Progressive Bronchial Obstruction During the Acute Stage of Respiratory Tract Infection in Asthmatic Children

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To study the time-course of infectious asthma, we retrospectively examined FEV1 from 5 days before to 10 days after the onset of illness in 31 asthmatic children (20 boys and 11 girls), aged 8 to 12 years. Infections were confirmed by a rise of at least fourfold in serum complement fixation titers (respiratory syncytial virus, adenovirus, and Mycoplasma pneumoniae) and hemagglutination inhibition titers (parainfluenza virus types 1, 2, and 3). All the patients had 20 percent or more fall in FEV1 from baseline value during acute phase, but were clinically tolerable and required minimum or no bronchodilators. Regardless of infectious agent, FEV1 began to fall on the first disease day or the previous day, and deteriorate for the first few days. Mean(SD) maximum fall in FEV1 ranged from 39(12) percent to 45(20) percent. Thereafter, FEV1 began to improve and returned to the preillness level by the seventh to tenth day. These results suggest that progressive bronchial obstruction may be inevitable during the acute stage of any infectious asthma.

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Key words: infectious asthma, Mycoplasma pneumoniae, respiratory virus

Infections of respiratory viruses and Mycoplasma pneumoniae, some of them of low pathogenicity to healthy children, frequently provoke exacerbations of bronchial obstruction in children with asthma.1-5 Besides, more than one third of all severe episodes of asthma are associated with viral respiratory tract infection.4 A previous study demonstrated that influenza virus infection in asthmatic children causes progressive bronchial obstruction during the acute stage of illness5 and the progressive bronchial obstruction may superficially diminish the efficacy of bronchodilators administered in some patients. Therefore, it is also useful for better prediction and treatment of exacerbations of asthma to elucidate the time-course of bronchial obstruction triggered by other respiratory viral and M pneumoniae infections.

Children with asthma who were admitted to our residential treatment center received routine physical examination every day, and also performed spirometry almost every day. When the children had signs and symptoms of respiratory tract infection, paired serum specimens were examined for viral and M pneumoniae titers to identify an infectious agent. There were some patients with stable conditions whose episodic bronchial obstructions were considered to be triggered mainly by a respiratory tract infection. The present study retrospectively investigated the time-course of bronchial obstruction triggered by symptomatic, uncomplicated respiratory tract infections, except those caused by influenza virus infection, in these children with stable asthma; the first day of illness, was considered to be first day with low-grade fever.

METHODS

Patients

Bronchial obstruction was diagnosed if wheezing was audible without stethoscope and/or there was a 20 percent or more fall in FEV1 from baseline value (see below). We retrospectively studied incidence of bronchial obstruction during serologically proven 43 respiratory syncytial virus (RSV), 54 parainfluenza virus, 27 adenovirus, and 36 M pneumoniae respiratory tract infections among 160 asthmatic children (104 boys and 56 girls), and compared it with the incidence during rubella virus infection in 16 asthmatic children (13 boys and 3 girls). The children were 8 to 12 years old, and all of them were staying in a residential treatment center because of uncontrollable asthma at their home. They all met American Thoracic Society criteria for the diagnosis of asthma.6 No one was steroid dependent or aspirin sensitive. None of them had respiratory tract infection for at least 6 weeks or clinical asthma that continued 1 day or more for at least 2 weeks before the onset of the study.

The time-course of percent fall in FEV1 was retrospectively examined from 5 days before to 10 days after the onset of each illness in 31 patients (20 boys and 11 girls) whose bronchial obstructions were clinically tolerable and required minimum or no bronchodilators among the 160 patients (Table 1).

Physical examination was done twice daily, in the morning and the evening, and wheezing during sleep was heard hourly from 8:30 pm to 6 am. Axillary temperature was measured routinely once in the morning, and as required.
Oral bronchodilators, a combination of short-acting salbutamol (2 mg) and aminophylline (100 mg), were given once or twice a day throughout the study in five patients, from the first disease day to the end in one patient, and from the third disease day to the sixth day in one patient. They were given in the late afternoon and before going to bed, or just before going to bed. Oral short-acting aminophylline (100 mg) was given three times a day throughout the study in two patients, and oral dl-isoproterenol hydrochloride (10 mg) was given three times a day from the first disease day to the end in two patients. The morning dose was given about 8 AM. Eight patients inhaled sodium cromoglycate (20 mg) (by inhaler) three times a day, and five took oral ketotifen (1 mg) twice a day regularly throughout the study. The morning dose of these anti-inflammatory medicines was given about 8 AM. Eight patients took both bronchodilator and anti-inflammatory medicine, and 12 patients took none of them throughout the study. Analgesic antipyretic, mefenamic acid or acetylsalicylic acid, was given as needed. However, treatment with it was withheld for at least 10 h before the spirometry. Antimicrobial medicine was not given to any patient during the study.

Written consent was given by each parent. The study was approved by the Clinical Research Committee, Children's Asthmatic Center, Kawasaki City Ida Hospital.

Measurement of FEV₁

The FEV₁ was measured at about 10 AM almost every day except Sunday, in each patient with one of following two spirometers: a 91 water-sealed spirometer (Ichikawa Shiseido, Tokyo, Japan), and a hot-wire auto-spirometer (AS-1500, Minato Ikagaku, Osaka Japan). The same spirometer was used for one patient throughout each infection. Measured FEV₁ was expressed as FEV₁ percent predicted based on the following equation of Sumida for Japanese schoolchildren as follows: FEV₁ (ml) in boys: 34.82Xheight(cm)−2.746; FEV₁(ml) in girls: 34.42Xheight(cm)−2.829.

Measured FEV₁ values were retrospectively examined from 5 days before to 10 days after the onset of illness. The best FEV₁ during 5 days after the onset was regarded as the baseline value in each patient.

Viral and Mycoplasma Pneumoniae Infections

Viral and M pneumoniae infections were suspected when a patient had two or more respiratory signs and symptoms, including nasal stuffiness, cough, sore throat, huskiness, throat injection, and headache in addition to fever of 37.5°C or more. Blood was drawn for serologic evaluation of antibody titers twice in each infection, on the second or third day of illness and about 3 weeks afterwards. The complement fixation test was used to detect antibodies to RSV, adenovirus, rubella virus, and M pneumoniae. The hemagglutination inhibition test was used to detect antibodies to parainfluenza virus types 1, 2, and 3. Each infection was confirmed by a rise of at least fourfold in serum titers. The day when a patient had fever of 37.5°C or more for the first time was regarded as the first day of each illness.

Analysis

Standard methods were used for calculation of means and SDs.

RESULTS

From routine physical examination, the clinical course of respiratory tract infections triggered by RSV, parainfluenza virus, adenovirus, and M pneumoniae was not associated with pneumonia and massive atelectasis in all patients.

Bronchial obstruction was recognized in 36 of 45 RSV infections (84 percent), 37 of 54 parainfluenza virus infections (69 percent), 14 of 27 adenovirus infections (52 percent), 24 of 36 M pneumoniae infections (67 percent), and 1 of 16 rubella infections (6 percent). The occurrence of bronchial obstruction is shown in Figure 1.

FIGURE 1. Occurrence of bronchial obstruction (see text) during infections of RSV (n=45), parainfluenza virus types 1, 2, and 3 (n=54), adenovirus (n=27), Mycoplasma pneumoniae (n=36), and rubella virus (n=16) in asthmatic children.
infections (67 percent), and 1 of 16 rubella virus infections (6 percent) (Fig 1). One patient with rubella virus infection was regarded as having bronchial obstruction due to wheezing in predawn hours. The mean(SD) baseline FEV₁ percent predicted was 89(12), 93(9), 89(11), and 91(11) in RSV, parainfluenza virus, adenovirus, and M pneumoniae infections, respectively. Information describing the time-course of bronchial obstruction is given in Table 2 and Figure 2. The mean(SD) maximum fall in FEV₁ was 43(16), 43(12), 39(12), and 45(20) percent in RSV, parainfluenza virus, adenovirus, and M pneumoniae infections, respectively.

### DISCUSSION

The present study showed that respiratory tract infections by RSV, parainfluenza virus, adenovirus, and M pneumoniae frequently provoked acute bronchial obstruction in children with stable asthma, comparative with earlier studies.1-3 Regardless of infectious agent, bronchial obstruction began on the first day of illness or the previous day, which was clinically indistinguishable from the first day on the basis of respiratory signs and symptoms in some patients. Bronchial obstruction progressively deteriorated during the first few days after the onset of bronchial obstruction. It began to improve from the third or fourth day and returned to the preillness level by the seventh to tenth day. The time-courses of bronchial obstruction were similar to the one during influenza virus infection.5 These results suggest that progressive bronchial obstruction may be inevitable during the acute stage of any kind of infectious asthma.

Significant bronchial obstruction rarely occurred during rubella virus infection, which frequently caused upper respiratory tract inflammation in addition to skin rash and viremia.12 On the other hand, the respiratory virus and M pneumoniae infections frequently cause bronchial obstruction in all kinds of asthmatic children. These agents generally invade into the lower respiratory tract even though signs and symptoms of infection are confined to the upper respiratory tract.13,14 In addition, the deterioration of bronchial obstruction for the first few days roughly coincided with the destruction of bronchial epithelium during these respiratory tract infections.15-18 Taken together, these results support the hypotheses that invasion of an infectious agent into the lower

### Table 2—The Time-Course of Mean (SD) Fall in FEV₁ From Baseline Value (See Text) From 2 Days Before to 10 Days After the Onset of Illness in Infections of RSV (n=8), Parainfluenza Virus (n=8), Adenovirus (n=7), and Mycoplasma Pneumoniae (n=8) in Asthmatic Children

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![Figure 2. The time-course of mean decrease in FEV₁ (percent) from baseline value in asthmatic children just before and after the onset of respiratory illness caused by RSV (n=8), parainfluenza (n=8), adenovirus (n=7), and Mycoplasma pneumoniae (n=8).](image-url)
respiratory tract and subsequent functional disorder related to the bronchial epithelium destruction are essential in causing infectious asthma in the asthmatic patient.

Although each infectious agent causes a different clinical course of signs and symptoms, the time-course of bronchial obstruction during any kind of infectious asthma was almost uniform. One of the explanations may be that particular respiratory viruses are not specifically associated with particular histologic change, and structural lesions and clinical dysfunctions correlate fairly well. It may also be due to the preselection of asthmatic children studied. All their bronchial obstructions were significant, but not so severe as to prevent them from performing spirometry thoroughly without bronchodilators or only on minimum doses. In other words, all the patients had almost the same level of bronchial reaction and subsequent development of bronchial obstruction during the respiratory infections by different agents. In asthmatic children with more labile airways, progressive bronchial obstruction during the acute stage of respiratory infection may be dangerously severe and may superficially diminish the efficacy of bronchodilators administered.

Since cromoglycate or ketotifen was given regularly in the same manner throughout the study in 13 patients, they might have little effect on the time-course of bronchial obstruction. The same holds true for the effect of bronchodilators that were given regularly throughout the study. However, bronchodilators that were given from the first or third day of illness surely ameliorated bronchial obstruction and affected the time-course. Despite including the cases affected by bronchodilators, continuous fall in FEV1 during the first few days of illness may at least suggest that the tendency of deterioration during this period is probable. Also, improvement of bronchial obstruction without further specific treatment by the seventh to tenth day of illness suggests that underlying inherent anti-inflammatory mechanisms may help uncomplicated infectious asthma to be self-limited.

There are a few limitations to the present study. First, it was difficult to determine uniformly the onset of illness in the infections caused by the different infectious agents. They have different courses of clinical manifestations, and sometimes they lack major signs and symptoms. For example, the first day of illness was sometimes indistinguishable from prodrome day(s) in M pneumoniae infection whose incubation period is relatively long. Nevertheless, we uniformly used an appearance of temperature of 37.5°C or more as a marker of the onset of illness in each infection. Second, there was not an agreement to determine the baseline pulmonary function value in each patient studied. Since there could have been asymptomatic bronchial obstruction in some asthmatic children even at their best, we did not use the predicted normal value as the baseline. A previous study reported that bronchial obstruction rarely occurs during the incubation period of influenza virus infection. Therefore, we used as the baseline the best recorded FEV1 among five consecutive morning values before the onset of illness. Finally, bronchial obstruction was triggered not only by the infection, but also by all the stimuli to airway in the environment even during the respiratory infection. It was impossible to distinguish bronchial obstruction triggered by the infection from ones triggered by other stimuli. In addition, interpretation of change was complicated when there was a vicious circle between bronchial obstruction and inflammation. To get the start essential time-course of bronchial obstruction in infectious asthma as accurately as possible, we selected patients without complications in the same environment throughout the study. Moreover, bronchial obstruction triggered by other stimuli was not necessarily irrelevant with one triggered by the infection since further increase in bronchial responsiveness and frequent coughing accompanied with the infection might make the bronchi more collapsible.

Although rhinovirus infection is frequently associated with an exacerbation of asthma, the present study excluded bronchial obstruction triggered by the infection of rhinovirus whose serotypes are more than 100 and not fully identified for the present. It also excluded patients whose asthma was not under good control before the onset of illness. Furthermore, we studied older children whose defense mechanisms against the viral and M pneumoniae infections are already developed moderately. Nevertheless, incidence of bronchial obstruction was at least the same as or even higher than those in other studies. One of the reasons to explain the high incidence may be that we tried to find out asymptomatic bronchial obstruction by objective spirometry and nocturnal bronchial obstruction during sleep by hourly observation in-hospital children with asthma.

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