Relation of the Timing of Onset of Rhinitis and Cough to Asthma Attack in Children

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Summary: If the risk of progression to asthma could be predicted in patients with rhinitis, prevention of asthma might become possible. The purpose of this study was to clarify the relationship between the duration of rhinitis symptoms and acute asthma attacks in children with a history of asthma who were not on treatment for asthma. In 94 children with a history of asthma who were asymptomatic after completing asthma treatment, we investigated the onset and duration of nasal discharge and cough related to allergic rhinitis. Then the children were followed up for 2 weeks and were classified into either an asthma attack group (Group A) or non-asthma group (Group B). A total of 78 subjects were evaluated after 16 were excluded. The duration of nasal discharge was significantly shorter in Group A than in Group B (5.5 ± 1.9 days vs. 10.4 ± 3.1 days, $P < 0.0001$). The interval between the onset of cough and nasal discharge was -1.0 ± 3.1 days in Group A and -5.7 ± 4.1 days in Group B ($P < 0.0001$). The risk of progression to asthma attack may be higher when the onset of cough precedes nasal discharge or when nasal discharge has a short duration and cough shows an early onset. These results may provide assistance when selecting patients for early anti-allergy therapy from among those presenting with upper respiratory tract symptoms.

Key words asthma, allergic rhinitis, children, nasal discharge, cough

INTRODUCTION

In recent years there have been many reports about the association of allergic rhinitis with asthma [1-6], and some reports have suggested its relevance to triggering acute asthma attacks [6-10].

Guidelines [3] have been established by Allergic Rhinitis and its Impact on Asthma (ARIA), working in partnership with the WHO, and a new concept of the relation between allergic rhinitis and asthma has been proposed based on "one airway, one disease"[5].

A number of reports have been published concerning the relationship between treatment of rhinitis and

prevention of asthma attacks [11-17]. It has been demonstrated that patients with rhinitis but without bronchial symptoms still show airway hyperreactivity and impairment of respiratory function on measurement of forced expiratory flow. However, it is difficult to test airway hyperreactivity and respiratory function in young children [18]. In previous studies of children with a history of asthma and rhinitis symptoms, whether or not treatment of rhinitis influenced the risk of acute asthma attacks was not determined.

Asthma may show remission after cough and rhinitis symptoms are controlled, while the new onset of such symptoms can be the prelude to an acute asthma

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Abbreviations: ARIA, allergic rhinitis and impact on asthma; GINA, global initiative for asthma; WHO, world health organization.

attack. If it was possible to predict the risk of progression to asthma in patients who present with rhinitis, it could also be possible to screen persons at risk and prevent asthma attacks from occurring. However, there have been few reports about predicting the risk of asthma attacks from the symptoms of rhinitis in such patients.

The purpose of this study was to clarify the relationship between the duration of rhinitis symptoms and acute asthma attacks in children with a history of asthma who had no asthma symptoms and were not on treatment at the time of presenting with rhinitis.

METHODS

Diagnosis of asthma

Children with more than three episodes of cough associated with expiratory wheezing were diagnosed as having asthma based on the guidelines of the Japan Society of Pediatric Allergy and Clinical Immunology [19].

Subjects

The subjects were 94 children with a history of asthma who had been asymptomatic for at least three months after completing asthma treatment. They ranged in age from 2 to 7 years and presented to Sugimura Children's Medical Clinic with the chief complaint of watery nasal discharge or cough. At the initial visit, they had no fever and wheezing was not audible on auscultation. Also, their parents had not noted wheezing at home. Children with fever at any time were excluded from this study.

The ethics committee of Sugimura Children's Medical Clinic approved the study protocol and associated documents, as did the parents of the participating children. The parents also gave written informed consent prior to enrollment of their children as subjects. Recruitment was carried out from January to May 2010.

Evaluation of the clinical course

At the initial visit, we investigated the timing of onset and the duration of nasal discharge and cough. The body temperature, respiration rate, and heart rate were measured. Nasal discharge was tested by Hansel staining. In brief, a sample of nasal discharge was collected with a cotton swab and a smear was made for Hansel staining, followed by observation under a microscope ($\times 400$ magnification). When eosinophils were detected by microscopy, the result was classified as positive.

The subjects were followed up for 2 weeks after the initial visit and were classified according to the pres-

ence or absence of wheezing during the follow-up period into an asthma attack group (Group A) or non-asthma group (Group B). These groups were compared with respect to the timing of onset and the duration of nasal discharge and cough. That is, the onset-to-visit interval was determined for nasal discharge and cough, as well as the interval between the onset of nasal discharge and the onset of cough (calculated by subtracting the 'date of onset of cough' from the 'date of onset of nasal discharge'). This interval had a negative value when the onset of nasal discharge preceded that of cough, while it had a positive value when cough preceded nasal discharge.

Treatment

The subjects started treatment with an antihistamine (mequitazine, 0.06 mg/kg b.i.d.) and an expectorant (carbocysteine, 10 mg/kg t.i.d.) at the initial visit. Leukotriene antagonists, β_2 -adrenoreceptor agonists, theophylline, and steroids were not used. Subjects who experienced a confirmed asthma attack during the evaluation period were also given a leukotriene antagonist and a β_2 -adrenoreceptor agonist or inhaled steroid.

Statistical analysis

Continuous variables, such as body temperature, respiration rate, heart rate, and the duration of nasal discharge or cough, were analyzed by Student's t-test in each group. Fisher's exact test was used for categorical variables, such as sex and the eosinophil-positive rate. In all analyses, $P < 0.05$ was considered significant.

RESULTS

A total of 78 subjects were classified into Groups A and B after 16 children was excluded from the study (10 had a temperature $\geq 37.5^\circ\text{C}$ during the follow-up period, two were diagnosed with hemolytic streptococcal infection, and four were incorrectly given an inhalant or antiallergic agent at home).

All asthma attacks were graded mild by the criteria in the 2008 GINA guidelines [20].

Demographic and baseline data obtained at the initial visit are summarized in Table 1. The age (mean $\pm$ standard deviation) of the children in Group A ($n=46$) and those in Group B ($n=32$) was 3.3 ± 1.2 years and 3.4 ± 1.4 years, respectively. Boys accounted for 43.5% and 37.5% of Group A and Group B, respectively. The heart rate (mean $\pm$ standard deviation) was $92.2 \pm 6.4/\text{min}$ in Group A and $94.3 \pm 7.2/\text{min}$ in Group B, while the respiration rate was $27.4 \pm 2.4/\text{min}$ and $27.4 \pm 2.7/\text{min}$, respectively. These data showed

no significant differences between the two groups.

Data on nasal symptoms, the duration of nasal discharge, the duration of cough, and eosinophil positivity of nasal discharge at the initial visit are listed in Table 2. The duration of nasal discharge was significantly

shorter in Group A (5.5 ± 1.9 days) than in Group B (10.4 ± 3.1 days; $P < 0.0001$). The interval between the onset of cough and that of nasal discharge was -1.0 ± 3.1 days in Group A and -5.7 ± 4.1 days in Group B, with the interval being significantly shorter in Group A

TABLE 1.
Characteristics of the Study Subjects

	Group A (asthma attack)	Group B (non-asthma)
Number	46	32
Number of Male gender (%)	20 (43.5)	12 (37.5)
Age (SD) in years	3.3 (1.2)	3.4 (1.4)
Heart rate (SD) per minute on initial visit	92.2 (6.4)	94.3 (7.2)
Respiratory rate (SD) per minute on initial visit	27.4 (2.4)	27.4 (2.7)

SD; Standard deviation

TABLE 2.
Symptoms and Eosinophils in Nasal Fluid on Initial Visit

	Group A (asthma attack)	Group B (non-asthma)
Duration (day) of nasal discharge (SD)	5.5 (1.9)***	10.4 (3.1)
Duration (day) of cough (SD)	4.4 (1.6)	4.6 (1.8)
Interval (day) of nasal discharge and cough (SD)	-1.0 (3.1)***	-5.7 (4.1)
Number of children with sniffle (%)	30 (65.2)	20 (62.5)
Number of children with sneeze (%)	20 (43.5)*	21 (65.6)
Numbers of children with eosinophils in nasal fluid (%)	21 (45.7)	14 (43.8)

SD; Standard deviation

***Group A is different from Group B at $P < 0.0001$

* Group A is different from Group B at $P < 0.05$

TABLE 3.
Sensitivity and Specificity by duration of nasal discharge

	Group A (asthma attack)	Group B (non-asthma)
Number of children with duration of nasal discharge ≤ 8 days	44	11
Number of children with duration of nasal discharge ≥ 9 days	2	21

Sensitivity of asthma attack 95.6%, Specificity of asthma attack 65.6%

TABLE 4.
Sensitivity and Specificity by an interval of nasal discharge and cough

	Group A (asthma attack)	Group B (non-asthma)
Number of children with interval of nasal discharge ≥ -5 days	44	13
Number of children with interval of nasal discharge ≤ -6 days	2	19

Sensitivity of asthma attack 95.6%, Specificity of asthma attack 59.4%

($P < 0.0001$). The prevalence of sneezing as a symptom was significantly lower in Group A than in Group B (43.5% [$n = 20$] vs. 65.6% [$n = 14$], $P < 0.05$). The duration of cough, prevalence of nasal congestion, and prevalence of eosinophil-positive nasal discharge showed no significant differences between Groups A and B, being 4.4 ± 1.6 days versus 4.6 ± 1.8 days, 65.2% ($n = 30$) versus 62.5% ($n = 20$), and 45.7% ($n = 21$) versus 43.8% ($n = 14$), respectively.

The sensitivity and specificity of various parameters were evaluated. Duration of nasal discharge at the initial visit ≤ 8 days showed a high sensitivity of 95.6% for predicting asthma attacks, while its specificity was 65.6% (Table 3). In addition, onset of nasal discharge preceding that of cough by ≤ 5 days showed a sensitivity of 95.6% for predicting asthma attacks and its specificity was 59.4% (Table 4).

DISCUSSION

The association of asthma with allergic rhinitis has long been reported [1-6] and a number of studies have suggested a relationship between these two conditions [6-10]. When the upper respiratory tract of a patient with allergic rhinitis is exposed to allergens, an allergic reaction (eosinophil infiltration, etc.) is also induced in the lower respiratory tract and hypersensitivity of the lower tract increases [21-23]. A relationship between allergic rhinitis and asthma has also been reported on the basis of histological findings [18,24-26]. Furthermore, it has been reported that asthma can be predicted in patients with rhinitis by evaluating respiratory function [18]. However, such evaluation is not possible in young children and there have been no reports about predicting the risk of progression from rhinitis to asthma in young children.

Children with a history of asthma often become asymptomatic after some time and reach a treatment-free stage. They may subsequently present with symptoms of upper respiratory tract infection such as a cough and running nose. At presentation, it is difficult to establish the risk of an acute asthma attack in patients who do not currently have asthma. It is unclear whether or not antiallergic agents should be administered to all such children due to the risk of asthma attack, so it is necessary to establish risk factors for progression to an acute attack. Therefore, the present study was undertaken to find predictors of the risk of asthma attack in children with a history of asthma.

Our findings indicated that the duration of nasal discharge was significantly shorter and the interval between the date of onset of nasal discharge and that of

cough was also significantly shorter in Group A (asthma attack) compared with Group B (non-asthma) ($P < 0.0001$) (Table 2). This suggests that, when nasal discharge and cough (due to upper respiratory tract infection) occur in children who have a history of asthma but no current asthma symptoms, a shorter interval between the onset of nasal discharge and cough is associated with a higher risk of an acute asthma attack. The sensitivity for predicting an asthma attack was 95.6% when the onset-to-visit interval of nasal discharge was ≤ 8 days (Table 3). Also, when the interval between the onset of nasal discharge and cough was ≥ 5 days or more (i.e., onset of nasal discharge preceded that of cough by ≥ 35 days), the sensitivity for predicting an acute attack was 95.6% (Table 4). Although the specificity of these two indicators was not high, determining the duration of nasal discharge or the interval between onset of nasal discharge and cough may be useful for estimating the risk of asthma attack. Moreover, the prevalence of sneezing was significantly lower in group A than in group B. This may also serve as a useful reference for predicting the risk of asthma attack.

The above results indicate that a rapid rate of progression of allergic inflammation of the upper respiratory tract (e.g., rhinitis symptoms) to also involve the lower respiratory tract is associated with a higher risk of an acute asthma attack. When rhinitis symptoms persist for a long period and there is a long interval before the onset of cough, this may indicate slow progression from upper respiratory tract inflammation to lower respiratory tract inflammation or may suggest mild lower respiratory tract involvement. On the other hand, when the interval between the onset of nasal discharge and cough is short or cough precedes nasal discharge, rapid progression to lower respiratory tract inflammation is likely. A histopathological relationship between the upper and lower respiratory tracts has been reported, and airway epithelial cells are involved the pathogenesis of asthma and allergic rhinitis along with various inflammatory mediators and neurotrophins [18,24-26]. The degree of involvement of these mediators/neurotrophins may have an influence on whether patients with allergic rhinitis develop asthma or not, but the details are not known and further studies are needed to clarify the influence of such mediators as well as the relationship between upper and lower respiratory tract inflammation.

Limitations

In the present study, we followed children with a history of asthma for 2 weeks. Most of the children in group B without asthma attack showed alleviation of

symptoms after 2 weeks, but the observation period was relatively short. Furthermore, it is unclear whether the subjects (who presented with nasal discharge and/or cough) had viral infection or bacterial infection.

CONCLUSIONS

When children who have a history of asthma without current treatment present with watery nasal discharge and/or cough, attention should be paid to the timing of onset and the duration of their symptoms. The risk of progression to asthma attack may be higher when the onset of cough precedes that of nasal discharge or when nasal discharge has a short duration and cough shows an early onset. Although it is not easy to predict asthma attacks from nasal discharge symptoms, our results may provide some assistance in selecting children for whom early anti-allergic therapy is indicated from among those presenting with upper respiratory tract symptoms.

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