Author's response to reviews

Title: Primary Ciliary Dyskinesia (Siewert's / Kartagener's Syndrome): Respiratory symptoms and psycho-social impact

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PDF covering letter
Responses to comments made by referees on version 1 of MS

Referee A: Michael Coren

p.3: “9+2 architecture”; “was” has been changed to “is”.

p.3, foot: “co-occurred” has been changed to “oc-occur”

p.4: “is more likely to be random situs” has been added

p.4, para2: “overall” has been added

p.5: Expand on the possible non-representativeness of the sample. Strictly this is not a matter of Method, but should come in the Discussion. We have therefore expanded the paragraph which was already present on p.12 of the manuscript:

“Although our data represent the largest published study of the symptoms and effects upon health in PCD, we are aware that there is a risk that our sample may be biassed. All of the subjects are volunteers who had chosen to join the PCD Family Support Group, so that it is possible either that our subjects are not representative, perhaps coming from the more severe end of the spectrum of disease, or, particularly in the younger patients, their condition is less severe but parents have chosen to be involved in the support group in order to have as much information as possible about the condition. Although both biases are possible, they also emphasise the need for properly representative and systematic studies of patients who are typical of the entire population. That would also require a concerted effort to identify a national sample of all individuals with PCD, independent of symptoms and presentation and diagnosis at clinics.”

p.5: typo. “fin” corrected to “in”.

Referee B: Liesl L Osman

We thank the referee for their thoughtful comments.

Treatments being received by patients. Our study was a questionnaire survey of a patient support group and therefore we did not have access to clinical records, and therefore cannot provide detailed information on specific antibiotics, length of course, sputum culture, clinical tests of respiratory function, etc., although we acknowledge that a large study with these measures would be of great value. Our study did however have some information on treatments being used by the individuals in our study, and we have therefore provided an analysis of these in our report. We are concerned that this may have exacerbated the problem identified by the referee, of “overkill through the presentation of too much data”, but on balance, given the important theoretical and clinical questions raised by the referee, and the absence in an on-line journal of the traditional length constraints suffered by print journals, we have decided to include the additional information on treatments (see table 2). We have included the following paragraph of description and analysis in the results section:

“Treatments. Although our study did not have access to clinical records, we did ask a number of questions about the treatments that patients used “to help with the symptoms of PCD”. Table 2 summarises the results. A clear majority of patients, although not all, were currently using physiotherapy and breathing exercises/techniques, and about half were taking regular antibiotics and bronchodilators. The use of expectorants and antacids or other drugs to help with heartburn or reflux were more common with increasing age. None of the treatments seemed to be used more commonly in patients who had been diagnosed longer ago.

An important question concerns the relationship between treatment usage and symptoms. We therefore carried out a regression analysis relating symptom measures to the seven treatments about which we had asked. At the first step, age and years since diagnosis were entered into the analysis, and then a forward entry stepwise process was used to examine the predictive effects of the therapies. The SGRQ Symptoms score was predicted firstly by Antacids/Heartburn-Reflux treatments (beta = – .445, p<.001), and then by use of bronchodilators (beta=–.275, p=.012). Given the scoring of the treatment measures (high scores indicate treatment use), and the scoring of the symptom measures (low scores indicate poorer functioning), the negative beta coefficients indicate that those taking the treatments have lower symptom
scores than those not taking them. Broadly similar results were found for the other outcome measures. The SGRQ Activity score was predicted firstly by Antacid use (beta = −.469, p < .001), and then by expectorant use (beta = −.323, p = .016). The SGRQ Impact score was predicted firstly by expectorant use (beta = −.461, p = .001), and then by Antacid use (beta = −.296, p = .024). Finally, the SGRQ Mental Component Score was predicted only by Antibiotic use (beta = −.283, p = .037). Mucolytic use, physiotherapy and breathing exercises were not predictive of any of the symptom scores after other treatments had been taken into account. It should be noted that in each of the analyses the beta coefficient is negative, meaning that those taking the treatment had poorer health.”

It is clear that this additional information is of some theoretical interest, strongly suggesting that the treatments described here are a response to symptoms, rather than a factor in the reduction of symptoms. We therefore also included an additional paragraph in the Discussion section.

“Although earlier diagnosis may contribute to a better clinical outcome, it is not clear from our data what is the main causative component of that better outcome. We had basic self-report measures of the treatments received by these patients, and we looked for correlations with outcome. Although they were present and highly significant, in each case the regression coefficients were negative, meaning that those taking the treatments had poorer health. The implication is that the treatments taken are a response to symptoms, rather than that they are having a positive impact upon them. That is supported by the majority of the significant effects concerning expectorants and antacids (which are readily available as non-prescription medicines) rather than antibiotics, bronchodilators, or physiotherapy and breathing exercises, which are more associated with hospital treatment. That interpretation is supported by the sole correlate of antibiotic use being with the SF-36 Mental Component Score, suggesting antibiotics can be a response to anxiety and other psychological responses by patients to their illness.”

Current UK practice. We agree with the referee that the current treatment regimes used by UK clinics treating patients with PCD are of great interest, and that there are likely to be large differences in everyday practice and advice, and in adherence/concordance of patients to the treatments which are recommended. Although two of the authors are medically qualified, and one sees patients on a regular basis, we feel it is outside of our expertise to comment on the appropriate management of PCD in UK clinics, or on its variability. The 1998 paper by Bush et al., which we reference, does however provide an authoritative review of this topic. There is also a clear need for a formal survey across a range of representative clinics.

Clarification of the meaning of prophylaxis. Our use of this term was not intended to be precise in the technical sense of a specific intervention to prevent disease or symptom occurrence, although it came across in that way. In the discussion we have therefore removed the word, and in its place we have said,

“There is a need for properly designed, prospective studies both of early diagnosis itself, and of interventions such as regular sputum culture, routine use of antibiotics, and physiotherapy, all of which may reduce morbidity”.

We have also added a reference there to the important clinical review by Bush et al., which provides a clear account of UK practice. The word ‘prophylaxis’ occurred only in one other place in the manuscript, and we have also replaced that to make our meaning clearer:

“Age at diagnosis in relation to symptoms. An important question concerns the impact of the age at diagnosis upon symptoms. An earlier diagnosis allows the possibility of medically based interventions to try and prevent the longer-term complications of the condition.”

We hope these changes are satisfactory, and indicate only that we are referring to the whole panoply of clinically driven interventions which may be helpful in PCD.

Statistical artefact. It is always possible that significant statistical effects are mediated by moderator or mediator variables that have not been assessed. That however has to be for other, more extensive, studies to decide. What is clear in our data is that there is sufficient variance in current age and age of diagnosis (and hence of years since diagnosis) to allow statistical analysis. That variability is shown in figure 1 of our original MS (although that puts us in a difficult position, since the referee has also asked to remove figure 1 as being ‘unnecessary’ – on balance we have decided to leave it in, in order to answer the question about variability). Cohort effects can very readily lead to bias in studies such as this, and if
all of the people with early diagnosis had indeed been young, then that could be a problem. However figure 5 in our original MS shows that there is variability across the entire age range. On balance we feel therefore that our original argument is justified by our data, and in the absence of a more specific hypothesis as to why our conclusion is artefactual, we feel it should be included as it stands. We would hope that other authors in the future might wish to study this topic in more detail, as it is clearly of clinical and practical importance to patients with PCD. Might we suggest that if our analysis is still felt to be a problem then the paper should go to a statistical referee for a further opinion?

Discretionary revisions.

1. We have removed figure 7, as suggested, informing readers in passing that a graph is available from the first author. We have however retained figure 1, partly because it is relevant to the question of whether there is sufficient variability in age at diagnosis relative to current age (see above), and partly because it provides evidence for the somewhat surprising and counter-intuitive conclusion that patients with situs inversus are not diagnosed earlier than those with situs solitus.

2. We have retained the paragraph on family history, not least because it might be that our sample is possibly biassed due to having two or more affected family members, and hence being more likely to join the support group. Retention will allow future researchers to compare their data with ours. The paragraph is also extremely brief, consisting of only 28 words.

3. This topic was one of particular interest to the first author, and it is of some interest in theoretical terms. We have however removed it as requested. The paragraph now reads:

“PCD-SI compared with PCD-SS. Individuals with PCD-SI and those with PCD-SS were compared on the various measures of symptoms and health status. Simple t-tests showed no differences between PCD-SI and PCD-SS, and neither were there effects of situs on symptoms after taking age into account using a multiple regression. A detailed table of results is available from the first author on request.”

4. Figure 7 has been removed (see above).

5. We have added a paragraph to the introduction which describes an estimate of the prevalence:

“The prevalence of PCD in the UK is difficult to estimate precisely. Although a figure of 1 in 15,000 has been quoted, which may itself be an underestimate, that would mean there are about 70 new cases born each year, and about 3,000 patients in total”.

Major compulsory revisions

1. Comments on clinical management of PCD in the UK and justification of benefit of early diagnosis. We hope our comments above on this topic are satisfactory. We do not wish to go beyond the limits either of our expertise or of our data.

In revising our paper we have also taken the opportunity to prepare its references with Reference Manager in the format of BioMed Central. We hope that the revised version of this manuscript will now be suitable for publication.

Chris McManus
October 2003