◎原 著

Relationship between bronchial hyperresponsiveness and nasosinus lesions in patients with bronchial asthma

Takashi Mifune, Shingo Takata, Makoto Okamoto, Hirofumi Tsugeno, Kozo Ashida, Seishi Harada, Fumihiro Mitsunobu, Yasuhiro Hosaki, Yoshiro Tanizaki, Mine Harada*

Department of Medicine, Misasa Medical Branch, Okayama university Medical School
*The second Department of Medicine, Okayama University Medical School

Abstract : Pathological changes of nasosinus occur often in subjects with bronchial asthma. Coexisting nasosinus lesion may affect pathophysiology of lower respiratory tract in asthmatics. The extent of nasal and sinus lesion was quantified in 17 patients with bronchial asthma, and their relationships to atopic status, asthma severity and bronchial hyperresponsiveness were evaluated in this study. Opacification degree of maxillary sinuses and nasal mucosa thickening were quantified using CT scans. The opacification degree was evaluated as (total opacification area)/(total maxillary sinus area). Although the opacification degree of maxillary sinuses in atopic patients showed no significant difference compared with that in non-atopic patients, maximum nasal mucosa thickening in atopic patients had a significant difference compared with that in non-atopic patients ($p=0.028$). In severe asthmatics, the opacification degree of maxillary sinuses was significantly more prominent compared with those in moderate and mild asthmatics ($p=0.0005$, $p=0.036$, respectively). Significantly marked nasal mucosa thickening was recognized in mild asthmatics compared with that in moderate asthmatics ($p=0.0462$). Regarding bronchial hyperresponsiveness, a significant correlation between Dmin and the opacification degree of maxillary sinuses was observed ($rs=-0.551$, $p=0.0276$). Nasal mucosa thickening had no correlation with bronchial hyperresponsiveness. The results suggest that sinusitis may affect bronchial hyperresponsiveness and asthma severity. Treatment of sinusitis may lead to improvement of asthma symptoms.

Key words : bronchial asthma, sinusitis, CT findings, hyperresponsiveness

The association of asthma with nasosinus disease has been recognized more than a century ago. Since 1980, several studies have documented that severe asthma improved after coexisting sinusitis was effectively treated either medically or surgically[1,2]. These findings suggest coexisting chronic sinusitis is a precipitating factor for bronchial asthma.

However, the influence of nasosinus disease on pathogenesis of asthma is poorly understood. Some investigators have shown the reduction in asthma symptoms and improvement in bronchial hyperresponsiveness during pollen seasons with the use of intranasal corticoids[4,5]. These data suggest that there may be a relationship in inflammatory events between the upper and lower airways, and that nasosinus disease may affect asthma exacerbation.

In the present study, the opacification of maxillary sinuses and nasal mucosa thickening were quantified in the patients with bronchial asthma, and the correlation between the extent of nasosinus lesion and bronchial hyperresponsiveness was evaluated.

Methods

Subjects characteristics

The subjects in this study were 17 patients with asthma (13 females and 4 males, mean age 51.6 years ranged from 25 to 73 years) (Table 1). Asthma was defined according to the definition of the Guidelines for the Diagnosis and Management of Asthma[3]. All subjects had experiences of episodic symptoms of wheeze, coughing, and dyspnea, and were being treated with inhaled β-adrenergic agonists for symptomatic relief. None of subjects had received surgical treatments of sinusitis. Clinical features were evaluated by asthma type, disease severity and bronchial hyperresponsiveness. Serum IgE level and IgE antibodies against common aeroallergens were examined by radioimmunosorbent test (RIST) and radioallergosorbent test (RAST), respectively. Patients with positive IgE RAST scores and/or IgE level more than 250 IU/ml were assessed as atopic. Disease severity was evaluated according to the criteria for asthma severity of the Guidelines for the Diagnosis and Management of Asthma[3]. Ten

Table. 1 Clinical and laboratory data in 17 asthmatics

Subject No.	Sex/Age (years)	atopy	Pulmonary function				
			FVC liters	FVC,% predicted	FEV1 liters	FEV1,% predicted	FEV1/VC %
1	F/25	+	3.17	105.3	2.60	88.1	82.0
2	M/58	−	3.20	91.2	2.03	72.8	67.2
3	F/51	−	2.80	107.6	2.33	101.9	83.2
4	M/32	+	5.16	125.5	3.39	88.5	65.7
5	F/62	+	2.40	101.3	1.55	82.9	64.6
6	M/38	+	4.48	109.0	2.56	67.4	57.1
7	F/61	−	2.88	127.0	2.22	131.4	77.1
8	F/54	−	3.52	141.8	2.66	129.5	75.6
9	F/55	+	3.00	118.1	2.51	106.7	83.7
10	M/45	+	2.35	94.4	1.79	86.9	76.2
11	F/66	+	2.37	63.9	1.73	54.7	73.0
12	F/73	−	1.45	64.7	0.79	48.2	54.5
13	F/64	+	1.76	84.6	1.16	85.9	65.9
14	F/26	−	2.19	99.3	1.53	97.0	69.9
15	F/47	+	2.67	87.3	2.50	82.5	93.6
16	F/42	+	4.02	130.5	2.20	80.6	57.4
17	F/63	−	1.76	76.9	1.14	66.3	64.8

patients were regarded as atopic, and 7 cases were non-atopic. Regarding asthma severity, 4 subjects had mild, 10 had moderate and 3 had severe asthma.

Evaluation of bronchial hyperresponsiveness

Bronchial hyperresponsiveness to inhaled methacholine was measured with a device (Astograph-TCK-6100H, Chest, Tokyo, Japan) that displays a respiratory resistance (Rrs) dose-response curve measured by the forced oscillation method during tidal breathing with continuos inhalation of aerosolized methacholine solution. Dmin (the minimum dose of methacholine) was obtained as the cumulative dose at the point where respiratory conductance (reciprocal of Rrs) starts to decrease linearly.

CT evaluation

Computed tomographic (CT) scans of nasal cavity and maxillary sinuses were performed in all patients with a Toshiba Xpeed (Toshiba medical, Tokyo, Japan). All subjects had treated with antibiotics and decongestants for 1 week before CT scans. The eight contiguous 5.0mm horizontal scans were obtained from the level of the 2.0cm below nasal-meatal lines. Scans were performed at 120kVp and 300mA without contrast. The CT scans were photographed at a window level of 20 HU and a window width of 350 HU. Slices viewing maxillary sinuses were selected from eight scans. Four to seven slices viewing maxillary sinuses were obtained. These images were transferred to a Macintosh computer(Apple Computers, Cupertino, Calif., USA)with imagescanner (model ES－8000, EPSON, Tokyo, Japan). To obtain absolute measurements of maximum thickening of nasal mucosa and opacification degree of maxillary sinuses, the measurements were normalized using the scale on the CT image. Maxillary sinus area (M) in mm^2 and opacification area (O) in mm^2 in each view were determined. If maxillary sinus wall discontinued for a short distance, maxillary wall was assumed to continue linearly. In the slice of long discontinuation of the maxillary wall, the slice was excluded. The opacification degree of maxillary sinuses was calculated as (total O／total M)×100. The analyses were performed using the public domain NIH image program (developed at the U. S. National Institutes of Health and available on the Internet at http : ／／ rsb. info. nih.gov／nihimage／).

Data analysis

All data were presented as means±SD. The unpaired t test was used to examine the difference in atopic status and in asthma severity. Spearman's correlation coefficient by ranks was used to examine the relationships between the nasosinus lesion and bronchial hyperresponsiveness (Dmin). A p value of$<$0.05 was regarded as significant.

Results

The opacification degree of maxillary sinuses was 11.4±14.3% in atopic, and 10.9±6.23% in non-atopic patients. There were no significant differences between the two types ($p=0.93$). Significant differences were observed in nasal mucosa thickening between atopic (8.53±1.36mm) and non-atopic subjects (7.17±1.17mm) ($p=0.028$) (Fig. 1).

Maxillary mucosal lesions were different according to disease severity. The opacification degree of maxillary sinuses was more extensive in subjects with severe asthma than other two groups (7.2±8.6% in mild asthma group, 7.1±5.4% in moderate asthma group and 30.0±12.3% in severe asthma group). The difference in opacification degree was

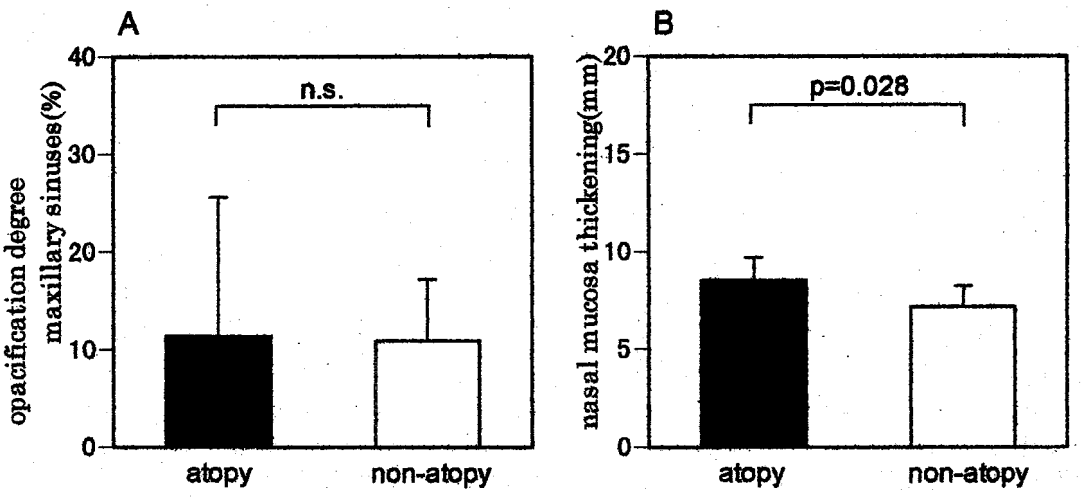

Fig. 1. Correlation between atopic status and the opacification degree of maxillary sinuses (A), and between atopic status and nasal mucosal thickening (B). There was a siginificant difference of nasal mucosa thickening between atopic and non-atopic subjects.

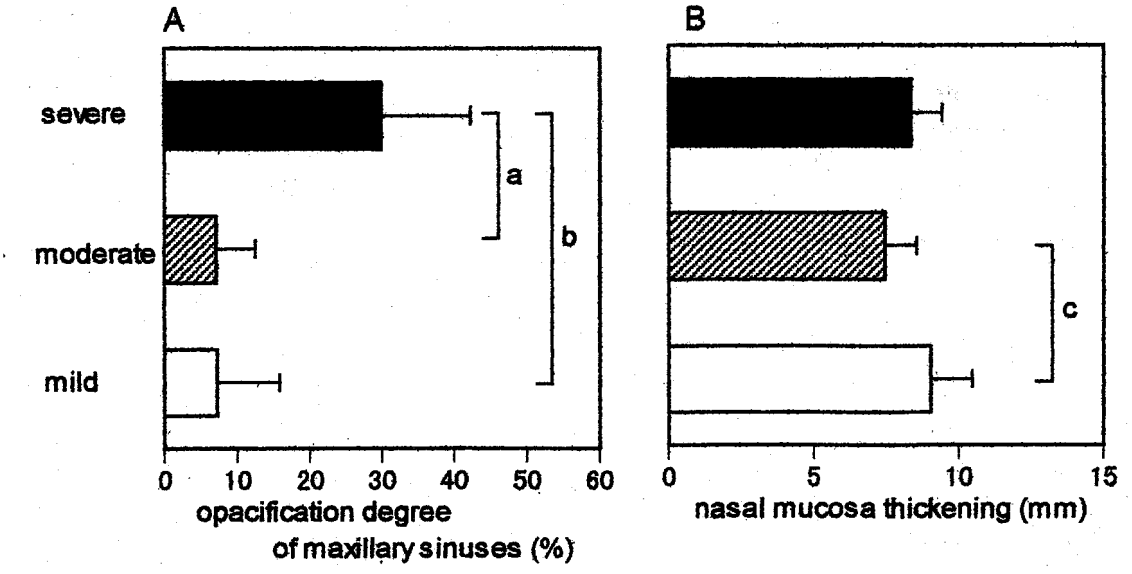

Fig. 2. Correlation between asthma severity and the opacification degree of maxillary sinuses (A) and between asthma severity and nasal mucosa thickening (B). There was a siginificant difference of the opacification degree of maxillary sinuses between severe and moderate asthmatics (a ; $p=0.0005$), andbetween severe and mild asthmatics (b ; $p=0.036$). There was a siginificant difference of nasal mucosa thickening between moderate and mild asthmatics (c ; $P=0.0462$).

significant between mild asthma group and severe asthma group (p=0.034), and between moderate asthma group and severe asthma group (p=0.0005). (Fig. 2A). Nasal mucosa thickening was 9.0±1.5mm in subjects with mild asthma, 7.4±1.1mm in those with moderate asthma, and 8.3±1.1mm in those with severe asthma. Significant differences were observed between moderate and mild asthmagroup (p=0.046) (Fig. 2B).

Regarding bronchial hyperresponsiveness, the opacification degree of maxillary sinuses showed significant negative correlation with Dmin (rs=−0.551, p=0.0276). On the other hand, nasal mucosa thickening showed no significant correlation with Dmin (rs=0.09, p=0.72) (Fig.3).

Discussion

It is often suggested that important relationship may exist between upper and lower airways. In patients with viral upper respiratory tract infections, bronchial hyperresponsiveness may be increased[6]. Improvement in asthma scores were reported after treatment with intranasal glucosteroids in patients with allergic rhinitis and concurrent asthma, but not after treatment with intranasal cromolyn[7]. Furthermore, recent studies revealed that patients with chronic sinusitis had bronchial hyperresponsiveness. Bucca et al. has demonstrated that some patients with chronic sinusitis had bronchial hyperresponsiveness during sinusitis exacerbation. Some of their patients had cough and wheeze, suggesting the coexistence of lower airway disease[8]. Okayama and colleagues have showed that patients with chronic sinusitis who had normal lung functions without any pulmonary symptoms had bronchial hyperresponsiveness and bronchial hyperresponsiveness significantly decreased after the surgical

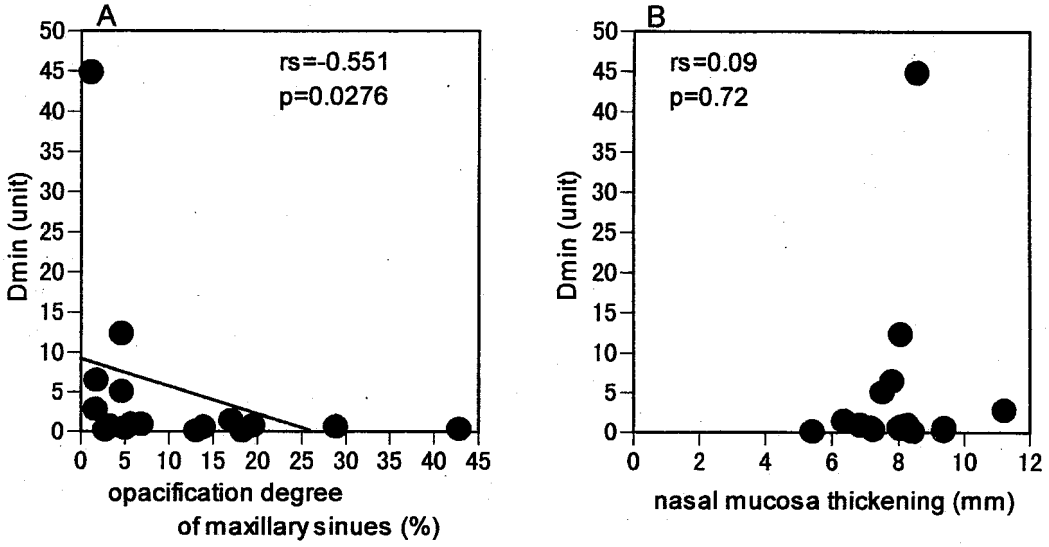

Fig. 3. Correlation bronchial hyperresponsiveness and nasosinus lesion. There was a siginificant correlation between Dmin and opacification degree of maxillary sinuses (a). Nasal mucosa thickening showed no correlation with Dmin.

treatment of chronic sinusitis[9]. These data suggest that sinusitis may affect bronchial hyperresponsiveness in subjects with sinusitis. In subjects with bronchial asthma, we showed a significant negative correlation between the extent of maxillary sinus lesions and bronchial hyperresponsiveness in this study. Our data have shown that asthmatics with marked sinusitis might reveal increased bronchial hyperresponsiveness. And significant marked lesion in maxillary sinuses was observed in subjects with severe asthma in our study. This result suggest that sinusitis may have influence on exacerbation of asthma severity.

On the other hand, nasal mucosal thickening have shown no correlation with bronchial hyperresponsiveness, and had marked lesion in mild asthmatics in our study. Our results suggest that nasal mucosa disease is not likely to affect the pathophysiology of bronchial asthma. However, several studies have shown that treatments for allergic rhinitis affected asthma symptoms[10, 11]. Watson and colleagues reported that asthma symptoms and bronchial hyperresponsiveness to methacholine improved significantly after intranasal beclomethasone dipropionate for perennial rhinitis. As an adjunct to the study, they performed a radiolabeled deposition study of the beclomethasone aerosol and found that less than 2% of the drug was deposited into the chest area[4]. These studies indicate that nasal mucosa lesion may affect asthma pathophysiology. Although nasal mucosa thickening had no correlation with bronchial hyperresponsiveness in our results, other factors, such as nasal discharge, may affect bronchial hyperresponsiveness. We evaluated the maximum nasal mucosa thickening as a factor showing severity of nasal mucosa lesion. Other assessments of nasal mucosa lesion might have been needed to evaluate the relationship with bronchial hyperresponsiveness.

The mechanism that upper respiratory lesions affect lower respiratory lesions is unknown by now. Several mechanisms were proposed. The inflammatory cells or mediators in post-nasal discharge aspirating into lower respiratory tract could exacerbate bronchial hyperresponsiveness. In a rabbit model, increased bronchial hyperresponsiveness associated with sinusitis was demonstrated[12]. Another proposed mechanism is the increased oral inhalation of cold and dry air caused by nasal obstruction. However, this mechanism can not fully explain the present findings that the extent of sinus lesion have relationship with bronchial hyperresponsiveness, and nasal mucosa thickening had no correlation with bronchial hyperresponsiveness. Another mechanism is a nasopulmonaly reflex. The cholinergic nervous system irritated by sinus or nasal inflammatory change induce a secondary increase in pulmonary airway resistance. But mechanism that nasopulmonary reflex induce bronchial hyperresponsiveness is not fully explained. Thus, aspiration of post-nasal discharge is most likely to affect lower bronchial condition. But further studies are needed to clarify the mechanism that upper respiratory lesion affects lower respiratory lesion.

In conclusion, this study suggests that sinusitis may affect on asthma severity and bronchial hyperresponsiveness. Therefore, therapy for coexisting sinusitis is important in subjects with bronchial asthma.

References

1. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. 1984; Pediatrics : 73 : 526−529.
2. Slavin RG. Relationship of nasal disease and sinusitis to bronchial asthma. 1982; Ann Allergy : 49 : 76−79.
3. Mings R, Friedman WH, Linford P, Slavin RG. Five year follow-up of the effects of bilateral intranasal sphenoethmoidectomy in patients with sinusitis and asthma 1988; Am J Rhinol : 71 : 123−132.
4. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. 1993; J Allergy Clin Immunol : 91 : 97−101.
5. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. 1992; J Allergy Clin Immunol : 90 : 250−256.
6. Eggleston PA. Upper airway inflammatory diseases and bronchial hyperresponsiveness. 1988; J Allergy Clin Immunol : 81 : 1036−1041.
7. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, Marcoux JP. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. 1987; Mayo Clin Proc 1987 : 62(2) : 125−134.
8. Senior BA, Kennedy DW. Management of sinusitis in the asthmatic patient. 1996; Ann Allergy Asthma Immunol : 77 : 6−15.
9. Okayama M, Iijima H, Shimura S, Shimomura A, Ikeda K, Okayama H, Shirato K. Methacholine bronchial hyperresponsiveness in Chronic sinusitis 1998; Respiration : 65 : 450−457.
10. Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma 1997; J Allergy Clin Immunol : 100 : 781−788.
11. Corren J. Allergic rhinitis and asthma: how important is the link? 1997; J Allergy Clin Immunol : 99 : 781−786.
12. Brugman SM, Larsen GL, Henson PM, Honor J, Irvin CG. Increased lower airways responsiveness associated with sinusitis in a rabbit model. 1993; Am Rev Respir Dis : 147 : 314−320.

気管支喘息症例における気道過敏性と鼻腔・副鼻腔疾患の関係に関する検討

御舩尚志，高田真吾，岡本　誠，柘野浩史，芦田耕三，原田誠之，光延文裕，保崎泰弘，谷崎勝朗，原田実根*

岡山大学医学部附属病院三朝分院内科
*医学部第二内科

鼻腔・副鼻腔疾患はしばしば気管支喘息症例に合併が認められ，喘息症例の下気道病態に影響を及ぼしている可能性が考えられる。今回，気管支喘息17例において，CTを用いて上顎洞の不透明化率・鼻腔粘膜肥厚を計測し，アトピー性の有無，喘息の重症度，気道過敏性との関係を検討した。上顎洞不透明化率は全上顎洞面積の総計に対する不透明化領域面積総計として計算を行った。上顎洞不透明化率はアトピー性の有無で差は認められなかったが，鼻腔粘膜はアトピー性喘息症例で有意に肥厚していた。重症気管支喘息における上顎洞不透明化率は，中等症および軽症喘息症例に比べ有意に高値であった。鼻腔粘膜肥厚は中等症喘息症例に比べ，軽症症例で有意に肥厚していた。気道過敏性（Dmin）は上顎洞不透明化率とのあいだに弱い負の相関が認められた（$rs=-0.551$, $p=0.0276$）．鼻粘膜肥厚と気道過敏性は相関が認められなかった。今回の結果から副鼻腔病変が気道過敏性・喘息重症度に影響を及ぼしている可能性が考えられ，副鼻腔疾患の治療により喘息症状の改善に繋がる可能性が考えられた。

索引用語：気管支喘息，副鼻腔炎，ＣＴ所見，気道過敏性