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Pathophysiological condition of the nose of asthmatic children with subclinical nasal allergy

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SUMMARY

Nasal mucociliary transport time, nasal hypersensitivity to histamine, the number of basophils and eosinophils in the superficial mucous layer of the inferior turbinate, and the amount of histamine in the nasal secretion were measured in the asthmatic children with subclinical nasal allergy (asthma group). These results were compared with those in nasal allergic patients with nasal symptoms (nasal allergy group). Saccharin time did not show any significant difference between the asthma and nasal allergy group. The threshold for nasal hypersensitivity to histamine was significantly higher in the asthma group than in the nasal allergy group. Accumulation of basophils and eosinophils in the superficial mucous layer of the inferior turbinate were observed in both groups. There was a statistical correlation between the number of basophils and the number of eosinophils in the superficial nasal mucosa in the nasal allergy group, but not in the asthma group. These data suggest that basophilic cell function in the superficial mucous layer in the nose is of greater significance in the development of nasal symptoms in response to nasal allergy than either mucociliary activity or nasal mucosal hypersensitivity to histamine.

INTRODUCTION

There is little doubt that mediators released from mast cells play an integral part in the pathogenesis of nasal allergies. The sequence of events in the pathogenesis of these conditions is believed to be inhalation of antigen, deposition of antigen on the nasal mucosa and interaction of antigen with mast cell-bound antibody. The subsequent release of chemical mediators causes clinical nasal symptoms. However, the interrelationship between a pathophysiological condition of the nasal mucosa and the development of clinical nasal symptoms remains obscure in atopic and in sensitized patients.

We have found that 60% of asthma combined with nasal allergy, and 90% of asthmatic patients with nasal allergy do not have typical nasal symptoms (Ukai et al.,

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1981). In addition, we have shown that the skin test, nasal smear, response to nasal provocation and the nasal signs in the asthmatic children without nasal symptoms were little different from those in nasal allergic children with nasal symptoms (Ukai et al., 1981).

Asthmatic children with subclinical nasal allergy, which means nasal allergy without typical nasal symptoms, provide an excellent model for investigating the mechanism involved in the development of nasal symptoms of nasal allergy. This article describes the pathophysiological condition found in the nose of asthmatic children with subclinical nasal allergy.

MATERIALS AND METHODS

Fifty-one asthmatic inpatients (29 males and 22 females) with subclinical nasal allergy (asthma group) in Mie National Hospital, who satisfied the criteria for the definition of asthma, were studied. All of them showed a positive skin test and nasal provocation to house dust. Their ages ranged from 4 to 16 years with an average age of 9.6 years. They had been receiving desensitized immunotherapy against house dust for at least one year. The age at onset of asthma was under three years in most of the patients. The mean value of FEV_1 in this group was 67.9% + 22.0. This group was compared with 54 nasal allergic patients (27 males and 27 females) with typical symptoms of nasal allergy with a positive skin test and nasal provocation to house dust extracts (nasal allergy group). Their ages ranged from 6 to 16 years with an average of 11.2 years. None of the subjects had suffered from asthma or other atopic diseases. They had also been receiving desensitized immunotherapy against house dust for one year. The average age at onset of nasal allergy was 6 years. Eleven subjects (6 males and 5 females), between the ages of 4 to 14 years, without a history of atopic disease (normal control group), who were admitted to our clinic for tonsillectomy, were selected as a non-allergic control group.

The mucociliary transport time was measured by the saccharin technique described by Sakakura et al. (1983). Histamine was measured by means of a modification of the fluorometric method. Nasal secretions were obtained by forcibly blowing into a plastic drape. All secretions were aspirated into a test tube, to the last drop, and frozen at $-60\,^{\circ}C$ for analysis for histamine content later. As the coefficient of variation of the triplicate samples from each subject was quite small, the histamine value is given as an average of the three samples. The degree of nasal mucosal hypersensitivity was measured using histamine hydrochloride. Ten microliters of serial tenfold dilution starting from 10^2 µg/ml up to 10^5 µg/ml were used. Each dilution was applied to the anterior part of each inferior turbinate using a dropper. Application was stopped whenever an attack of sneezing occurred within one minute after instillation. Specimens for measuring the number of basophilic and eosinophilic cells in the superficial mucous layer of the infe-

rior turbinate were obtained by scratching the anterior part of the inferior turbinate. The samples were immediately smeared onto the slide, air-dried, stained with Hansel's solution for 70 sec and examined under a light microscope. The classification and gradation of numbers of eosinophilic and basophilic cells described by Okuda (1977) were used.

RESULTS

Saccharin time on the nasal mucosa

In eleven subjects in the asthma group (19%) and in three subjects in the nasal allergy group (17%) mucociliary transport time was >30 min, whereas it was <30 min in all the control subjects (Figure 1). The mean mucociliary transport time was 18.4 ± 7.9 min in the asthma group, 14.8 ± 9.4 min in the nasal allergy group and 14.9 ± 6.1 min in the control group. There was no statistical difference between the three groups.

Histamine levels in nasal secretion

The amount of histamine found in each subject showed considerable variation

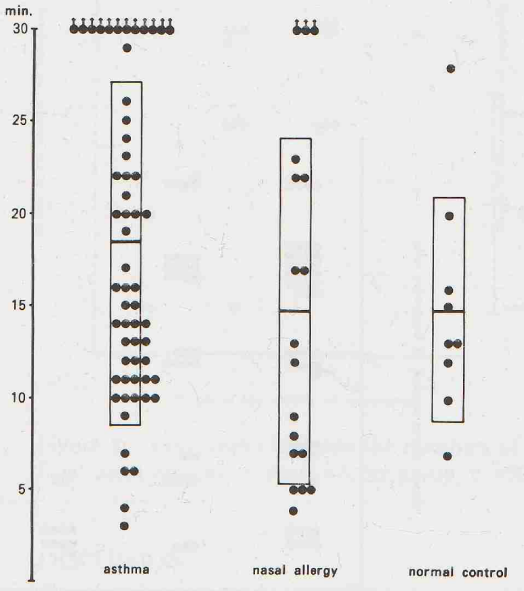

Figure 1. Saccharin time on the nasal mucosa.

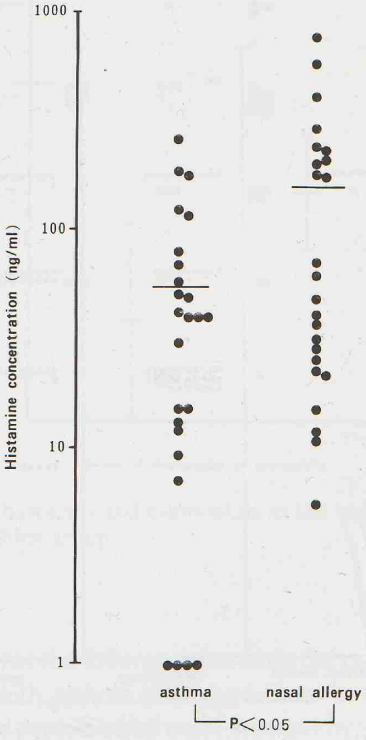

Figure 2. Concentration of histamine in the nasal secretion.

(Figure 2), ranging from below 5 up to 265 ng/ml for the asthma group, and from below 5 up to 768 ng/ml for the nasal allergy group. Five of the asthma group and one of the nasal allergy group had a histamine level below 5 ng/ml in their specimens. The geometric mean of the histamine levels in the asthma group was 54 ng/ml and in the nasal allergy group 154 ng/ml. This difference was significant using the Mann-Whitney U test ($Z = 2.01$, $p < 0.05$).

Nasal mucosal hypersensitivity to histamine

The end point was 10^5 μg/ml in 7 (63%) of the control group, 10^3 μg/ml (50%) of the nasal allergy group, and 10^4 μg/ml in 18 (35%) of the asthma group. The mean of the logarithm of threshold to histamine was 4.04 ± 1.14 in the asthma group, 3.53 ± 1.03 in the nasal allergy group and 4.82 ± 0.60 in the control group. As shown in Figure 3, the threshold for nasal hypersensitivity to histamine in the asthma group was significantly higher than in the nasal allergy group ($p < 0.025$), but significantly lower than in the control group ($p < 0.005$).

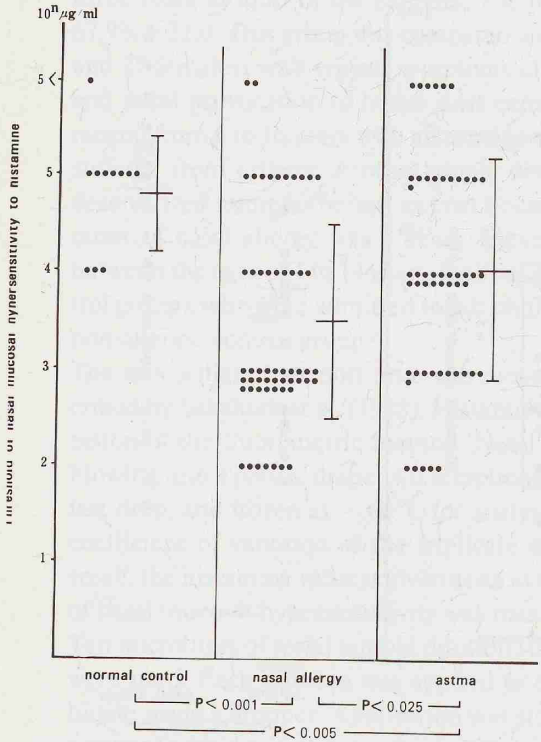

Figure 3. Nasal mucosal hypersensitivity to histamine.

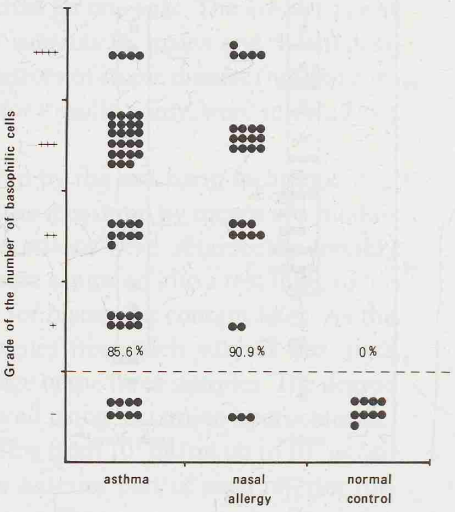

Figure 4. The numbers of basophilic cells in the superficial mucous layer of the inferior turbinate.

Number of basophilic cells in the superficial mucous layer of the inferior turbinate
Basophilic cells in the superficial mucous layer of the inferior turbinate were observed in 44 of the asthma group (85.6%) and in 26 of the nasal allergy group (90.0%), but in none of the control group. This accumulation of basophilic cells was graded (+ + +) in 51% of the asthma group, in 59% of the nasal allergy group, and in none of the control group (Figure 4).

Correlation between the numbers of basophils and of eosinophils in the superficial nasal mucosa
There was a statistical correlation between the numbers of basophils and eosinophils in the superficial mucous layer of the inferior turbinate in the nasal allergy group ($p < 0.01$) (Figure 5a), but not in the asthma group (Figure 5b). There was also a statistical correlation between the number of basophils in the superficial mucous layer of the inferior turbinate and the number of eosinophils in the nasal secretion in the nasal allergy group, but not in the asthma group.

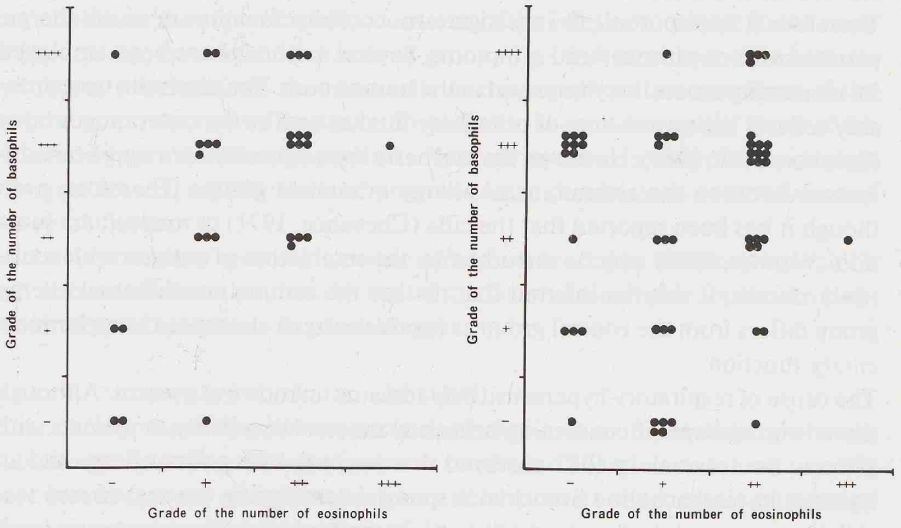

Figure 5. Correlation between the numbers of basophils and eosinophils in the superficial nasal mucosa. a. nasal allergy group, b. asthma group.

DISCUSSION
Our results summarized in Table 1 suggest that the difference between the nasal symptoms in the subclinical nasal allergy with asthma group and those in the nasal allergy without asthma group might be explained by nasal mucosal hypersensitivity and the consequent amount of histamine released from the basophilic cells.

Table 1. Mechanisms involved in the development of nasal symptoms of nasal allergy.

	asthma group	nasal allergy group
nasal symptoms	-	+ + or + + +
saccharin time	within normal range	within normal range
threshold of hypersensitivity against histamine	high	low
amount of histamine in nasal secretion	low	high
the number of basophilic cells in superficial nasal mucosa	increased	increased
correlation between basophils and eosinophils in superficial nasal mucosa	no	yes

After antigen is deposited on the surface of the mucous blanket in the nose, it may have to penetrate through this mucous barrier before it can interact with mast cell-bound antibody, since basophilic cells are not always present on the surface. Therefore it is important to investigate mucociliary function in nasal allergic patients with or without nasal symptoms. Several methods have been employed for measuring mucociliary transport in the human nose. The saccharin time probably reflects the transit time of periciliary fluid as well as the outer mucus layer (Sakakura et al., 1983). However, the saccharin time did not show a significant difference between the asthma, nasal allergy or control groups. Therefore, even though it has been reported that the cilia (Chevance, 1971) or mucociliary function (Wanner, 1979) may be disturbed by the interaction of antigen with sensitized mucosa, it may be inferred that neither the asthma nor the nasal allergy group differs from the control group as regards antigen clearance through mucociliary function.

The cause of respiratory hypersensitivity remains unknown at present. Although there is no agreement concerning bronchial mucosal sensitivity in patients with asthma, Boulet et al. in 1983 observed that patients with pollen allergy had an increase in methacholine bronchial responsiveness during the season and seasonal symptoms did relate to an increase in methacholine responsiveness in all subjects.

In this study, nasal mucosal sensitivity to histamine was significantly increased in the nasal allergy group compared to the asthma group. Such data suggest that the organ with typical clinical symptoms has increased mucosal sensitivity.

Using the blowing method, the mean amount of histamine in nasal secretions in the allergy group was significantly higher than that found in the asthma group. Although the levels of histamine in nasal secretions collected by the nasal lavage method were higher in nasal non-allergic than in nasal allergic subjects (Eggleston et al., 1978), our data show a close correlation between histamine content

(obtained by the blowing technique) and nasal symptoms. It is possible that histamine obtained by the nasal lavage method may be rapidly metabolized in the nasal allergy group or a large amount of histamine may still remain unmetabolized in nasal secretions obtained by the blowing method. We observed an accumulation of basophilic cells in the superficial mucous layer of the inferior turbinate in the nasal allergy and asthma groups, but not in the control group. Several studies have been devoted to the numbers of basophilic cells found in nasal mucosa, but no general agreement has been achieved. The number of mast cells tends to decrease during acute allergic reactions but increases during chronic inflammatory states (Hlavacek and Lojda, 1963). Hastie et al. (1979) reported an increased number of basophilic cells in allergic nasal mucosa, supporting our data. On the other hand, Mygind et al. (1974) compared 16 patients with perennial rhinitis with 16 normal controls, and found no differences in the number of mast cells in the nasal submucosa. The number of mast cells on the mucosal surface or in the superficial mucous layer may be of significance.

There was a significant correlation between the number of basophils with that of eosinophils in the superficial mucous layer of the inferior turbinate in the nasal allergy group, but not in the asthma group. This indicates that the chemical mediators released from the mast cells in the superficial mucous layer of the asthma group are not sufficient for eosinophilic chemotaxis unlike those of the nasal allergy group, although patients in both groups were sensitive to house dust allergen, reacted equally to nasal provocation, and display an accumulation of basophilic cells.

In conclusion, nasal mucosal hypersensitivity, evidenced by increased basophilic cell release of histamine, may be one of the factors responsible for the development of nasal symptoms in nasal allergy.

RÉSUMÉ

Chez deux groupes de patients, enfants asthmatiques souffrant d'allergie nasale subclinique (groupe asthme), et patients souffrant d'allergie nasale avec symptômes nasaux (groupe allergie nasale), on a déterminé les facteurs suivants: temps de transport mucociliaire, hypersensibilité à l'histamine des muqueuses nasales, nombre de cellules basophiles et éosinophiles se trouvant dans la couche supérieure muqueuse du cornet inférieur, taux d'histamine dans la secrétion nasale. Les résultats des deux groupes ont été comparés. Le temps saccharine n'a pas montré de différence significative entre le groupe asthme et le groupe allergie nasale. Le seuil pour l'hypersensibilité à l'histamine était significativement plus élevé dans le groupe asthme que dans le groupe allergie nasale. Dans les deux groupes on a observé dans la couche supérieure muqueuse nasale du cornet inférieur, une accumulation de cellules basophiles et éosinophiles. Dans le groupe allergie nasale, mais non dans le groupe asthme, il y eut, entre le nombre de cel-

lules basophiles et celui de cellules éosinophiles se trouvant dans la muqueuse nasale, une corrélation statistique. Cette donnée suggère que, pour expliquer le mécanisme jouant un rôle dans le développement de symptômes nasaux d'allergie nasale, la fonction des cellules basophiles se trouvant dans la couche supérieure muqueuse constitue un facteur plus important que l'activité mucociliaire et l'hypersensibilité à l'histamine de la muqueuse nasale.

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