**Table 1** Functional and clinical outcomes following omalizumab therapy

| | Pretreatment | Post-treatment | p |
|---|---|---|---|
| $FEV_1$ (ml) | 1360 (955–2200) | 1850 (1270–2290) | 0.08 |
| $FEV_1$ (% predicted) | 66% (39–73) | 74% (70–84) | 0.03 |
| Annual rate of exacerbations | 1 (1–4) | 0 (0–1) | 0.01 |
| Daily symptoms (≥2 times per week) | 15/18 patients (83%) | 8/18 patients (44%) | 0.04 |
| Nocturnal symptoms (≥2 times per week) | 15/18 patients (83%) | 4/18 patients (22%) | 0.04 |
| Oral corticosteroids | 17/18 patients (94%) | 6/18 patients (33%) | 0.0005 |
| Itraconazole | 10/18 patients (55%) | 3/18 patients (16%) | 0.037 |

Results are expressed as median with range in brackets or as a percentage. The Wilcoxon test was used to evaluate any significant differences ($p<0.05$) between continuous variables and the $\chi^2$ test was employed for comparison of categorical variables.

also seems to improve pulmonary function even when oral corticosteroids were reduced or discontinued. Given the retrospective nature of this study and the small number of cases analysed, the results must be interpreted with caution. Although all patients met the criteria of APBA proposed by Rosenberg,[7] the differentiation between this entity and Aspergillus-induced asthma is problematic, so we decided to blanket them under the term 'Aspergillus-associated airway disease'. While the pathogenesis of ABPA remains not fully understood, IgE has been advocated as a key pathogenic mechanism of the disease. Since the total serum IgE level is a marker of immunological activity in ABPA, the attenuation of the hyper-IgE response seems to be a reasonable target. Further studies are warranted to clarify the utility of omalizumab in AAAD, especially in ABPA.

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## CORRESPONDENCE

# ABPA in adulthood: a CFTR-related disorder

In Western countries, allergic bronchopulmonary aspergillosis (ABPA) in childhood is very unusual beyond the context of cystic fibrosis (CF). It is presumed to be different in adulthood, although three studies[1–3] reported an increased frequency of cystic fibrosis transmembrane conductance regulator (CFTR) mutations in adults with ABPA. Out of the 63 patients investigated in these studies, none was reported as pancreatic insufficient, all had sweat chloride values <60 mmol/l, only two carried the intron 8 splice variant 5T and a single patient was found to be compound heterozygous for two CFTR mutations. However, Miller *et al* studied only 10 patients and did not sequence all CFTR exons, while the two other reports, including one from our institution, were hampered by the small number of mutations initially looked for (n=13 and 16, respectively). Accordingly, current guidelines for diagnosis of CF do not list ABPA as a suggestive phenotype feature nor even explicitly as a CFTR-related disorder.[4]

We hypothesised that extending DNA analysis to the >1300 mutations currently considered as potential CF causing (http://www.genet.sickkids.on.ca/cftr/app) would provide more accurate insights on the link between ABPA and CFTR in adulthood.

The characteristics of the study group are detailed in the princeps paper.[2] DNA samples were no longer available for 3 out of the 21 original patient cohort, one of whom had

**Table 1** Relevant data and genetic findings in 18 adult patients with allergic bronchopulmonary aspergillosis (ABPA)

| Subject no. | Age (years)* | Gender | Sweat ($Cl^-$) (mmol/l) | BC | CFTR mutations | |
|---|---|---|---|---|---|---|
| | | | | | Princeps study[2] † | Current study |
| 1 | 30 | M | 17 | + | F508del | F508del/D1152H |
| 6 | 30 | M | 32 | + | | L997F/L997F |
| 7 | 74 | M | 34 | – | | G576A/D443Y–R668C |
| 8 | 55 | M | 36 | + | | R1070W/3659delC |
| 2 | 65 | M | 33 | + | F508del | F508del |
| 3 | 64 | M | 6 | + | G542X | G542X |
| 4 | 58 | F | 8 | + | R117H | R117H |
| 5 | 63 | F | NA | + | 1717-1G→A | 1717-1G→A |
| 9 | 59 | F | 14 | + | | R75Q |
| 10 | 47 | F | 19 | + | | L967S |
| 11 | 68 | F | 21 | + | | I177F |
| 12 | 67 | F | 34 | – | | V1153E |
| 13 | 46 | F | NA | + | | |
| 14 | 60 | F | 37 | + | | |
| 15 | 84 | M | 23 | + | | |
| 16 | 79 | F | 40 | + | | |
| 17 | 63 | M | 15 | + | | |
| 18 | 58 | M | 13 | – | | |

*In 1997.
†Investigated set of mutations: F508 del, G542X N1303K, R117H, 621+1G→T, R334W, ΔI507, W1282X, R553X, R1162X, 1717–1G→A, G551D, 3849+10kbC→T; BC: bronchiectasis (high-resolution CT scan).
CFTR, cystic fibrosis transmembrane conductance regulator; F, female; M, male; NA, declined sweat testing.

been found to carry the R1162X mutation. Sequencing of all 27 CFTR exons, including flanking intronic regions, and a search for large rearrangements were undertaken in the remaining 18 DNA samples. Calling all the patients back for further familial genetic studies could not be considered and we assumed that two identified mutations are located in trans. ORs were calculated and proportions were compared with prior probability using the likelihood ratio test and assuming an expected carrier rate of 1/25 (4%) in the Belgian general population.

Mean age (±SD) at the time of DNA sampling was 58.9 (±14.2) years. Bronchiectasis were present in 14/18 patients. Sweat chloride values between 40–59 mmol/l and 30–39 mmol/l were observed in 1 (5.5%) and 6 patients (33%), respectively. A total of 18 putative mutations were identified in 17/36 alleles (table 1), most of which were mild/uncommon.

CFTR mutation carrier frequency was much higher in patients with ABPA (12/18, 67%) than expected in the general population ($p < 0.0001$; OR 48.0, 95% CI 5.2 to 445.3). The probability of bearing two CFTR mutations was even more strikingly different ($p<0.0001$; OR 714, 95% CI 75 to 6797).

This study considerably extends previous findings by demonstrating a strong link between ABPA in adults and CFTR mutations. Although not altering the message, limitations of this work include the small population size which is inherent to the rarity of ABPA, the absence of DNA testing in parents and the dilemma of the clinical relevance of putative CFTR mutations. The hitherto best studied CFTR-related disorders are congenital bilateral absence of the vas deferens (CBAVD) and idiopathic chronic pancreatitis (ICP). It has been estimated that 85% of patients with CBAVD and 30% of those with ICP carry at least one CFTR mutation while ~50% and 10–15%, respectively, are compound heterozygous, with the F508del mutation and IVS8-T5 variant being most frequently detected.[5] The present study supports the concept that ABPA in pancreatic-sufficient adults is a CFTR-related disorder, with rare class IV–V mutations being mostly found and IVS8-T5 not seeming to play a significant role. Moreover, as ABPA is usually associated with bronchiectasis, a major phenotypic feature of CF, appropriate investigations to exclude milder forms of CF are warranted in these patients.

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## Vitamin D and COPD: seasonal variation is important

Janssens *et al*[1] have demonstrated the relationship between vitamin D status and lung function in patients with chronic obstructive pulmonary disease (COPD). However, in their study there was only one assessment of vitamin D status per patient. Given the minimal component of diet to vitamin D status (serum 25-hydroxyvitamin D (25(OH)D) concentration),[2] it is mostly determined by sunlight exposure and has a seasonal variation in healthy individuals.[3]

In a study of 24 patients with COPD (mean (SD) age 69 (5.8) years and smoking history 43 (15.8) pack-years) with measurements undertaken in the same individuals at the end of summer (August/September) and winter (March/April), we have also shown that vitamin D status correlated with forced expiratory volume in 1 s ($FEV_1$) ($r=0.486$, $p=0.016$), which remained significant ($p=0.048$) when corrected for age, gender, body mass index and activity level. However, we also showed that the relationship between spirometry ($FEV_1$ and forced vital capacity (FVC)) and vitamin D status was stronger in the winter ($FEV_1$: $r=0.451$, $p=0.027$; FVC: $r=0.367$, $p=0.078$) than in the summer ($FEV_1$: $r=0.399$, $p=0.053$; FVC: $r=0.264$, $p=0.213$). For spirometry there were non-significant seasonal trends with a mean difference of 0.051 (95% CI −0.15 to 0.12) and 0.071 (95% CI −1.1 to 0.25) for $FEV_1$ and FVC, respectively (table 1).

Janssens *et al*[1] showed that patients with COPD have poorer vitamin D status than healthy smokers. Our results confirmed this finding and, additionally, showed differences between the vitamin D status both in summer and winter compared with age-, gender-, month- and geographical region-matched controls from the UK National Diet and Nutrition Survey (NDNS).[4] For the winter values the mean difference was 11.9 nmol/l (95% CI 7.4 to 16.3) ($p<0.0001$) and for summer values the mean difference was 20.9 nmol/l (95% CI 15.5 to 26.3) ($p<0.0001$). Furthermore, in the winter there were three subjects who had 25(OH)D concentrations >50 nmol/l but none with a concentration >75 nmol/l, a concentration regarded by many as being appropriate to define vitamin D sufficiency.[2] In the summer, eight patients had a 25(OH)D concentration >50 nmol/l and only one patient had a concentration >75 nmol/l. We did not find any association between oily fish intake and vitamin D status.

Sunlight exposure is also determined by the distance from the equator and therefore the findings from one region may not represent those of another. In a study which evaluated the vitamin D status in patients with asthma compared with healthy controls (which showed no significant difference in status between these groups),[5] the serum 25(OH)D concentration was twice as high in patients from Aberdeen (latitude 57°N) than in those from Norwich (latitude 52°N).

**Table 1** Mean (SD) values for summer and winter measurements

| | Winter | Summer | p Value |
|---|---|---|---|
| Vitamin D (nmol/l) | 35.1 (10.5) | 49.3 (13.0) | 0.000 |
| PTH (μg/l) | 5.4 (1.7) | 4.7 (1.6) | 0.018 |
| Calcium (mmol/l) | 2.4 (0.1) | 2.4 (0.1) | 0.239 |
| Corrected calcium (mmol/l) | 2.4 (0.1) | 2.4 (0.1) | 0.375 |
| $FEV_1$ (l) | 1.18 (0.41) | 1.23 (0.43) | 0.121 |
| FVC (l) | 2.66 (0.66) | 2.73 (0.72) | 0.420 |
| PEF (l/min) | 205 (82) | 214 (87) | 0.650 |

There was a significant seasonal difference for vitamin D and parathyroid hormone.
$FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; PTH, parathormone.