

CORRESPONDENCE

Disseminated bronchiectasis and cystic fibrosis gene mutations

To the Editor:

The recently published paper by SANDFORD *et al.* [1] reviewing the genetic risk factors for chronic obstructive pulmonary disease is bright and revealing; nevertheless, incidental conclusions referring to the role of cystic fibrosis (CF) gene mutations as a predisposing condition for lung disease ("heterozygosity for $\Delta F508$ appears to predispose for disseminated bronchiectasis, but the involvement of cystic fibrosis transmembrane receptor (CFTR) in other obstructive pulmonary diseases remains unproven"; p. 1385) deserve logical comments that are not intended as criticisms to the mentioned review.

The putative pathogenic role of CF gene mutations is in opposition to the given (and as reported by the authors) selective advantage of carriers. We admit that the contrast is only apparent: the selective advantage might be effective at younger ages and not necessarily imply better health, despite the presumed protection towards a specific (infectious?) disease.

All papers reporting a higher incidence of CF gene mutations in patients with bronchiectasis exclude the diagnosis of CF in their series on the basis of a "normal" sweat test, inconclusive genetic analysis, or both [2–8], and patients were not discussed with CF clinicians. Currently accepted diagnostic criteria for CF include any of the major clinical features accompanied by: 1) a positive sweat test (sweat chloride level >60 mEq·L⁻¹) performed by experienced personnel and confirmed by repeated test (results based upon sodium concentration, as in [7], are not considered reliable for diagnosis establishment or exclusion), or 2) disease-causing mutations on both chromosomes. Nevertheless, diagnosis of CF cannot be unequivocally ruled out in symptomatic patients. It has been established that the sweat test can give normal or borderline results in patients with established CF, diagnosed on the basis of full-blown clinical pattern, two mutated alleles and abnormal nasal potential difference [9]. This can also be true for definite CF gene mutations or peculiar mutation combinations [10–12], but the list of mutations associated with the "normal" sweat test can be far from complete. Many patients with established CF, especially in southern European and Mediterranean countries, have only one allele with one commonly detectable mutation. The genetic analysis can never definitely exclude CF, intended as homozygosity for two mutated CF alleles, given: 1) the number of known and unknown disease-causing mutations, 2) the possibility that unfortunate combinations of adverse CF gene polymorphisms can cause disease [13], and 3) the difficulty of investigating the promoter region.

Finally, studies that could not detect an increased incidence of pulmonary manifestations in CF carriers in comparison to controls are in keeping with the common experience of CF clinicians, who often include the pa-

tients and their families [14–15]. In conclusion, in our opinion, patients with disseminated bronchiectasis and one mutated CF allele are very likely to have a second, unidentified, mutated allele on the other chromosome (possibly with a mutation associated with a "normal" or borderline sweat test), or a combination of unfavourable CF gene polymorphisms and a not-so-mild form of undiagnosed CF. This approach should be adopted rather than proving that CF gene mutations are risk factors for disseminated bronchiectasis. These patients should consequently be referred to a CF Centre or to expert CF clinicians, in order to be evaluated extensively. They should undergo nasal potential difference measurement and be treated aggressively, according to protocols designed for CF patients.

We realize that the true question might now be: what is a CF diagnosis? Recent findings from molecular genetics have broken the hitherto accepted nosographic boundaries of CF and new diagnostic criteria are needed. Patients with congenital bilateral absence of the vas deferens (CBAVD) are currently considered compound heterozygotes for CF gene mutations [16]. These patients may or may not have an abnormal chloride concentration in the sweat and/or chronic sinusitis and airways disease (milder than CF patients), fitting in the range of clinical manifestations from severe (classical) CF to normality, apparently in association with a varying rate of normally functioning CFTR protein [17]. In our opinion, patients with bronchopulmonary, gastrointestinal and/or genital manifestations compatible with CF and sharing a common genetic background with CF patients should be considered to have CF, although in a mild or an atypical form. If the name CF still recalls a very specific paediatric disease, a term such as CFTR deficiency [18] or CFTR-related disease [19] should be introduced.

References

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