Severity of chest disease in CF patients in relation to their genotypes

Al-Jader et al (J Med Genet 1992;29:883-7) assessed severity of lung disease by calculating % predicted values for FEV1, and FVC and comparing single values in subjects of different ages, as did Johansen et al in a similar study. Although in widespread use, this method has deficiencies, especially when analysing lung function data over time. The widely held assumption that a given % predicted value means the same for subjects of different ages is untrue; older subjects will have a lower % predicted value than younger ones with comparable lung function.2

Furthermore, patients with any CF genotype are likely to have milder disease and better lung function. This source of bias influences the plot of FEV1 against age presented by Al-Jader et al and Johansen et al.1 In each case the plot first shows a linear fall in FEV1, with time followed by an upturn in the curve for older patients. On the basis of this, Johansen et al claim the Δ FEV1 heterozygotes have less severe lung disease. However, if the three most extreme data points from the oldest patients were excluded from the graph in both studies, then the relation between FEV1, and time becomes approximately linear, and the difference between heterozygotes and homozygotes is no longer apparent.

We have examined longitudinal lung function data in Grampian CF patients.1 Forty-four patients were Δ FEV1 homozygotes, nine were G551D/Δ FEV1 compound heterozygotes, and 18 patients had other genotypes, including nine heterozygotes for Δ FEV1 and an unidentified mutation. Annual spirometric data were retrospectively collected from case notes. A regression line was constructed for each patient’s lung function data over time, and a slope value calculated. A logarithmic transformation was applied to linearise the data, and mean slope values were calculated for each group. Mean slope values of the groups were not significantly different. Therefore, we too were unable to show differences in severity of lung disease in CF patients with different mutations.

Al-Jader et al suggest that patients with the genotype Δ FEV1 + 1 G→T/Δ FEV1 may have more severe disease and R117H heterozygotes milder disease, but differences in lung function data were not significant. Moreover, only four patients with R117H were studied, so it is not valid to make any general inference about that mutation. There is a need for different centres to pool data before firm conclusions can be made about clinical features of CF patients with rare mutations.

This letter was sent to Dr Al-Jader et al to reply as follows.

We were interested to learn that Packe et al1 were unable to show differences in severity of lung disease with different mutations by analysis of longitudinal data; this finding is in keeping with ours2 by analysis of cross-sectional data.

The observation that, “older subjects have lower % predicted values for respiratory function tests than younger ones with comparable lung function” was unknown to us. However, the paper would seem to refer to an adult population (30 to 70 years) in whom the objective genotype and phenotype are defined abnormality. We see no problem with the use of this method (FEV1, and FVC, % predicted by vitalograph) versus age in our cross sectional study of patients aged 5 to 31 years. In addition to the use of respiratory function tests, we also scored chest x ray appearances (by Chrispin-Norman score) in four age bands: <.50 years, 5.0-9.9, 10.0-14.9, and >15.0 years. Patients homozygous and heterozygous for Δ FEV1 showed similar declines in score; from this, similar declines in lung function could be inferred.4

We question whether it is valid to remove the three most extreme data points from the oldest patients as plotted on the FEV1 % predicted graphs of Johansen et al1 and from our graphs and to consider the remaining data without these points. As we discussed in our paper,2 the upturn in the curves for the heterozygous patients could relate to the death of the more severely affected patients and survival of those with a more advantageous genotype. Further work will establish whether this is so.

Regarding our patients who are heterozygous for 621 + 1 G→T and heterozygous for R117H (n = 4), we accept that differences in lung function are not significant. We agree that there is a need for multicentre studies to examine the clinical features of CF patients with unusual mutations.

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