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Methacholine Inhalation Challenge in Patients with Post-*Mycoplasma pneumoniae* Pneumonia

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SUMMARY We studied methacholine bronchial inhalation challenge in 12 patients at 4th week and 12th week after recovered from *Mycoplasma pneumoniae* pneumonia, compared with 12 healthy subjects as controls. The aerosolized methacholine was produced by an atomized nebulizer of the Provocationtest I, Pari-Starnberg, Germany and the aerosol was kept into a reservoir bag. Then, it was inhaled slowly by a subject. Increasing concentration of methacholine solutions (0, 0.5, 1, 5, 10, and 25 mg/ml) were used. The results revealed that 67% of the patients had bronchial reactivity to methacholine at the first time of challenge with a mean concentration of methacholine producing a fall in FEV_1 of 20% from baseline (PC_{20}) of 12.3 ± 6.44 mg/ml. Fifty percent of the patients were still positive to the test on the second time of challenge with a mean PC_{20} of 20.1 ± 6.89 mg/ml. None of the healthy subjects had bronchial hyperreactivity (PC_{20} > 25 mg/ml). Two patients experienced wheezing and asthmatic attacks requiring bronchodilator therapy during acute phase pneumonia. They were also diagnosed as having bronchial asthma for the first time. Many patients had prolonged coughing during the recovery phase lasting more than 4 weeks. This prolonged coughing seemed to have a correlation with the development of bronchial hyperresponsiveness (BHR). We concluded that *M. pneumoniae* could induce BHR which may be transient or persistent. The effect of mycoplasma respiratory tract infection may result in airway inflammations and asthamtic attacks.

Airway hyperresponsiveness (AHR) is a major characteristic feature in the pathogenesis of bronchial asthma.[1] Recent studies have suggested that asthma is a special type of airway inflammation that is characterized by an increase in eosinophils in the respiratory epithelium.[2] Respiratory tract infections are the most common of the stimuli that precipitate acute exacerbation of asthma.[3,4] Several studies have shown that viral infections such as, respiratory syncytial virus, parainfluenza virus, rhinovirus, and influenza virus are the most common organisms that provoke asthma.[5-8] There is evidence that viral respiratory tract infections can induce AHR and have role in pathogenesis of asthma.[4,9,10] *Mycoplasma pneumoniae* is a well known pathologic organism in acute respiratory tract infection.[11] *M. pneumoniae* respiratory tract infection has also been frequently associated with exacerbations of asthma in both children and adults.[12] Recently, there has been a report from Japan describing a previously healthy patient who had developed pneumonia from *M. pneumoniae* which led to an initial onset of bronchial asthma.[13] Thus, *M. pneumoniae* may also have important role in the pathogenesis of asthma.

The purpose of this study was to determine the AHR in the patients after recovery from *M. pneumoniae* pneumonia.

MATERIALS AND METHODS

Subjects

Since January 1994, 12 patients with *M. pneumoniae* pneumonia were diagnosed and included in the study. They were previously healthy without any allergic diseases such as, allergic rhinitis, bronchial asthma, and atopic

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eczema. They were also negative for allergic diseases in their familial history except one patient (No.10 in Table 1) who had her mother with allergic rhinitis. One patient (No. 4 in Table 1) had a past history of *M. pneumoniae* infection in the previous year. They were non-smokers. Most of them had never worked in the place that was well-known to cause occupational asthma. Almost all were the official workers. Three were medical personel. *M. pneumoniae* pneumonia was diagnosed, based on the patients' acute febrile illness with mild productive cough, abnormal physical findings on chest examination and a picture of infiltration on chest reontgenography, together with high titres of mycoplasma antibody by complement fixation of more than 1:40. There was also a four-fold rise in titre. The clinical features such as onset and pattern of fever, cough and wheezing were recorded for evaluation. The laboratory findings and chest X-ray pattern were recorded. All patients were admitted and were treated orally with 2 g of erythromycin or 300 mg of roxithromycin for 14 days. Lung function tests (spirometry) were performed before the patients were discharged from the hospital. Then they were scheduled for clinical evaluation and spirometry at 2, 4, 6, 8, 12 weeks and at 3-month intervals during follow-up. Methacholine inhalation challenges (MIC) were performed on the 4^{th} week (the first PC_{20}) and the 12^{th} week (the second PC_{20}). Skin tests to common aeroallergens were taken on the 4^{th} week.

Twelve normal non-smoker subjects were also scheduled to perform MIC as a control group.

All subjects were asked to refrain from using caffeine and other drugs at least 12-24 hours before testing.

Procedure

MIC was performed at 09.00 hours by the same technician using the procedure as previously described.[14] Briefly, stock solution of methacholine in a citrate buffer was prepared under sterile condition for each concentration; 0 (diluent), 0.5, 1, 5, 10, and 25 mg/ml. Methacholine solution was aerosolized by using the Provocation-test I (Pari-Starnberg, Germany). Six millilitres of the solution were filled in an atomized nebulizer part of the equipment. It was estimated that 0.4 ml of the solution was used to produce 10 litres of the methacholine aerosol kept into a reservoir bag.

Before methacholine inhalation, baseline spirometric tests were performed with subjects standing using the Autospiror Discom-21 (Chest Corporation, Tokyo, Japan). At least three satisfactory and two reproducible spirometric maneuvers were required according to American Thoracic Society recommendation.[15] The largest FEV_1 value from acceptable maneuver was used for the baseline FEV_1. Then subjects inhaled diluent aerosol from the reservoir bag via slow inspiratory vital capacity maneuver until the bag was empty. Three minutes after the inhalation, the best spirometry was repeated. The largest FEV_1 from an acceptable maneuver was used as the post-diluent control value. After that, subjects inhaled a various increasing concentration of the methacholine aerosol (0.5, 1, 5, 10, and 25 mg/ml, respectively) from the reservoir bag. Spirometry was performed in a similar manner after inhalation of each concentration of methacholine, the largest FEV_1 from an acceptable maneuver was selected for analysis. If the decline of FEV_1 after any inhalation was more than 20% from the control value, the test would be terminated. At the end of the test, the subjects who had the decline of FEV_1 more than 15% would be administered with 4 puffs of salbutamol from a metered-dose inhaler via a spacer and spirometry was repeated 10 minutes later. Subjects were told about the possible late phase reaction occurring 6-8 hours after the test and they were discharged from the clinic after their FEV_1 had returned to within 10% of their baseline values.

Data analysis

Subjects were categorized as having AHR (positive test) if they showed a more than 20% decrease in FEV_1 (PC_{20}) from baseline after inhalation of diluent or any concentration of methacholine up to and including 25 mg/ml.[16]

Data were analyzed by the computer, using the Statistical Package for the Social Sciences program (SPSS). Results were presented as the mean ± standard deviation (SD). For comparison of the mean value, the *t*-test was used. The p value of less than 0.05 was considered statistical significance.

RESULTS

The results of this study are presented in Table 1, Table 2 and Fig.1. There were no statistically significant differences in age, sex, height, skin test response to common aeroallergens, and spirometric parameters among the normal subjects and the patients with post-*Mycoplasma pneumoniae* pneumonia (Table 1). There were no positive AHR in 12 non-smoker normal subjects. Everyone in this group was able to inhale all of each concentration of the methacholine up to 25 mg/ml without any effects. The maximum decreasing FEV_1, in this group was 5%.

Clinical characteristics of the patients with *M. pneumoniae* pneumonia were shown in Table 2. There were four males and eight females. Their ages ranged from 18 to 46 years with a mean of 27.5 ± 7.78 years. Patient number 4 had a past history of *M. pneumoniae* pneumonia the previous year. She was treated with 1 g of erythromycin for 10 days and she experienced chronic cough lasting 2-3 months. Patient number 10 had atopic tendency in her familial history but she had never had any allergic symptom before. The onset of fever was usually insidious ranging between 7 and 21 days (mean 13.9 ± 4.38)

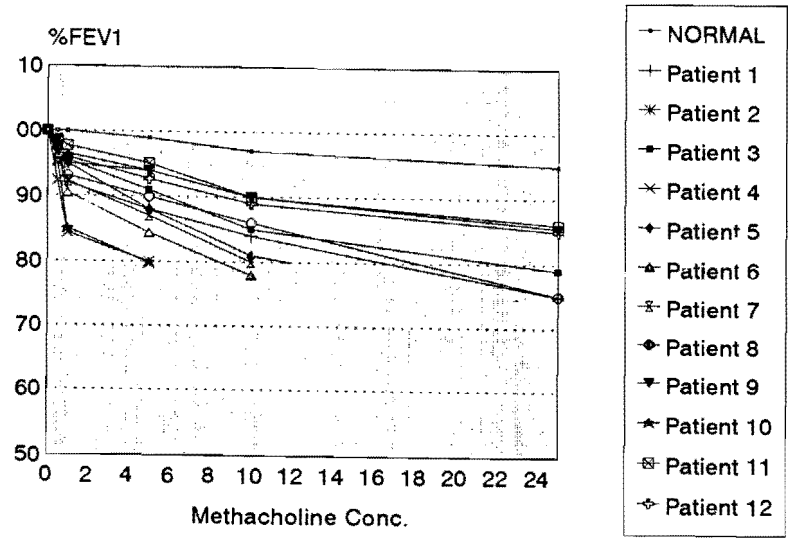

Fig. 1 Percentage of FEV1 decline from baseline observed wtih the methacholine challenge for normal subjects and post-*Mycoplasma pneumoniae* pneumonia patients. Average concentration of PC_{20} for post-*M. pneumoniae* pneumonia patients was 12 ± 6.44 mg/ml.

AHR = Airway hyperresponsiveness
BHR = Bronchial hyperresponsiveness
FEV_1 = Force expiratory volume at 1 second
FVC = Force vital capacity
MIC = Methacholine inhalation challenge
PC_{20} = Concentration of methacholine producing a decline in FEV_1 of 20% from baseline
Ab.Titer = Antibody titre
Bilat. = Bilateral infiltration
RLL = Right lower lobe infiltration
RUL = Right upper lobe infiltration
LLL = Left lower lobe infiltration

Table 1 Dermographic characteristics and lung function parameters of the patients compared to normal subjects

	Patients	Normal subjects	Value
1. Number	12	12	NS
2. Sex			
- Male	33%	33%	NS
- Female	67%	67%	NS
3. Age (yr)	27.5 ± 7.78	28.6 ± 8.91	NS
4. Height (cm)	159 ± 9.13	160.4 ± 6.72	NS
5. FVC (L)	3.37 ± 0.4	3.41 ± 0.6	NS
6. %FVC	94.4 ± 10.8	96.6 ± 9.0	NS
7. FEV_1 (L)	2.94 ± 0.75	2.99 ± 0.68	NS
8. %REV1/FVC	87.2 ± 10.2	87.6 ± 10	NS
9. Skin test	neg.	neg.	NS
10. 1st PC_{20} (mg/ml)	12.3 ± 6.44	>25	<0.05
11. 2nd PC_{20} (mg/ml)	20.1 ± 6.89	>25	<0.05

before admission. Most patients were diagnosed of having upper respiratory tract infection and most of them were administered with orally amoxycillin or roxithromycin for 4-5 days with slight improvement. The patients usually experienced with severe hacking cough with mild mucoid sputum as well as mild dyspnea. Eight patients (66%) had prolonged coughing for more than 3 weeks. Two (16%) were found to have wheezing on the chest examination during the phase of pneumonia. The pneumonic infiltrations usually involved the lower lung fields either unilateral or bilateral found on the chest reontgenography and they were resolved within 3-4 weeks after treatments. Fifty-eight percent of the cases had four-fold rising of mycoplasma antibody titres on the second samples of 1:160. Spirometry during the acute phase of pneumonia was usually found to be a restrictive pattern or a mixed type of restrictive and obstructive which returned to normal within 2-4 weeks during follow-up. All patients had negative skin tests to common aeroallergens.

At the time of the first MIC test, eight patients (67%); female 75% and male 50%, showed positive BHR with the average PC_{20} of 12.3 ± 6.44 mg/ml. Compared to normal subjects, the response to methacholine in the patients with post-*Mycoplasma pneumoniae* pneumonia was statistically different ($p<0.05$). on the second time of the test, six patients (50%) still had positive results with the average PC_{20} of 20.1 ± 6.89 mg/ml. Compare to the first time, the response to methacholine on the second time was statistically different ($p<0.05$).

Some clinical features seemed to be correlated with the positive AHR. These were duration of fever prior to diagnosis (mean 16.25 days in positive MIC group and 7.75 days in negative group), wheezing during the phase of pneumonia and prolonged coughing during the recovery phase. However, the number of the cases studied were

Table 2 Clinical characteristics of patients with *Mycoplasma pneumoniae*.

No	Sex	Age	Ht (cm)	Fever (d)	Wheez	Cough (wk)	X-ray	Ab titre	FEV_1	PC_{20}^1 (mg/ml)	PC_{20}^2 (mg/ml)
1	F	24	150	14	No	>3	Bilat.	1:160	2.36	18	25
2	M	21	172	7	No	<2	RLL	1:160	3.84	>25	>25
3	F	29	153	12	No	>4	LLL	1:80	2.08	22	>25
4*	F	46	151	21	Yes	>4	LLL	1:160	2.01	5	12
5	M	20	170	14	No	>4	RLL	1:160	4.02	12	25
6	F	22	157	20	No	>4	RLL	1:320	2.83	8	25
7	F	39	150	18	No	>3	Bilat.	1:160	1.98	10	25
8	M	18	180	15	No	<2	RLL	1:80	4.00	20	>25
9	M	31	156	7	No	<2	Bilat.	1:160	3.00	>25	>25
10**	F	28	159	16	Yes	>4	LLL	1:160	2.33	4	9
11	F	25	160	10	No	<2	RUL	1:80	3.37	>25	>25
12	F	27	161	7	No	<2	LLL	1:80	3.51	>25	>25
Mean		27.5	159	13.9		>3			2.94	12.3	20.1
SD		7.78	9.13	4.83		0.91			0.75	6.44	6.89

Ht = Height
d = Days
wk = Weeks
PC_{20}^1 = Concentration of methacholine producing a fall in FEV_1 of 20% from baseline on the first time of MIC.
PC_{20}^2 = PC_{20} on the second time of MIC.
* = This case had recurrent *M. pneumoniae* infection.
** = This case had atopic tendency.

too limited to say that this correlation was statistically significant. Two patients (numbers 4 and 10) had wheezing and prolonged coughing for more than 4 weeks. They responded to the methacholine at a low dose of 5 mg/ml on the time of the test. Patient number 10 still had the positive test at the low dose of 9 mg/ml on the second time. These two patients were diagnosed as having bronchial asthma for the first time and they required treatments with bronchodilators and corticosteroids.

Percentages of the decline of the mean of FEV_1 from baseline in normal subjects and the FEV_1 of each patient are presented in the Fig.1.

DISCUSSION

Several studies have suggested that respiratory tract viruses and *M. pneumoniae* are important in precipitation of asthma. Huhti and coworkers[17] reported that 67 patients with asthma experienced a total of 142 asthmatic attacks that required hospitalization, 27 (19%) episodes developed in association with concommitant mycoplasma or viral infections. Seggev and associates[18] found that in a group of 95 adult patients with asthma, 20 (21%) had evidence of a recent mycoplasma infection during asthmatic exacerbation. Gil *et al.*[12] reported isolation of *M. pneumoniae* from asthmatic patients in higher percentage (24%) than controls (5%) and suggested it could possibly have induced wheezing.

In a follow up study by Mok and associates[10] of 50 children with *M. pneumoniae* respiratory tract infection, five developed clinical signs of asthma for the first time. However, all five children had a familial and personal history of atopy. Therefore, in children with atopic tendency, mycoplasma infection might trigger allergic sensitization. Petrovski[20] had documented six patients with *M. pneumoniae* infection who had then developed a post-infection asthma syndrome that had required the treatment with bronchodilators. Recently Yano *et al.*[13] reported a patient who had previously been admitted with *M. pneumoniae* pneumonia, then developed an initial onset of asthma with positive immediate skin test to *M. pneumoniae* antigen in addition to multiple skin tests. They also demonstrated IgE antibody specific to *M. pneumoniae* and a bronchial inhalation challenge with *M. pneumoniae* antigen yielded a positive result. It seemed that *M. pneumoniae* was able to cause an asthmatic attack in previously healthy adults.

In our study, the clinical features of almost all patients with *M. pneumoniae* pneumonia were not much different from previous reports in the literature,[21, 22] except for two patients who developed wheezing and asthmatic attack during acute phase of pneumonia. Many patients had prolonged coughing for several weeks after recovery from mycoplasma pneumonia which was usually recognized in the previous reports. Eight patients (67%) had BHR to methacho-

line challenge at the 4th week after mycoplasma infection. This result would confirm that *M. pneumoniae* was able to cause AHR and asthmatic attacks in normal persons. However, whether it would cause chronic asthma or not, this would be confirmed by further study. Sabato *et al.*[23] reported persistent spirometric abnormalities at 3 years' follow-up in children with proven *M. pneumoniae* but no asthmatics were detected. Todisco *et al.*[24] reported three-year follow-up of respiratory function in 13 school-age children with post-viral and mycoplasma pneumonia. They found that a mixed type transient ventilatory defect with large and small airway involvement was observed during the acute phase of the pneumonias. Residual smalll airway involvement was found over the next 12 months. but no pulmonary function abnormalities were presented after 3 years. However, in the case reported by Yano *et al.*,[13] an AHR to methacholine was still demonstrated even 2 years after the initial onset of his illness.

A possible mechanism of the development of BHT and asthma by *M. pneumoniae* may be somewhat similar to that in viral infection. The essential features of *M. pneumoniae* respiratory tract infection are similar to many respiratory viral infections such as, RSV, influenza, and rhinovirus. There are many sites of involvement in the respiratory tract from nasopharynx to alveolus, especially in the airways causing tracheobronchitis and bronchiolitis.[25] *M. pneumoniae* is able to cause airway inflammation with sloughed epithelial cells and exposed free nerve ending of cholinergic fibres and accentuated irritant receptor. It was possible that during viral infection T helper cells are stimulated to release interleukin-4 which may have an important role in stimulating IgE production from B lymphocytes.[26] As mycoplasma is antigenically similar to some viruses, it could stimulate IgE production. The susceptible patients, such as those having recurrent infection or atopic tendency, who had infections mainly involving the tracheobronchial tree with severe inflammation and epithelial damage would have severe and prolonged coughing with the wheezing of the asthmatic syndrome. It is also possible to postulate that subsequent sensitization of these inflammed airways is caused by other allergens such as house dust mites or other irritants such as air pollutants which are able to produce more and persistent BHR, resulting in chronic asthma.

M. pneumoniae was able to induce a type I immunologic response in the infected patients. Tipirneni and coworkers[27] detected IgE antibodies to *M. pneumoniae* in 5 of 152 patients with asthma and other atopic diseases. Shimizu *et al.*[28] studied immunoglobulin levels and the number of eosinophils in the peripheral blood and BHR in children with *M. pneumoniae* pneumonia. They found that level of total serum IgE was higher in acute phase and decreased gradually. The number of eosinophils in the peripheral blood increased from the acute to convalescent phases. Moreover, they found that BHR increased after mycoplasma pneumonia and the AHR persisted for over one month in two non-asthmatic children. Yano *et al.*[13] reported that serum specific IgE was detected in 57% of 14 patients with mycoplasma pneumonia. They also reported previously that there would be a close relationship between the presence of *Mycoplasma*-specific IgE and chronic cough lasting 3 months or more after mycoplasma pneumonia.[20]

In conclusion, we have demonstrated the presence of BHR in adult patients with postmycoplasma pneumonia. The BHR may be transient or persistent, this would be clarified in further study. It might be postulated that prolonged or recurrent infections with *M. pneumoniae* or secondary or concomitant viral infections or secondary sensitization with other allergens or irritants are able to cause persistent BHR and asthma. We suggest that *M. pneumoniae* respiratory tract infections should not be overlooked. As the organism can be treated with erythromycin or roxithromycin it would be essential to test for it. Although the organism can be easily treated, if the dosage and the duration of the treatment are not adequate, the infection may be prolonged and it may result in the development of BHR and asthma.

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