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Studies in chronic allergic bronchopulmonary aspergillosis
4 Comparison with a group of asthmatics

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Malo, J. L., Inouye, T., Hawkins, R., Simon, G., Turner-Warwick, Margaret, and Pepys, J. (1977). *Thorax*, **32**, 275–280. **Studies in chronic allergic bronchopulmonary aspergillosis. 4 Comparison with a group of asthmatics.** A comparison is made of lung function tests and radiographic findings in 20 asthmatic patients with allergic bronchopulmonary aspergillosis paired in terms of sex, age, and duration of asthma with 20 other asthmatics in whom the diagnosis of aspergillosis was excluded in order to see if the aspergillosis causes more lung damage.

One hundred per cent of the patients with aspergillosis and 75% of the patients with asthma alone showed a significantly reduced forced expiratory volume in one second (FEV_1) before bronchodilator. All the patients in the two groups had a significantly reduced maximal expiratory flow at 50% vital capacity breathing air ($\dot{V}_{50}$air) but the severity of the reduction was statistically greater in the aspergillosis group. Reversibility in FEV_1 of 15% and more was found in 50% of patients with asthma alone as against 31% of patients with aspergillosis. The degree of reversibility of FEV_1 was also statistically greater in patients with asthma alone. Improvement of less than 20% of $\dot{V}_{50}$ after helium-oxygen breathing was found in 33% of the patients with asthma alone and in 75% of the patients with aspergillosis. Patients with aspergillosis also showed significantly ($0{\cdot}001 < P < 0{\cdot}01$) more reduced gas transfer factor.

Radiological features of overinflation were as common in the two groups. Tubular and ring shadows were found in 95% and 60% respectively of patients with aspergillosis as against 45% and 15% of patients with asthma alone.

Patients with allergic bronchopulmonary aspergillosis, most of whom are asthmatics, generally develop bronchiectasis at the site of the fleeting pulmonary shadow. A comparison is made of these patients with asthmatics without aspergillosis in order to see if the recurrent shadows and progression of the disease cause more functional impairment, less reversibility of airways obstruction, and more radiological changes.

Material and methods

PATIENTS

Twenty patients with allergic bronchopulmonary aspergillosis were matched with the same number of patients with asthma alone according to sex, age, and duration of asthma. There were 8 men and 12 women in each group. All the patients were over 30 years of age and had had asthma for 30 years or more. The mean age and duration of asthma were $45{\cdot}3 \pm 8{\cdot}1$ and $39{\cdot}5 \pm 7{\cdot}5$ years respectively in the group of patients with aspergillosis as compared with $44{\cdot}3 \pm 7{\cdot}7$ and $41{\cdot}1 \pm 7{\cdot}0$ years respectively in the group with asthma alone. Patients in the two groups were paired so that the age and the duration of asthma were always close and at most within a 10-year period.

The group of patients with allergic aspergillosis was selected according to the major criteria listed in Table 1. These major criteria were a history of asthma with at least one past fleeting shadow in the chest radiograph with blood eosinophilia to-

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Table 1 *Diagnostic features in patients with allergic aspergillosis*

	No. of patients
Main diagnostic criteria	
Asthma	20
Previous episode of transient shadow in chest radiograph with blood eosinophilia	20
Immediate positive prick test with an extract of *A. fumigatus*	20
Supporting evidence	
Presence of serum precipitins against *A. fumigatus* in the past	16
at the time of the study	17
History of 'plugs' in sputum	14
Culture of *A. fumigatus* from sputum in the past	7

gether with a positive immediate prick reaction to an extract of *Aspergillus fumigatus*. A total of 110 different acute episodes of fleeting shadows, a mean of 5·5±5·2 per patient, were recorded in these patients. The mean interval from the time of diagnosis of aspergillosis was 10·1±5·2 years. All these patients had prick skin tests done with a routine battery of 23 common allergens and all had three or more positive reactions.

The patients with asthma alone did not satisfy the full criteria of aspergillosis. All but one were atopics. Five of them had a positive prick reaction to an extract of *A. fumigatus* but none of these patients had positive precipitins against *A. fumigatus*.

At the time of the study 10 patients were on oral corticosteroids continuously in the group with allergic aspergillosis and eight in the group with asthma alone. The smoking habits of the two groups were the same. Five of the asthmatics reported symptoms of chronic bronchitis whereas nine of the patients with allergic aspergillosis had such symptoms.

All the patients included in the study were seen between 10 am and 3 pm. No bronchodilator medication, such as sympathomimetics and xanthine derivatives, was taken on the day of the visit. Patients on oral steroids, beclomethasone dipropionate or sodium cromoglycate were told to take these drugs as usual.

PHYSIOLOGICAL ASSESSMENT

At the time of the study all the patients had measurements made of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Maximal expiratory flow volume (MEFV) curves breathing air and a helium (He)-oxygen (O_2) mixture in concentrations of 79% and 21% respectively were made in all the patients with aspergillosis and in 18 asthmatics. The patients were then asked to inhale a solution of 1 ml of salbutamol at 5 mg/ml mixed with 2 ml of normal saline. This was administered through a Wright's nebuliser for 15 minutes at a constant flow. Measurements of FEV_1, FVC, and MEFV curve breathing air were repeated after 15 further minutes. This assessment of reversibility was available for comparison in 16 out of the 20 patients in each group. Complete lung volumes, airway resistance (Raw), and gas transfer factor (DLCO) were measured one hour later in the group with asthma alone and on a different day in the group with aspergillosis.

FEV_1 and FVC were measured on a Vitalograph (Vitalograph Ltd). The MEFV curve was produced on a wedge spirometer Ohio 840 (Airco Ltd) and traced on an oscilloscope DM 64 (Telequipment Ltd). After the tracing with air the patient was connected to a closed circuit and asked to take three slow vital capacity (VC) breaths of the He-O_2 mixture. Another MEFV curve was then produced before the patient was allowed to breathe air. Several curves were recorded and two curves with a similar VC, one made with air and the other measurement breathing He-O_2, were kept for analysis. The expiratory flows at 50% VC breathing (V_{50}air) and the He-O_2 mixture (V_{50}He) were measured as well as the ratio $V_{50}He/V_{50}air$.

Lung volumes and Raw were measured in a body plethysmograph according to the technique of DuBois *et al.* (1956a and b). DLCO was assessed by the single-breath technique (McGrath and Thomson, 1959).

Reference values for FEV_1, FVC, and lung volumes were taken from Goldman and Becklake (1959), from Cotes (1975) for DLCO and the transfer coefficient (KCO), and from Bass (1973) for V_{50}air. Raw was considered as normal if less than 0·25 kPa l^{-1} s^{-1} and specific airway conductance (SGaw) between 1·3 and 3·6 s^{-1} kPa^{-1}. FEV_1, FVC, and V_{50}air were considered to be significantly reduced if less than 85% of the predicted value. This limit was 75% in the cases of DLCO and KCO. Reversibility was measured as a change in expiratory values after the inhaled bronchodilator and compared as percentages of the pre-bronchodilator values. Significant reversibility was considered to be present when the change in expiratory measurement after bronchodilator was 15% or more.

RADIOLOGICAL ASSESSMENT

Each patient had a posteroanterior chest radiograph taken at 1·8 m on full inspiration. Thirty-five of the patients also had a left lateral radiograph. The following basic features were

analysed. The length and width of the lung were measured according to the method of Hodson *et al.* (1974); the transverse cardiac diameter, the position and shape of both domes of the diaphragm, and the diameter of the right basal artery were measured according to Simon (1975). The diameter of the left basal artery was taken when the diameter of the right was ill defined. The normal values for the above parameters were taken from Simon (1975). The vascular shadows in all of the six conventional lung zones were assessed.

Special attention was paid to examination for the following abnormal shadows (Simon, 1975):

1 tubular shadows: two parallel hair-line shadows, the width of the transradiant zone between the lines being larger than that seen in a normal bronchus at this level;
2 ring shadows: hair-line ring shadows 1–2 cm in diameter;
3 shrunken but aerated segment or lobe;
4 narrowing or loss of vascular shadows.

All the films were read 'blind' by the same observer (Dr. George Simon).

Both the Student's paired and unpaired *t* tests were used for the comparison of the physiological results and both gave similar results for P values in every instance, suggesting that the pairing of the two groups was satisfactory.

Results

PHYSIOLOGICAL RESULTS

Table 2 shows the incidence of reduction in FEV_1, FVC, and V_{50}air before and after bronchodilator in the two groups of patients. More patients with aspergillosis had airways obstruction in terms of FEV_1 and FVC measurements. All the patients had a significantly reduced V_{50}air. Reversibility of 15% or more in the airways obstruction measured by the FEV_1 and FVC was observed more often in the group with asthma alone than in the aspergillosis group. Both groups had the same incidence of improvement in V_{50}air.

Table 3 shows the incidence of abnormalities in the other physiological parameters. More patients with aspergillosis showed a significant reduction in VC but slightly less had hyperinflation as shown by an increase in the FRC. Increased airway resistance and decreased specific airway conductance were more frequent in the asthma alone group. There was more frequent improvement in the V_{50} after He-O_2 breathing in patients with asthma alone.

Tables 4 and 5 give the levels of statistical difference between the actual matched values in the two

Table 2 *Incidence of reduction and reversibility in expiratory measurements*

	Patients with asthma		*Patients with aspergillosis*	
	No.	*%*	*No.*	*%*
Value < 85% predicted BEFORE bronchodilator				
FEV_1	15/20	75	20/20	100
FVC	10/20	50	11/20	55
$\dot{V}_{50}$air	20/20	100	20/20	100
Value < 85% predicted AFTER bronchodilator				
FEV_1	7/16	44	14/16	87
FVC	5/16	31	9/16	56
$\dot{V}_{50}$air	16/16	100	16/16	100
Reversibility* ≥ 15%				
FEV_1	8/16	50	5/16	31
FVC	7/16	44	5/16	31
$\dot{V}_{50}$air	6/16	38	6/16	38

*% Reversibility = $\frac{\text{change after bronchodilator}}{\text{pre-bronchodilator value}} \times 100$.

When patients with normal values before bronchodilator are excluded, 8/12 (67%) asthmatics and 5/16 (31%) patients with aspergillosis had reversible FEV_1, whereas 4/10 (40%) asthmatics and 2/11 (18%) patients with aspergillosis had reversible FVC.

Table 3 *Incidence of abnormalities in functional measurements*

	Patients with asthma		*Patients with aspergillosis*	
	No.	*%*	*No.*	*%*
VC < 85% predicted	8/20	40	12/20	60
FRC > 120% predicted	10/20	50	8/20	40
DLco < 75% predicted	2/20	10	3/20	15
Kco < 75% predicted	2/20	10	0/20	0
Increased Raw*	15/20	75	8/20	40
Decreased SGaw*	14/20	70	8/20	40
Change in $\dot{V}_{50}$ < 20% after He-O_2	6/18	33	15/20	75

*See text for definitions of increased and decreased values.

Table 4 *Statistical analysis of expiratory measurements and reversibility*

	*Level of statistical difference**
Value BEFORE bronchodilator	
FEV_1	NS
FEV	NS
$\dot{V}_{50}$air	$0{\cdot}02 < P < 0{\cdot}05$
Value AFTER bronchodilator	
FEV_1	$0{\cdot}001 < P < 0{\cdot}01$
FVC	$0{\cdot}02 < P < 0{\cdot}05$
$\dot{V}_{50}$air	$0{\cdot}02 < P < 0{\cdot}05$
Reversibility**	
FEV_1	$0{\cdot}02 < P < 0{\cdot}05$
FVC	$0{\cdot}02 < P < 0{\cdot}05$
$\dot{V}_{50}$air	NS

*Comparison of physiological values as expressed in percentages of predicted to provide adjustment for age and height and as measured by the paired *t* test.

**% Reversibility = $\frac{\text{change after bronchodilator}}{\text{pre-bronchodilator value}} \times 100$.

When the normal values before bronchodilator are excluded the level of statistical difference is the same in the case of FEV_1, whereas the difference is not statistically different in the case of FVC.

Table 5 *Statistical analysis of functional measurements*

	*Level of statistical difference**
VC	$0{\cdot}02 < P < 0{\cdot}05$
FRC	NS
DLco	$0{\cdot}001 < P < 0{\cdot}01$
Kco	NS
Raw	NS
SGaw	NS
Change in $\dot{V}_{50}$ after He-O_2	$0{\cdot}02 < P < 0{\cdot}05$

*Comparison of physiological values as expressed in percentages of predicted to provide adjustment for age and height and as measured by the paired *t* test.

groups. Of the values of FEV_1, FVC, and $\dot{V}_{50}$air before use of the bronchodilator, only the $\dot{V}_{50}$air was statistically different, whereas all the three expiratory measurements after the bronchodilator were significantly lower in patients with aspergillosis. The reversibility of the airways obstruction was greater in the asthma alone group. Patients with aspergillosis showed significantly greater reduction in VC and less improvement in the $\dot{V}_{50}$ after He-O_2 breathing. A good degree of statistical difference was shown by the DLCO values which were more markedly reduced in the patients with aspergillosis.

RADIOLOGICAL RESULTS

The results of the radiological analysis are shown in Table 6. When two or more of the listed features of overinflation are considered, the same percentages of patients were affected in the two groups. An increase in the retrosternal space was nevertheless found more often among the asthma alone group. Tubular shadows were demonstrated in 95% of the patients with aspergillosis but were also present in almost half of the asthmatics. The other chronic changes, such as ring shadows, lobar shrinkage, and loss of vascular shadows, were more frequent in the patients with aspergillosis. The diameter of the right or left basal artery was within normal limits in all patients, and the domes of diaphragm were curved in all instances.

Table 6 *Incidence of radiological findings*

	Patients with asthma		*Patients with aspergillosis*	
	No.	*%*	*No.*	*%*
Features of overinflation				
Lung length/width ratio ≥ 1	6/20	30	9/20	45
Transverse cardiac diameter < 11·5 cm	8/20	40	9/20	45
Diaphragm level below ant. rib level of 6$\frac{1}{2}$	1/20	5	2/20	10
Retrosternal space > 3·5 cm	5/20	25	1/20	5
Two or more of above features	6/20	30	7/20	35
Permanent changes				
Tubular shadows	9/20	45	19/20	95
Ring shadows	3/20	15	12/20	60
Lobar shrinkage	1/20	5	8/20	40
Loss of vascular shadows	1/20	5	10/20	50

COMPARISON BETWEEN CLINICAL, PHYSIOLOGICAL, AND RADIOLOGICAL FINDINGS

In comparing the symptomatology of the patients with the results of their functional measurements, it was found that the group of patients with asthma who had no symptoms of chronic bronchitis (15) were not statistically different from the other asthmatics with such symptoms (5) as regards all the physiological tests. The asthmatics without symptoms of chronic bronchitis were also not statistically different from the patients with aspergillosis who had no symptoms of chronic bronchitis (11) except that their DLCO was significantly ($0{\cdot}02 < P < 0{\cdot}05$) better preserved. The asthmatics without symptoms of chronic bronchitis were finally compared with the patients with aspergillosis who reported symptoms of chronic bronchitis, the latter showing significantly lower values for $\dot{V}_{50}$air before bronchodilator, FEV_1, FVC, and $\dot{V}_{50}$air after bronchodilator, less reversibility of FEV_1 and FVC, less change in $\dot{V}_{50}$ after He-O_2 breathing, and lower VC and DLCO, the levels of statistical differences being the same as those listed in Tables 4 and 5.

In comparing the symptomatology of the patients with their chest radiographs, it was found that in the group of asthmatics only one of the five patients who had symptoms of chronic bronchitis also had evidence of ring and tubular shadows, the remaining four having normal radiographs. In the group of patients with aspergillosis, the nine patients reporting daily sputum production had a mean of 4·2 lung zones showing ring and tubular shadows whereas in the 11 patients without symptoms of chronic bronchitis these changes were present in 2·3 lung zones.

Discussion

Patients with allergic bronchopulmonary aspergillosis are known to develop bronchiectasis at the site of acute shadows as demonstrated by bronchography (McCarthy *et al.*, 1970). It is likely that with progress of the disease these patients will lose some of the reversibility of the airways obstruction linked to their asthma and show a functional pattern of fixed airways disease like that generally found in bronchiectasis. McCarthy and Pepys

(1971) reported that the degree of reversibility in airways obstruction was reduced in patients with aspergillosis. The same authors also showed significantly reduced gas transfer factor in 25 out of the 35 patients studied. More recently, Safirstein *et al.* (1973) found that a reduction in gas transfer factor was a feature of aspergillosis. Patients with aspergillosis have also been shown to develop chronic and fixed radiological shadows (McCarthy *et al.*, 1970; Safirstein *et al.*, 1973) which help to differentiate them from patients with uncomplicated asthma.

Even if it is possible that the physiological and radiological changes were the result of the progress of the aspergillosis, some of the changes may have been secondary to long-standing asthma. We found that the functional impairment of the patients with aspergillosis was greater than in the asthma alone group. The reduction in gas transfer factor, in particular, was more marked in patients with aspergillosis. This is probably secondary to the development of bronchiectasis, and it has been shown (Pande *et al.*, 1971) that the reduction in gas transfer is the best index of the presence and extent of bronchiectasis. We also found that the patients with aspergillosis had less reversible airways obstruction. More patients with asthma alone had a significantly increased airways resistance and decreased specific airways conductance whereas more patients with aspergillosis had a significantly reduced FEV_1 and FVC. This might mean that obstruction was predominantly in the larger airways in patients with asthma alone. Patients with aspergillosis might also have more collapsible airways due to the presence of bronchiectasis. If this were so, any forced expiratory manoeuvre would more likely show impairment in these patients than measurements like airways resistance which are done without expiratory effort.

All the patients in the two groups had a reduced $\dot{V}_{50}$air. The normal values for this are still debated (Green *et al.*, 1973). It is likely that the $\dot{V}_{50}$air measurement is a more sensitive index of airways obstruction than the FEV_1, which might explain why the former value was more often reduced than the latter. Fewer patients with aspergillosis improved their $\dot{V}_{50}$ after He-O_2 breathing by a value of 20% or more. There were thus more non-responders to He-O_2 in this group if we use the classification initially suggested by Despas *et al.* (1972). The fact that these patients with aspergillosis had more severe airways obstruction than the asthmatics could explain why they had a smaller improvement in $\dot{V}_{50}$ after He-O_2. Benatar *et al.* (1975) have found that the response to He-O_2 breathing is dependent on the severity of the airways obstruction.

A high incidence of chronic radiological changes, namely tubular and ring shadows, lobar shrinkage, and loss of vascular shadows, was found among the patients with aspergillosis. These changes were generally not present in the radiographs of the asthmatics except for tubular shadows which were found in almost half of them. More studies are needed in larger asthmatic groups in order to find the incidence of these chronic radiological abnormalities and to see if they are related to the symptomatology and to the severity of the functional impairment.

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