



## Scientific Letter

**The Relation of *CFTR*-Genotype and Associated Comorbidities to Development of Pulmonary Atelectasis in Cystic Fibrosis Patients**


To the Director,

Cystic fibrosis (CF) is the most frequent life-threatening autosomal recessive disease in Caucasians. In Spain, close to 50% are heterozygous, while 28% are homozygous for F508del (Phe.508.del).<sup>1</sup> Respiratory complications produce highest morbidity and mortality in CF patients and represent approximately 62.53% of total deaths according to the European Registry 2019.<sup>1</sup> Among these complications, atelectasias have received the least scientific attention and little medical literature addresses this complication. The estimated incidence scatters around 4–11%, being less frequent the segmental atelectasis (0.81%).<sup>2–4</sup>

No international consensus on atelectasis etiology, prognosis or treatment has been elaborated.<sup>5–7</sup> Its etiology could be secondary to either mucus plugs<sup>8,9</sup> or serious affectations of the pulmonary parenchyma in which, the progressive and irreversible damage of the airway would cause distortion, obstruction and bronchial dilatations.<sup>5,8,10,11</sup> Its severity ranges from asymptomatic to major complications, depending on various unknown factors.

Considering the scarcity of published works on atelectasis in CF, we have proposed to analyze whether genetics, certain CF typical respiratory of this complication and other comorbidities are associated to development of this complication.

All cases of diagnosed stable CF children and adults ( $\geq 18$  years) who suffered persistent atelectasis as a pulmonary complication, diagnosed by image techniques, with at least a two-year-follow-up of the patient after the first episode were included until December 2017 (named as cases), and in which the study variables could have been collected. Likewise, age and gender-matched control patients were enrolled (date of birth of  $\pm$ three years).

The following variables were assessed: *CFTR*-mutations (dividing them into homozygotes and heterozygotes for F508del (Phe.508del) mutation, F508del (Phe.508del) mutation with one allele pending sequencing and other different mutations), pulmonary complication such as *ABPA*,<sup>12</sup> hemoptysis, pneumothorax and chronic bronchial infection (*CBI*) before the episode of atelectasis or, as in the case of *CBI*, at the time of the pulmonary collapse was described, and other comorbidities related to the disease, including pancreatic insufficiency and *CF*-related diabetes (*CFRD*). We also collected pulmonary function at the time of collapse (basal), and the last one registered, and the annual decline, in both groups.

The study has been approved by the Research Ethics Committee of the University La Paz University Hospital in Madrid, Spain (PI-2130). Patients were not involved.

For the statistical analysis, the SPSS program, version 13, was used. The data were expressed as mean plus standard deviation or percentage of the variable. The comparison of independent quantitative variables was performed by the *Mann–Whitney* test, the quantitative repeated variables by the *Wilcoxon* test and the qualitative variables by the *Chi-square* test.  $p < 0.05$  was considered significant.

Among a total population of 969 patients with CF attended in the included CF centers, 38 patients (3.9%), with a mean age at diagnosis of atelectasis of  $20.05 \pm 12.67$  years, suffered at least one episode of atelectasis. Of the 38 patients, 23 were women (60.5%), with a mean age of  $24.58 \pm 11.9$  years. Among the 39 controls, 26 were women (66.7%), with a mean age of  $25.08 \pm 11.84$  years. The pulmonary functional data are shown in [Table 1](#). No significant demographic differences were identified, as well as in mutations or comorbidities ([Table 2](#)).

In contrast, comparing both groups, we found significant differences regarding pulmonary function both in the basal study data collection and in the last one. There was no significant decline of pulmonary function per year between groups ([Table 1](#)).

Remarkably, a significantly elevated frequency of atelectasis was identified in patients with history of *ABPA* in relation to control group (23.7% vs 2.6%,  $p = 0.006$ ), but not in other complications ([Table 2](#)). However, we saw those 31 cases and 31 controls suffered *CBI* for one or several microorganisms, without statistical significance for the microorganisms studied ( $p = 0.523$ ) ([Table 2](#)).

22 patients did not show radiological improvement (57.9%), 7 patients presented partial (18.4%) and 6 complete improvement (15.8%).<sup>6</sup>

Within our series, a prevalence of atelectasis of 3.9% for the observational period has been estimated, like that found in other studies.<sup>2–4</sup> Unlike other series, in which atelectasis is more frequent in children (the airways are smaller and with a greater tendency to collapse and associated with progressive structural lung disease), our average age at diagnosis of atelectasis was  $20.05 \pm 12.67$  years.<sup>9,13,14</sup>

In the search for correlations that may lead to possible risk factors predisposing development of atelectasis in CF, we have tried to find among our variables, if one of them could favor them.

F508del (Phe.508.del) mutation homozygous is generally associated with a more severe phenotype and prognosis.<sup>15</sup> However, we did not find that this mutation was related to an increased risk of suffering this pulmonary complication, nor did we observe differences between the mutations in cases and controls ([Table 2](#)).

We clearly observed that the patients with atelectasis had a worse pulmonary function before manifestation of the complication ([Table 1](#)). So, patients with moderate-severe pulmonary function are more prone to develop pulmonary collapses, because

**Table 1**  
Pulmonary function test.

	Atelectasis (cases)	Controls	p
Height (cm)	160.56 ± 13.92	160.14 ± 9.62	0.900
Weigh (kg)	51.65 ± 17.25	49.54 ± 16.07	0.860
BMI (kg/m <sup>2</sup> )	19.89 ± 3.98	20.42 ± 3.72	0.582
ppFVC -1 (%)	66.0 ± 24.1	87.78 ± 21.97	<b>0.0014</b>
ppFEV1 -1 (%)	49.02 ± 22.05	75.55 ± 27.15	<b>0.040</b>
FEV1/FVC -1	65.98 ± 18.45	71.0 ± 15.36	0.20
ppFVC -2 (%)	72.18 ± 24.58	90.12 ± 22.55	<b>0.020</b>
ppFEV1 -2 (%)	61.74 ± 29.45	75.38 ± 27.57	<b>0.040</b>
FEV1/FVC -2	61.0 ± 12.0	72.7 ± 15.06	<b>0.001</b>
Annual worsening ppFVC/year	1.90 ± 6.91	1.54 ± 6.01	0.810
Annual worsening ppFEV1/year	0.49 ± 6.22	1.60 ± 4.64	0.390
Annual worsening FEV1/FVC/year	1.17 ± 8.22	0.51 ± 1.72	0.63

pp, percent predicted; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; BMI, body mass index.  
-1: basal data. -2: last data (define time difference mean and SD).

**Table 2**  
Other variables analyzed.

	Controls	Cases	p
<i>Mutations</i>			
Homozygous F508del	13 (33.3%)	7 (18.4%)	0.348
Heterozygous F508del	16 (41%)	21 (55.3%)	
F508del/unknown	5 (12.8%)	3 (7.9%)	
Others	5 (12.8%)	7 (18.4%)	
<i>Pancreatic insufficiency</i>			
Cystic fibrosis-related diabetes (CFRD)	26 (66.7%)	23 (60.5%)	0.373
Hemoptysis	5 (12.8%)	7 (18.4%)	0.359
Embolization	3 (7.7%)	5 (13.2%)	0.341
ABPA	2 (5.1%)	4 (10.5%)	0.325
Pneumothorax	1 (2.6%)	9 (23.7%)	0.006
	0	2 (5.2%)	0.253
<i>Chronic bronchial infection (CBI) (last data collection)</i>			
Methicillin-Sensitive Staphylococcus aureus (MSSA)	31 (79.5%)	31 (81.6%)	0.52
Methicillin-Resistant Staphylococcus aureus (MRSA)	20 (51.3%)	12 (31.6%)	0.064
<i>Pseudomonas aeruginosa</i>	5 (12.8%)	4 (10.5%)	0.517
<i>Stenotrophomonas maltophilia</i>	24 (61.5%)	19 (50%)	0.215
<i>Achromobacter xylosoxidans</i>	5 (12.8%)	4 (10.5%)	0.517
Non-tuberculous mycobacterias	2 (5.1%)	4 (10.5%)	0.325
<i>Mycobacterium tuberculosis</i>	3 (7.7%)	4 (10.5%)	0.485
Others	0	0	
*Aspergillus spp.	8 (20.5%)	11 (28.9%)	0.277
*Candida spp.	4 (10.3%)	3 (7.9%)	
*Haemophilus spp.	1 (2.6%)	2 (5.3%)	
	3 (7.7%)	1 (2.6%)	

of intrapulmonary ventilatory differences. This finding has not been analyzed in medical bibliography until now, probably because of the scarcity of studies, which cover a small number of patients.<sup>5-7</sup>

In other published series including CF patients, it has been postulated that haemoptysis or hyperglycemia would be possible risk factors in the occurrence of atelectasis, due to possible increased viscosity of bronchial mucus.<sup>4</sup> However, we did not see differences in the comorbidities studied regarding pancreatic insufficiency or CFRD. This could be explained because both phenotypes are more linked to the F508del (Phe.508.del) mutation,<sup>16</sup> which is represented in a similar frequency in the two groups. Although we have not analyzed other complications, it has been reported that non-CF patients with severe acute pancreatitis have an increased risk to develop atelectasis.<sup>17</sup>

If we refer to lung complications, we have only found significant differences in relation to ABPA. ABPA significantly predominated in patients with pulmonary atelectasis.<sup>18</sup> We attribute this to the production of sputum “plugs” due to *Aspergillus*-colonization and the resulting allergic reaction, which further increases sputum viscosity and mucosal edema, causing structural lung damage.<sup>19,20</sup>

Regarding airway colonization with pathogens, the cohort with atelectasis revealed a trend to more frequent airway colonization with *Pseudomonas aeruginosa*, followed in frequency by MSSA. However, these findings did not reach statistical significance in our

cohort. This would suggest that if we included a greater number of patients, we could reach statistical significance.

As study limitations, we must point out its retrospective nature and the relatively small number of included patients, and the way to obtain the control group, although we have not found differences in mutations of both groups. Being a relatively rare complication, it has been easier for us to resort to this kind of analysis, to be able to collect the largest possible number of cases in the given time.

In conclusion and in relation to the variables studied, the presence of atelectasis is more frequently associated with patients who previously suffered from ABPA and who already had a moderate-severe impaired lung function. Probably, if the sample size were enlarged, we could find other variables, which would be risk factors for atelectasis as pulmonary complication in CF.

We think multicentric studies should be carried out leading to international guidelines for therapy and prevention of pulmonary atelectasis in CF.

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## Conflict of interest

The authors declare no conflict of interest in the study design, collection, analysis and interpretation of the data, as well as in the writing of the manuscript or in the publication of the results.

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