might be an amplification process that is responsible for the long duration of symptoms. A mechanism could be initial activation of mast cells by complement cleavage products. Mast cell products, such as tryptase, could contribute to the duration of symptoms by means of additional cleavage of complement proteins. Patients with this disorder do not have other symptoms of allergic reactions, such as asthma or anaphylaxis. This is explained by the absence of receptors for C3a and C5a on mucosal-type mast cells, whereas they are expressed on cutaneous mast cells.[9]

In conclusion, this report describes a heretofore unrecognized pathway for complement activation in patients with urticaria and angioedema and autoimmune thyroid disease.

Charles H. Kirkpatrick, MD

From the Division of Allergy and Clinical Immunology, Department of Medicine, University of Colorado Denver Anschutz Medical Campus, Aurora, Colo. E-mail: charles.kirkpatrick@ucdenver.edu.

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Do asthma symptoms lag behind cold symptoms in a viral illness?

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 tract infection,[3] and antiviral medications are being developed that could be used to treat or prevent exacerbations of asthma.[4] It is unknown whether 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 tract symptoms and airway obstruction by 2 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 1 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 aged 6 to 8 years provided 5 consecutive weekly samples of nasal mucus during peak rhinovirus seasons, and cold and asthma symptoms were recorded daily on a 4-point scale (none, mild, moderate, or severe) by the children together with their parents. Albuterol use and peak expiratory flow (PEF) were also recorded on a daily basis. Loss of asthma control was defined as at least moderate asthma symptoms (frequent cough or wheeze, some shortness of breath, and reduced activity but not affecting sleep) and either a decrease in PEF of greater than 20% or use of albuterol more than 2 days per week.[6] Respiratory tract viruses were identified by 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 (36%) of the 58 children had at least 1 episode of loss of asthma control associated with a viral infection, and there were 27 total episodes. Of these 27 illnesses, asthma symptoms were reported first in 6 (22%) cases, cold symptoms started first in 12 (44%) cases, and both started simultaneously in 9 (33%) cases (Fig 1, *A*). On average, cold symptoms preceded asthma symptoms by 0.48 ± 1.6 days ($P = .17$, signed-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, that to peak asthma symptoms was 2, that to maximum daily albuterol use was 3, and that to maximum reduction in PEF was 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 after experimental viral inoculation, but there is relatively little information about the temporal relationship of naturally acquired cold and asthma symptoms in children. Message et al[5] induced rhinovirus 16 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, whereas chest symptoms began on day 1 and peaked on day 6. Significant decreases in PEF and FEV_1 were first observed on days 1 and 3, respectively, and the greatest decrease in PEF was on day 5. Thus in this experimental infection model upper respiratory tract and asthma symptoms both begin on day 1, but cold symptoms peaked an average of 2 to 3 days before maximal asthma symptoms. Individual patterns of symptoms were not included in the published data.

The data from this induced rhinovirus inoculation compared with our natural rhinovirus infection study both show asthma and cold symptom onset occurring on the same day on average. However, they noted a lag in peak asthma-type symptoms after peak cold-type symptoms.

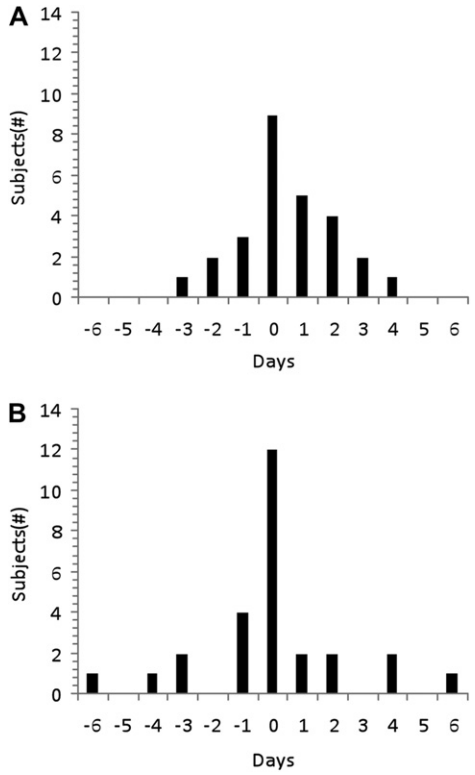

FIG 1. Timing of asthma symptoms relative to cold symptoms. For virus-induced episodes of loss of asthma control, days were numbered starting with the first day of either cold or asthma symptom onset **(A)** or peak symptoms **(B)**. The time lag in days was calculated for each illness. Positive numbers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

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 tract 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 might have more difficulty distinguishing upper versus lower respiratory tract 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 might 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 the relatively small sample size. In addition, the symptom scores were reported as a simple 4-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 tract 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 antiviral medication at the onset of cold symptoms to prevent asthma exacerbations might not be optimal. Virus-induced exacerbations peak during the rhinovirus seasons in the spring and fall, and perhaps the regular use of a prophylactic antiviral medication during these seasons would have greater efficacy than using it at the onset of cold symptoms.

Douglas F. McMahon, MD[a,b]
Victoria Rajamanickam, MS[c]
Lisa Salazar, BA[a]
Ronald Gangnon, PhD[c]
James E. Gern, MD[a,b]

From the Departments of [a]Pediatrics, [b]Medicine, and [c]Bioinformatics, University of Wisconsin School of Medicine and Public Health, Madison, Wis. E-mail: dmcmahon@uwhealth.org.

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Delayed-onset adenosine deaminase deficiency: Strategies for an early diagnosis

To the Editor:

Adenosine deaminase (ADA) deficiency is a well-known cause for severe combined immunodeficiency (SCID). However, hypomorphic mutations in the *ADA* gene can lead to a different immunodeficiency with variable phenotype including signs of immune dysregulation.[1,2] Early diagnosis and therapeutic management often remain a challenge. We report on 2 ADA-deficient patients with delayed-onset (P1) and late-onset[1] phenotype (P2) illustrating these difficulties and describe how