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Do Asthma Symptoms Lag Behind Cold Symptoms in a Viral Illness?

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To the editor

Acute asthma exacerbations are the major cause of morbidity, mortality, and health-care costs in the asthmatic population.^{1,2} The majority of exacerbations are associated with a viral respiratory infection,³ and antiviral medications are being developed that could be used to treat or prevent exacerbations of asthma.⁴ It is unknown if these medications would best be initiated at the first sign of a cold, or alternatively used as daily prophylaxis during seasons of high viral prevalence. Experimental inoculation studies of adults suggest that peak cold symptoms typically precede lower respiratory symptoms and airway obstruction by two or more days.⁵ This finding suggests that to prevent virus-induced exacerbations of asthma, there is a window of opportunity for initiation of antiviral medications at the first sign of a cold. Notably, experimental inoculation studies are usually conducted when baseline nasal symptoms are absent or mild, and recognition of naturally-acquired cold symptoms could be more difficult.

We hypothesized that asthma symptoms lag behind naturally-acquired cold symptoms by at least one day. To test this hypothesis we analyzed data from a prospective study that examined the roles of viral infections and allergy in the development of asthma exacerbations in children.⁶ In this study, 58 children with asthma ages 6-8 years provided five consecutive weekly samples of nasal mucus during peak rhinovirus seasons, and cold and asthma symptoms were recorded daily on a four-point scale (none, mild, moderate,

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severe) by the children together with their parents. Albuterol use and peak expiratory flow were also recorded on a daily basis. Loss of asthma control (LAC) was defined as at least moderate asthma symptoms (frequent cough or wheeze, some shortness of breath, reduced activity but not affecting sleep) and either a drop in peak expiratory flow (PEF) >20% or use of albuterol more than 2 days per week.⁶ Respiratory viruses were identified using multiplex PCR and partial sequencing of picornaviruses. The beginning of an illness was defined as the onset of either cold or asthma symptoms.

Overall, 21 of the 58 children (36%) had at least one LAC episode associated with a viral infection, and there were 27 total episodes. Of these 27 illnesses, asthma symptoms were reported first in 6 cases (22%), cold symptoms started first in 12 cases (44%), and both started simultaneously in 9 cases (33%, Figure 1a). On average, cold symptoms preceded asthma symptoms by 0.48 $\pm$ 1.6 days ($p=0.17$, Sign rank test). We also tested relationships between the onset of symptoms and peak cold and asthma symptoms. The median number of days from illness onset to peak cold symptoms was 3, peak asthma symptoms 2, maximum daily albuterol use 3, and maximum reduction in PEF 4. These data lead us to conclude that during a viral illness, children with asthma do not reliably perceive that the onset of cold symptoms precedes the development of asthma symptoms. In addition, the relationship between illness onset and peak cold or asthma symptoms is similarly variable.

Previous studies have analyzed the onset of cold and asthma symptoms following experimental viral inoculation, but there is relatively little information about the temporal relationship of naturally-acquired cold and asthma symptoms in children. Message et al⁵ induced RV16 infection in seronegative atopic asthmatic adults and reported the group mean timing of cold and asthma symptoms. On average, cold symptoms began on day 1 and peaked on day 3, while chest symptoms began on day 1 and peaked on day 6. Significant falls in PEF and FEV1 were first observed on days 1 and 3 respectively, and the greatest drop in PEF was on day 5. Thus, in this experimental infection model upper respiratory and asthma symptoms both begin on day 1, but cold symptoms peaked an average of 2-3 days before maximal asthma symptoms. Individual patterns of symptoms were not included in the published data.

The data from this induced RV inoculation compared to our natural RV infection study both show asthma as well as cold symptom onset on average occurring on the same day. However, they noted a lag in peak asthma type symptoms following peak cold type symptoms. There are several differences in study design that could account for the apparent differences in the timing of peak cold and asthma symptoms. In the natural setting, it is more difficult to determine whether upper respiratory symptoms are due to viral infection, allergies, or both. Symptoms from serial colds can blend into each other with additional contributions from allergens and irritants. Furthermore, our study subjects were children, who are at the greatest risk for virus-induced exacerbations of asthma, but may have more difficulty distinguishing upper vs. lower respiratory symptoms. Notably, our study was very inclusive, and no children were excluded for having recent infections of the nose or sinuses, or for ongoing allergic rhinitis symptoms. These factors may contribute to the difficulty in using early detection of cold symptoms to identify impending virus-induced exacerbations of asthma in children. Limitations of our study include relatively small sample size. In addition, the symptom scores were reported as a simple four-point scale that did not differentiate individual cold and asthma symptoms. Although there is no validated measure for the combination of cold and asthma symptoms in children, our cold and asthma scoring system has been shown to be responsive to detection of respiratory viruses, and the simplicity of the scale encouraged high rates of adherence to study procedures.^{6,7}

In conclusion, this observational study of natural colds in children with asthma provided new information about the timing of onset and peaks of virus-induced cold and asthma symptoms under real-life conditions. Our data show that children and their parents do not reliably perceive an upper airway prodrome before virus-induced asthma symptoms. Antiviral medications with activity against rhinoviruses are in development, and these findings indicate that the strategy of starting an anti-viral medication at the onset of cold symptoms to prevent asthma exacerbations may not be optimal. Virus-induced exacerbations peak during the rhinovirus seasons in the spring and fall, and perhaps the regular use of a prophylactic anti-viral medication during these seasons would have greater efficacy than using it at the onset of cold symptoms.

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Figure 1a.

Figure 1b.

Figure 1. Timing of asthma symptoms relative to cold symptoms. For virus-induced episodes of loss of asthma control, days were numbered starting with the first day of either cold or asthma symptom onset (a) or peak symptoms (b). The time lag in days was calculated for each illness. Positive numbers (days) indicate cold symptoms were noticed first and negative numbers indicate asthma symptoms were first.