also possible that as time passes, older patients become resigned to the disease, and attitudes change. We found good agreement between the results obtained with a respiratory-specific instrument, such as the SGRQ, and those gained with the generic instrument SF-36 and this is a good indicator both of the specificity of the information and of their general validity. Furthermore, almost all patients diagnosed by tertiary centres participated to the survey, despite the poor response rates in other postal studies [21]. Thus the sample can be considered representative of the general population of patients with PCD, or at least those being seen in a tertiary centre. What we are not able to determine is whether our findings apply to PCD patients seen in general respiratory clinics, where expertise in the treatment of the condition may be less.

The remarkably high rate of response by the patients unfortunately is not associated with good adherence to the different treatment modalities and this is particularly true in the adults. It is clear that current educational programs are insufficient and that other means of changing behaviour need to be implemented [22]; this represents an important unmet need of those patients.

As expected, evaluating all the patients together, the Symptoms, Activity and Impacts scores of SGRQ increased significantly with age, as seen in healthy subjects. The correlation with age is lost in the separate evaluation of adults; again this may be due to loss of statistical power, or be a genuine finding. In fact productive cough, breathlessness and the presence of bronchiectasis were reported with increasing frequency in older patients, considering the group as a whole. This age effect was lost in the adult subgroup, perhaps because almost all of them had marked respiratory compromise. Even though the eight sub-scales of the St. George's Respiratory Questionnaire

provide a detailed picture of respiratory health-related quality of life, the wide variance in overall health status is better described by the SF-36 physical and mental component scores. These scores have also the advantage of well-described Italian population normals [12,14]. This allowed us to show that the expected decline of PCS and MCS scores (and also of each subscale) with age was significantly higher in our PCD patients. This early decline was not observed by McManus and co-workers [7] who found little abnormality in standard measures of SF-36 during childhood and adolescence, and furthermore they reported that scores were stable after diagnosis. Again this was not observed in our study population who showed a progressive worsening of the disease with time. In our study population it seems that deterioration occurs mainly prior to and during adolescence, since after the age of eighteen much of the correlation with age is lost. There are a number of possible reasons for this, which need to be addressed by future work; these include an adolescent rebellion and refusal to perform treatment, adolescent risk-taking behaviour such as smoking or substance abuse, and change of pattern of care to a possibly less specialist adult unit.

The causes for these discrepancies are not known. One could speculate that, in the English population, any or all of earlier diagnosis, more aggressive early treatment or better adherence to treatment might be possible explanations. In this regard, the age of diagnosis in the current population (9.4 years) was significantly later than in the English population reported by Corren et al. [23], which was 4.4 years. Another possibility could be better continuity between paediatric and adult care, something which is not yet well structured in Italy. However, a longitudinal analysis to is the only way to resolve these issues, and international studies on the topic should be encouraged. McManus et al. [7] reported a continual decline with age (one and half standard deviations below the population mean) on the physical scores of the SF-36 which reflects a moderate degree of morbidity on normal physical functioning which is progressive across the life-span; this is partially confirmed by the present report. However, they did not show a significant effect of time since diagnosis either on the MCS and PCS of the SF-36 questionnaire as well as on Symptoms and Activity scores of the SGRQ [7].

Early identification of the disease is an important unmet need of those patients. This is particularly evident in female patients, since Yentl syndrome (gender bias towards diagnostic procedures and treatment) described for asthma [24] appears to be present also in PCD. On the other hand, it is reassuring to observe that the gender bias observed in relation to diagnosis is not found in relation to care since no difference between female and male patients is reported in scores of SGRQ and SF-36 questionnaires.

In addition to previously used instruments, we used a novel Questionnaire on PCD/Kartagener Syndrome, the first specific and structured questionnaire on disease. This provides more information on PCD than the original McManus questionnaire, which assessed only presence of SI, family history, smoking, and treatments.

In this regard, our study demonstrate that the prevalence of cardiac defects is similar to that recently reported in the general population when transthoracic echocardiography was performed [25]. This may reflect the number of diagnostic procedures which are requested in patients with unexplained respiratory symptoms, particularly in subjects with SS. In our study population cardiac defects were discovered prior to the diagnosis of PCD.

The classical diagnostic tests required for an appropriate diagnosis, such as ciliary beat frequency and pattern, and transmission electron microscopy, were not performed in all the patients This underlines another unmet need, namely the right of each patient to be properly diagnosed in tertiary centres. Furthermore, follow up procedures such as audiometry, sputum culture, and lung function evaluations were not performed in some patients. Audiometry is essential in paediatric patients since hearing loss is found in up 25% of children with PCD [23] and sputum culture and regular spirometry should be part of the routine follow up of chronic inflammatory airways diseases [4,5]. HRCT of the lungs and of paranasal sinuses were not done in, respectively, 12% and 40% of the patients, especially in the younger ones. Chest HRCT is used to define the extent of bronchiectasis and can be used to monitor progression of the disease, however there is little evidence that regular

CT scans affect outcome in PCD and the potential high lifetime cumulative radiation exposure should be considered [1].

High-quality genetic counselling is another priority to ensure that parents clearly understand and weight the risks of the same disease in subsequent pregnancies in the context of a complex condition where multiple genes are involved and where prenatal screening is usually not possible. Obviously an early diagnosis is a essential for counselling since late diagnosis may preclude planning of further pregnancies. Education of the family is a further important concern, since one out of five patients was exposed to passive smoking in their home. This prevalence is lower than that reported in general in the Italian population [26], but it cannot be considered satisfactory. Considering all patients together more than 10% of the patients never used daily physiotherapy and more than 25% were not currently using airway clearance techniques in their daily management at the time of the survey. The figures for those aged ≥ 18 years were 12% and 28% respectively, but daily physiotherapy was reportedly performed by 79% of patients age less than fourteen years. This lack of utilisation of airway clearance was despite intensive education from tertiary care centres. The level of compliance with physiotherapy was the same whether patients were recruited from tertiary centres or responded through the web site. Thus, another unmet need for patients and parents is to understand that physiotherapy should be performed on daily basis and increased during infective episodes, since antibiotics alone should not be relied upon. Ways to modify behaviour should be studied and ideally implemented immediately after the diagnosis as well as during follow-up of the patients in particular since there is clear a deterioration in treatment adherence in patients after age 18 years [22,27]. Compliance with physiotherapy decreases with time, probably reflecting the fact that patients progressively give-up and passively accept their disease, leading to treatment (both physiotherapy and antibiotics) being reactive to symptoms rather than as prevention of deterioration. Thus another unmet need is the necessity of continuous physical and psychological support.

The physical care of the PCD patient is important, but the psychological effects on both the family and the patient must also be considered. It is interesting to note that a few recently diagnosed patients describe worsening of QoL immediately after diagnosis and this probably represents an transitory emotional distress which is often seen as an understandable reaction to a severe illness. It is therefore important that the specialist team working together with family physicians evaluate whether the initial reaction of anger and denial is replaced by acceptance and coping with the proper management of the disease [28].

In conclusion, better education of general physician and paediatricians on the disease is essential; once PCD patients are diagnosed they need integrated management between specialized centres, district hospitals, and family doctors. This is expected to increase shared knowledge, to decrease mistrust of general practitioner who are generally poorly informed of what is a rare disease, and possibly to facilitate early diagnosis [29]. There is also the need for support from peer groups and volunteers to diminish stigmatization and to give practical help to patients with PCD and to their families.

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FIGURE legends:

Figure 1: prevalence of different clinical features of the study population.

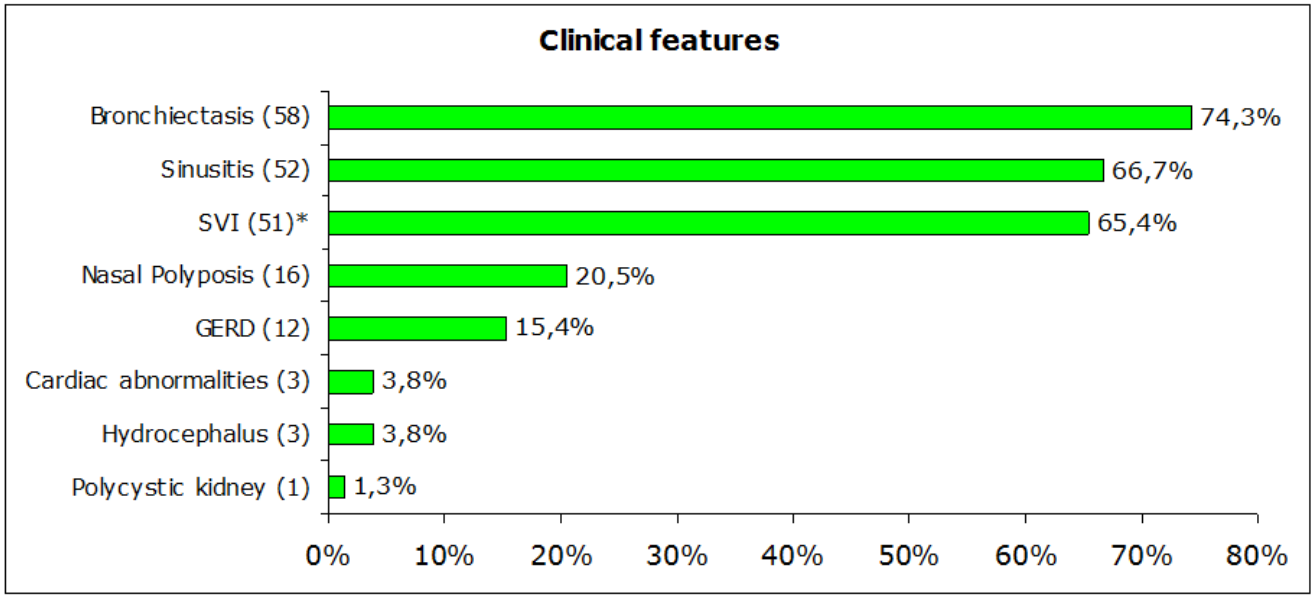

Figure 2: prevalence of diagnostic tests performed in the study population

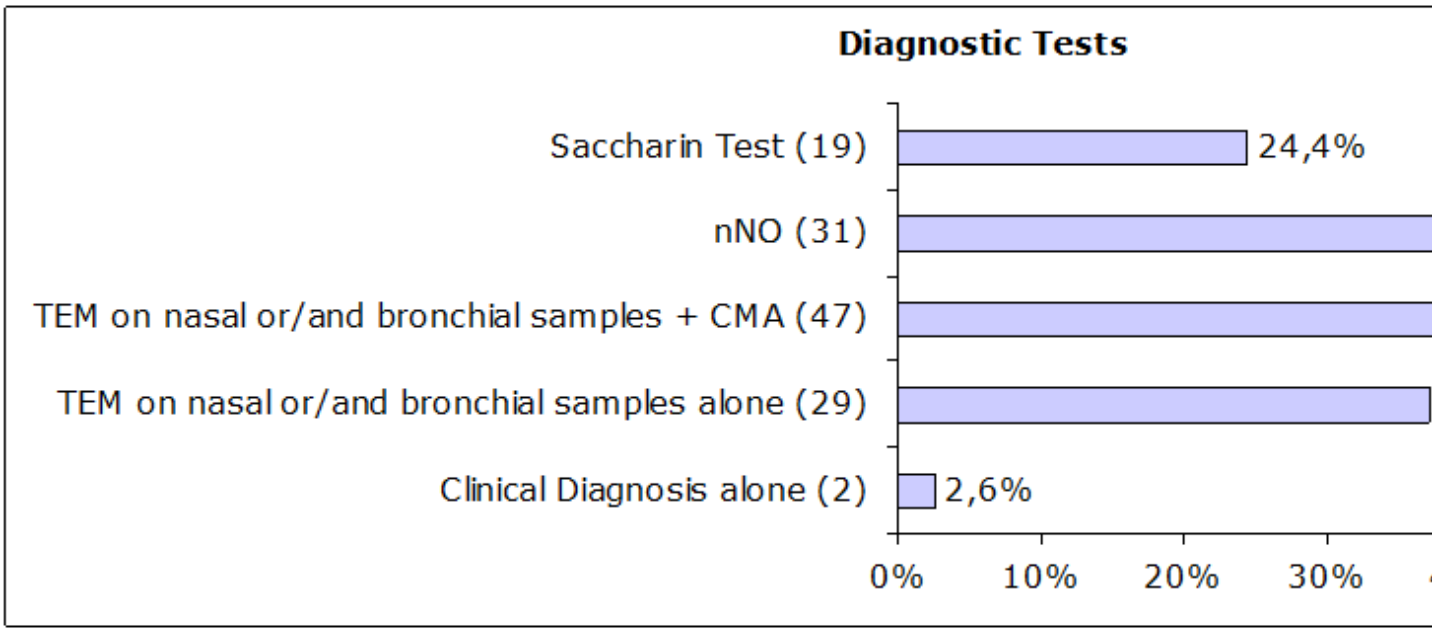
Diagnostic Tests
Saccharin Test (19)
24,4%
nNO (31)
TEM on nasal or/and bronchial samples + CMA (47)
TEM on nasal or/and bronchial samples alone (29)
Clinical Diagnosis alone (2)
2,6%
0%
10%
20%
30%

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TABLE 1. MULTIPLE LINEAR REGRESSION ANALYSIS ON DEPENDENT VARIABLES SGRQ-SYMPTOMS, SGRQ-ACTIVITY, SGRQ-IMPACT, SF-36: PCS, SF-36: MCS AND VARIOUS INDEPENDENT VARIABLES

Dependent variable	Independent variable **Age**		Independent variable **Age at Diagnosis**		Independent variable **Time since Diagnosis**	
	β *	*p*	β	*p*	β	*p*
SGRQ-Symptoms	NS	NS	0.243	0.040	0.242	0.041
SGRQ-Activity	NS	NS	0.404	0.001	NS	NS
SGRQ-Impacts	NS	NS	0.452	<0.0001	0.464	<0.0001
SF-36: PCS	NS	NS	NS	NS	NS	NS
SF-36: MCS	NS	NS	-0.388	0.001	-0.351	0.002

Definition of abbreviations: NS, not significant.

* Regression coefficient.

TABLE 2. DIAGNOSTIC PROCEDURES PERFORMED IN FOLLOW-UP

	Patients with at least 1 evaluation	Time between 2 evaluations (mean ± SD)
Thorax HRCT	69 (88,5%)	2,1 ± 1,3 years
Paranasal sinuses CT	48 (61,5%)	3,3 ± 2,4 years
Flow/Volume curve	71 (91,0%)	23,5 ± 23,3 weeks
Body Plethysmography	21 (26,9%)	22,7 ± 22,5 weeks
Sputum Culture	71 (91,0%)	21,9 ± 30,9 weeks
Audiometric test	55 (70,5%)	78,1 ± 72,1 weeks

TABLE 3. TREATMENTS USED BY PCD PATIENTS

	Usage			**Correlation of usage with:**		
	Never Used	***In the past***	***At present***	***Age***	***Age at diagnosis***	***Years since diagnosis***
Daily Physiotherapy	10 (12,82%)	10 (12,82%)	58 (74,36%)	-0.125 (NS)	0.097 (NS)	-0.230 (*p:*0.04)
Regular antibiotics	9 (11,54%)	13 (16,67%)	56 (71,79%)	0.147 (NS)	0.186 (NS)	-0.003 (NS)
Regular Bronchodilators	10 (12,82%)	14 (17,95%)	54 (69,23%)	-0.069 (NS)	0.107 (NS)	-0.176 (NS)
Intermittent Bronchodilators	20 (25,64%)	11 (14,10%)	47 (60,26%)	-0.006 (NS)	-0.043 (NS)	0.032 (NS)
Mucolytics (N-acetylcysteine)	17 (21,79%)	29 (37,18%)	32 (41,03%)	0.258 (*p*:0.02)	0.244 (*p:*0.03)	0.069 (NS)

TABLE 4. INCIDENCE OF SURGERY IN PCD PATIENTS

Surgical procedures	Incidence
Nasal polypectomy	8 (10.3%)
Lobectomy	7 (8.9%)
Adenotonsillectomy	7 (8.9%)
Tympanostomy tube insertion	4 (5.1 %)
Cardiac surgery	3 (3.8%)
Ventriculoperitoneal shunt	3 (3.8%)
Lungs tranplant	1 (1.3%)