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BPI-ANCA in chronic obstructive pulmonary disease with pulmonary *Pseudomonas aeruginosa* colonisation: a novel indicator of poor prognosis

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Bactericidal/permeability-increasing protein (BPI) is one of the target antigens of anti-neutrophil cytoplasmic antibodies (ANCA), which have clinical and laboratory significance in systemic and rheumatoid vasculitides. The detection rate of BPI-ANCA in pulmonary disease has increased in recent years: pulmonary inflammation of BPI-ANCA(+) in patients with cystic fibrosis and chronic pulmonary infection is linked to declining lung function [1]. *Pseudomonas aeruginosa* is one of the most common pathogens of respiratory infections in patients with chronic obstructive pulmonary disease (COPD), which significantly increases the chances of lower respiratory tract infections and acute exacerbation of COPD, resulting in increased hospitalisation. Although there is literature on BPI-ANCA in lung disease such as cystic fibrosis and pulmonary tuberculosis [1–3], there is none on its presence in COPD or links with clinical manifestations, hospitalisations and prognosis. We hypothesised that BPI-ANCA status is linked to lung function and a physiological test of general health (the six-minute walking time) and predicts poor outcome in patients with COPD.

To test our hypothesis, we recruited 126 patients with chronic COPD and *P. aeruginosa* colonisation from the Second Affiliated Hospital of Nanchang University from June 2014 to August 2016. The diagnostic criteria for inclusion and acute exacerbations met the 2014 GOLD Global Initiative for Chronic Obstructive Pulmonary Disease [4]. Isolation of *P. aeruginosa* in three or more consecutive sputum cultures, taken at least one month apart during a 6-month period, was considered as chronic colonisation. Exclusion criteria were respiratory, cardiovascular, haematological or immune system diseases and severe metabolism abnormalities. The study was in accordance with the 1964 Helsinki declaration and approved by ethics committee of the Second Affiliated Hospital of Nanchang University with written informed consents obtained from all participants. Lung function tests (predicted% forced expiratory volume in 1 min (FEV_1%pred) and forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC)), COPD assessment test (CAT) and the 6-min walking test (6MWT) were conducted for each patient during a clinically stable period at entry and at 6, 12 and 18 months. Hospital readmissions for acute exacerbations and days of hospitalisation were noted. CAT consisted of eight items covering the most burdensome symptoms and limitations of COPD; each item had a score of 0–5 points and a total score of 0–40 points [5]. Pulmonary function tests were performed using a German-born Master Screen Diffusion Pulmonary Function Tester. Lung ventilation function tests were performed in strict accordance with the quality control standards of the American Thoracic Society [6]. Lung volume measurements and flow rate capacity curves were performed to evaluate patients' pulmonary function. Each item was conducted three times repeatedly, and the best value of FEV_1%pred and FEV_1/FVC(%) was taken as the result [5]. 6MWD was the best of two walks [7]. Five millilitre fasting blood was collected, and serum were obtained after a centrifugation at 1026 g for 10 min. Serum IgG-BPI-ANCA was detected by ELISA (Catalogue number E180104AH: EuroImmun Medical Diagnostics, Beijing, China). At the termination of antigen–antibody reaction, optical density (OD) was detected by a Multiskan Mk3 Plate Reader (ThermoFisher Scientific, Shanghai, China), with a cut-off value of $0.2\times OD_{calibration}$. BPI-ANCA considered positive (BPI-ANCA(+)) when ratio (OD_{sample} to cut-off) >1 and negative (BPI-ANCA(–)) otherwise.

SPSS23.0 software was used for statistical analysis. K-S test and Levene's test were used to analyse the normality and variance homogeneity of measurements. Data are presented as mean with

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standard deviation (SD), differences between groups were compared using independent-sample *t* test and serial data by repeated-measures analysis of variance. Categorical data are expressed as percentages and analysed by Chi-square testing. $P < 0.05$ was considered statistically significant.

The 126 COPD patients with *P. aeruginosa* colonisation were divided into a BPI-ANCA(+) group ($n = 59$, 46.8%) and a BPI-ANCA(−) group ($n = 67$, 53.2%) who were matched for age, sex, 6MWD, CAT score and smoking history (Table 1). Pulmonary function indicators including FEV_1%pred and FEV_1/FVC(%) in the BPI-ANCA(−)group were higher than in the BPI-ANCA(+) group. Disease duration and hospitalisation days in the BPI-ANCA(+) group were significantly longer than that in the BPI-ANCA(−) group. Follow-up data at 6, 12 and 18 months of 112 patients (13 deaths and 1 developed other disease excluded) are shown in Table 2. After 6 months, none of the clinical indices differed between the groups. However, after 12 months, all indices, although deteriorating from baseline, were better in the BPI-ANCA(−) group. This trend was continued at 18 months. In serial analysis over the 18-month period, although all indices deteriorated markedly in both groups, the rate of deterioration was worse in the BPI-ANCA(+) group: the 6MWD, FEV_1%pred and FEV_1/FVC (%) had all fallen to approximately 60–62% of baseline in the BPI-ANCA(−) group, but the reduction in all three indices (to approximately 46–48% of baseline) was greater in the BPI-ANCA(+) group. Similarly, the increase in the CAT score by approximately 84% of baseline in the BPI-ANCA(+) group was greater than the increase in the score in the BPI-ANCA(−) group of approximately 55% of baseline. After 18 months of follow-up, hospital readmissions rate (40% vs 21%, $P = 0.02$) and hospitalisation days due to acute exacerbations (17.1 (4.1) days vs 14.3 (3.4) days, $P = 0.04$) were significantly higher in the BPI-ANCA(+) group than in the BPI-ANCA(−) group.

P. aeruginosa and BPI are simultaneously phagocytosed and presented to MHC class II molecules, leading to the generation of protective antibodies [8]. Binding of ANCA to this membrane-bound neoantigen results in the release of multiple pro-inflammatory cytokines and so a link with inflammatory pathophysiology [9]. Our data extend the clinical significance ofBPI-ANCA detection in cystic fibrosis and pulmonary tuberculosis [1–3], in that lung function and walking time are significantly worse in those COPD patients who are positive for this antibody. Furthermore, we show that the presence of the antibody identifies those patients whose 18-month prognosis is poor, with worse lung function, reduced walking distance (which are linked [10]), greater length of stay in hospital and more frequent admissions. However, due to the nature of our study, we cannot say if the presence of BPI-ANCA actively promotes the deterioration of the disease (perhaps by contribution directly to pulmonary pathophysiology), or if it is simply a marker of this deterioration. The CAT score is a relatively comprehensive and multidimensional assessment method to reflect the occurrence of acute exacerbations of COPD, whose prognostic effect is more sensitive and well correlated with clinically used indicators of disease severity such as pulmonary function [11].

Factors such as smoking, low body mass index, dyspnoea and other comorbidities are contributors to poor prognosis of COPD with lung *P. aeruginosa* [12], but the association between serum BPI-ANCA and disease prognosis has rarely been reported in the literature. Gallego

Table 1. Demographics and general clinical characteristics of participants.

Parameters	BPI-ANCA(+) ($n = 59$)	BPI-ANCA(−) ($n = 67$)	*P*
Age (year)	58.8 (10.0)	61.0 (11.2)	0.242
Sex (male/female)	40/19	47/20	0.776
Smoking status			0.260
Never smoked (*n*, %)	11 (18.6)	20 (29.8)	
Past smoking (*n*, %)	27 (45.8)	30 (44.8)	
Current smoking (*n*, %)	21 (35.6)	17 (25.4)	
Smoking history (pack year)	61.5 (34.2)	66.3 (27.3)	0.388
FEV_1%pred	50.8 (7.3)	52.4 (7.9)	0.036
FEV_1/FVC (%)	47.8 (8.7)	49.5 (6.0)	0.023
Disease duration (year)	10.2 (3.6)	7.9 (3.6)	<0.001
CAT score	13.6 (3.8)	12.0 (2.1)	0.062
6MWD (m)	366 (71)	378 (49)	0.273
Hospitalisation days	14 (4)	12 (4)	0.042

FEV_1%pred: predicted% forced expiratory volume in 1 min; FEV_1/FVC: forced expiratory volume in 1 s/forced vital capacity ratio; CAT: chronic obstructive pulmonary disease assessment test; 6MWD: 6-min walking distance. Data *n* (%) or mean (SD).

Table 2. Lung function, quality of life and activity tolerance changes of patients after follow-up of 6, 12 and 18 months.

Parameters	Group	6 months	12 months	18 months	*F*	*P*
FEV_1%pred	BPI-ANCA(−)	47.1 (16.8)	40.5 (6.7)	31.3 (8.2)	31.5	<0.0001
	BPI-ANCA(+)	42.8 (18.2)	37.6 (7.8)	23.6 (5.6)	43.8	<0.0001
	P	0.241	0.026	<0.0001		
FEV_1/FVC (%)	BPI-ANCA(−)	48.1 (16.2)	41.9 (7.7)	30.9 (3.9)	30.8	<0.0001
	BPI-ANCA(+)	43.7 (15.3)	38.8 (6.8)	22.8 (6.4)	21.8	<0.0001
	P	0.128	0.018	<0.0001		
CAT score	BPI-ANCA(−)	14.9 (5.2)	16.9 (5.4)	18.6 (4.3)	9.0	<0.0001
	BPI-ANCA(+)	16.3 (3.6)	20.0 (4.6)	25.1 (3.3)	74.9	<0.0001
	P	0.083	0.001	<0.0001		
6MWD (m)	BPI-ANCA(−)	307 (63)	281 (39)	223 (61)	31.2	<0.0001
	BPI-ANCA(+)	287 (56)	230 (69)	171 (50)	52.8	<0.0001
	P	0.062	<0.0001	<0.0001		

FEV_1%pred: predicted% forced expiratory volume in 1 min; FEV_1/FVC: forced expiratory volume in 1 s/forced vital capacity ratio; CAT: chronic obstructive pulmonary disease assessment test; 6MWD: 6-min walking distance.

et al. [13] found that lung function, daily exercise tolerance and quality of life during acute exacerbations declined in patients whose sputum culture was repeatedly positive for *P. aeruginosa* compared with those negative. A 10-year follow-up study of 46 patients with cystic fibrosis and *P. aeruginosa* colonisation found that BPI-ANCA(+) patients were more likely to develop adverse outcomes, indicating the close association between serum BPI-ANCA positivity and disease progression [14]. We note certain limitations: patient groups were not matched for lung function or clinical history on outset, and we have no data on other laboratory indices such as C reactive (CRP) and erythrocyte sedimentation rate (ESR) that may also predict clinical outcome and that our data may not be extrapolated to other forms of COPD. Finally, our sample size is too small to permit analysis by the actual titre of the BPI-ANCA, and this may be more instructive. Nonetheless, our findings are consistent with the view that serum BPI-ANCA marks poor prognosis. This paper represents an advance in biomedical science because it shows that, in COPD patients with *P. aeruginosa* colonisation, serum BPI-ANCA is a predictor of poor lung function and 18-month clinical deterioration and so maybe a useful tool in this disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

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