Prolonged Episodes of Persistent Asthma* 
A Distinct Clinical Pattern With Characteristic Clinical Features

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Study objectives: To investigate a clinical pattern of unexplained persistent asthma that is episodic in nature and lasts for months to years. This pattern of prolonged episodes of unexplained persistent asthma was not defined previously.

Designs: Investigating the clinical features using a retrospective cohort design.

Setting and patients: Eighteen subjects (ages, 13 to 64 years) from an allergy practice in a large prepaid health maintenance organization who had two or more prolonged episodes of unexplained persistent asthma lasting ≥ 2 months during a 12-year period.

Results: These subjects accounted for 39 asthmatic episodes lasting from 2 to 74 months (median, 7 months). The duration of the episodes positively correlates with the severity of asthma (p = 0.02) at the initial part of the episodes. All episodes demonstrated a similar pattern, with symptom severity greatest at the onset and gradually diminishing until recovery. The relatively symptom-free intervals between the episodes ranged from 1.5 to 63 months (median, 13 months). Fifty-six percent of the episodes (95% confidence interval [CI], 40% to 72%) were associated with symptoms very suggestive or suggestive of an infection of the upper respiratory tract at the onset of the episodes; 33% of the episodes (95% CI, 19% to 50%) had possible symptoms suggestive of an infection; whereas only 10% of the episodes (95% CI, 3% to 24%) had questionable or no symptoms suggestive of an infection of the upper respiratory tract. Thirty-four episodes had the onset between September and March, whereas only 5 episodes occurred between April and August (p < 0.001).

Conclusions: These observations indicate that prolonged episodes of unexplained, persistent asthma lasting for months to years constitute a distinct clinical pattern of asthma with characteristic clinical features.

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Key words: asthma; respiratory tract infections; seasons

Abbreviation: CI = confidence interval

Asthma is a chronic inflammatory disorder of the airways; in susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.1 Some types of asthma episodes are well studied, such as those brought on by seasonal pollen allergen exposures, those associated with upper respiratory viral infections and lasting for a few weeks,2 and those due to occupational exposures, such as western red cedar.3 Asthma in adults is characterized by remission and relapse in many patients.4,5 In a longitudinal study of 272 adults with “intrinsic” asthma of > 15 years, Rackemann and Edwards4 observed that 21.7% of patients recovered from the asthma, many of them after many years of “bad attacks”; in six patients, the asthma recurred after a long, symptom-free period. Furthermore, in most cases, the asthma began with a history of a cold, bronchitis, or pneumonia.4 In this study, whether patients had persistent asthma prior to remission was not certain. In a population study of the natural history of asthma, Bronnimann and Burrows6 followed 136 individuals from 1 to 79 years old for 9 years, and found that remission of asthma could occur at any age. Overall, 22% of participants went into remission, with the highest rate (65%) among those aged 10 to 19 years, and the lowest rate (6%)...
among those aged 40 to 49 years. They also found that 38% of participants whose asthma was already in remission at the outset of the study subsequently had a relapse of asthma during the study period. The authors did not, however, report detailed information on the persistence of symptoms during this period.

In this article, we report a case series of patients exhibiting a clinical pattern of prolonged episodes of unexplained, persistent asthma, a distinct clinical feature that has not been described previously. Utilizing patients who have two or more prolonged episodes of unexplained persistent asthma, we characterize the clinical features of the episodes, as well as the intervals between the episodes that were relatively asthma free.

**Materials and Methods**

**Definitions**

We defined a prolonged episode of persistent asthma as chronic asthma lasting ≥ 2 months and requiring regular medications to control the symptoms of asthma. We defined the severity of asthma by the number of medications required to control asthma (Table 1), where control is defined as infrequent night cough or wheeze, and infrequent chest congestion or wheezing at awakening. The episodes were classified into mild, moderate, or severe persistent asthma episodes according to the severity of asthma during the initial few weeks of the episodes when the asthma was controlled. In the course of a mild, moderate, or severe persistent asthma episode, patients may experience acute and brief episodes of increased asthma. During the relatively symptom-free period before or after the prolonged persistent asthma episodes, the patients do not require regular medications to control symptoms of asthma. Table 2 presents the definitions of the symptoms that are suggestive of an infection of the upper respiratory tract.

We followed the guidelines of the National Asthma Education and Prevention Program. Expert Panel Report 2, for defining intermittent and persistent asthma. For instance, intermittent asthma implies that asthma symptoms occur ≤ 2 times/week before treatment and exacerbations are brief, while persistent asthma implies more frequent, daily, or continuous symptoms before treatment.

**Patients**

We selected subjects using a retrospective cohort design and report on all patients treated between 1977 and 1989 by an allergy specialist (KCC) at a large, prepaid health maintenance organization (Kaiser Permanente Northwest Region) and who met the following three criteria.

1. Two or more prolonged episodes of persistent asthma with relatively symptom-free periods before, between, and after the episodes.
2. These episodes could not be explained by allergen exposure, environmental irritant exposure, occupational exposure, allergic bronchopulmonary aspergillosis, or beta-blocker use.
3. The resolution of the episodes could not be explained by allergen avoidance or allergy immunotherapy.

Episodes that began before 1977 or continued past 1989 were not included in our selection criteria. Eighteen subjects met these criteria and among them presented with a total of 39 prolonged episodes of persistent asthma.

**Spirometry**

Between 1977 and 1984, spirometric testing was performed with a Jones Pulmonary spirometer with a Datamatic microprocessor (Jones Instrument; Oak Ridge, IL). Between 1984 and 1989, we used a Puritan-Bennett VS 400 spirometer (Puritan-Bennett Pulmonary Products; Woburn, MA) connected to an Apple IIe computer (Apple Computer; Cupertino, CA). Predicted values are based on the equations of Morris et al. Spirometry was performed at each office visit. We use the lower limits of normality as defined by Morris et al to define "normal" lung function.

**Statistical Analysis**

Statistical methods include confidence intervals (CIs) for proportions, Kruskal-Wallis nonparametric analysis of variance, and χ² goodness-of-fit tests.

**Results**

**Patient Population**

At the onset of their first prolonged episode of persistent asthma, one patient was 13 years old and the remaining patients were 27 to 64 years old.

<table>
<thead>
<tr>
<th>Table 1—Definitions of the Severity of Asthma</th>
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<tr>
<td><strong>Severity</strong></td>
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<tr>
<td>Prolonged episode of persistent asthma: regular medications required to control symptoms of asthma</td>
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<tr>
<td>Mild persistent asthma</td>
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<tr>
<td>Moderate persistent asthma</td>
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<tr>
<td>Severe persistent asthma</td>
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<tr>
<td>Relatively symptom-free period: no regular medications required to control symptoms of asthma</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Minimal</td>
</tr>
<tr>
<td>Minimal with acute and brief episodes of asthma</td>
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These included 2 male and 16 female patients (17 whites and one Polynesian Chinese). Fifteen were atopic (defined by ≥ 5 mm wheals with flares following a prick or intradermal skin test to a battery of common inhalant allergens), with the onset of their first asthma symptoms between the age of 1 year and 45 years (median, 32). Three were nonatopic, with the onset of their first asthma symptoms at age 13, 37, and 48 years, respectively. Twelve subjects reported never having smoked cigarettes. Three were ex-smokers at the onset of their first prolonged episode of persistent asthma during the study period and indicated a smoking history of 10 to 24 pack-years. The remaining three were smokers who quit smoking at the onset of their prolonged asthma episode. Their reported smoking histories were 1, 3, and 10 pack-years. One ex-smoker resumed smoking with a total smoking history of 20 pack-years, whereas the rest of the subjects did not resume or start smoking during the course of the follow-up.

Prolonged Episodes of Persistent Asthma

Sixteen subjects had intermittent asthma before the appearance of their first prolonged episode of persistent asthma. One patient had intermittent asthma before and after a prolonged asthma episode, which occurred before the study period. The remaining patient reported no previous history of asthma. During the study period, 15 patients had two prolonged episodes of persistent asthma, whereas 3 patients had three prolonged episodes. In all, we observed 39 episodes lasting from 2 to 74 months (median, 7). At the beginning of the episodes, the severity of asthma in 8 of 39 episodes was mild, in 19 episodes it was moderate, and in 12 episodes it was severe. The respective duration of the mild, moderate, and severe persistent asthma episodes were 2 to 9 months (median, 4); 2 to 65 months (median, 7); and 2 to 74 months (median, 17; Fig 1).

All asthma episodes demonstrated a similar pattern, with severity greatest at the onset, gradually becoming milder, and finally showing full recovery. The regular medications required to control the symptoms of asthma decreased during the course of the episodes, and paralleled the decreasing asthma medication requirement for the decreasing asthma severity described in Table 1.

Two of the severe episodes lasted 2 to 4 months, whereas the other 10 severe episodes lasted 6 to 72 months (median, 18). Among these latter episodes, the asthma was severe for the first 3 to 24 months (median, 6). This represents a range of 14 to 66% (median, 33%) of the total duration of the episodes (Fig 2). The two episodes that lasted for 2 to 4 months were not included in this analysis because the follow-ups were not frequent enough to determine the duration of the severe phase accurately.

There were four hospitalizations and 12 emergency department visits due to asthma. All occurred during the initial severe phase.

Figure 1 displays the relationship between the severity of asthma and the duration of the episode. The horizontal line represents median value.

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Symptoms</th>
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<tr>
<td>Very suggestive</td>
<td>Fever, sore throat, increased nasal congestion, rhinorrhea, cough, yellowish/greenish nasal discharge/postnasal drainage and sputum</td>
</tr>
<tr>
<td>Suggestive</td>
<td>As above, but without fever</td>
</tr>
<tr>
<td>Possible</td>
<td>Yellowish/greenish nasal discharge or sputum, with mildly increased symptoms of nasal congestion and rhinorrhea, with or without sore throats</td>
</tr>
<tr>
<td>Questionable</td>
<td>As “Possible,” but no colored nasal discharge or sputum</td>
</tr>
<tr>
<td>None</td>
<td>Absence of above symptoms</td>
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sodes. There was a positive correlation \( (p = 0.02, \) Kruskal-Wallis nonparametric analysis of variance).

There were 21 intervals between the episodes, lasting 1.5 to 63 months (median, 13). During the intervals, the severity of asthma was none in 11 patients, minimal in 6 patients, and minimal with acute and brief episodes in 4 patients with intervals between episodes lasting 9 to 57 months.

Follow-up after the last prolonged episode ranged from 1 to 35 months (median, 11). The severity of asthma after the last episode was none in 4 patients, minimal in 11 patients, and minimal with acute and brief episodes in 3 patients.

The Presence of Symptoms Suggestive of an Infection of the Upper Respiratory Tract and the Season at the Onset of the Prolonged Episodes

At the onset of the 39 prolonged episodes of persistent asthma, the presence of very suggestive, suggestive, possible, questionable, and no symptoms of an infection of the upper respiratory tract were 3, 19, 13, 1, and 3 episodes, respectively. Thus 56% of the episodes (95% CI, 40% to 72%) were associated with symptoms very suggestive or suggestive of an infection of the upper respiratory tract, 33% of the episodes (95% CI, 19% to 50%) had possible symptoms suggestive of an infection, whereas only 10% of the episodes (95% CI, 3% to 24%) had no or questionable symptoms suggestive of an infection of the upper respiratory tract.

Thirty-four of these 39 episodes had their onset between September and March, whereas 5 episodes had their onset between April and August \( (p < 0.001, \) assuming no seasonal pattern, based on \( \chi^2 \) goodness-of-fit test).

Thirty-five episodes were associated with yellowish or greenish nasal discharge/postnasal drainage, and/or sputum of the same color at the onset of the episodes. In 29 of these episodes, the duration of the yellowish or greenish nasal discharge/postnasal drainage lasted \(< 10\) days. In the remaining six episodes, the yellowish or greenish nasal discharge/postnasal drainage persisted for 1.5 to 3 months.

Pulmonary Function Measured by Spirometry

The mean of the lowest spirometric parameters measured for the patients during the prolonged asthmatic episodes were as follows: FVC, 70% predicted; \( FEV_1 \), 64% predicted; and \( FEV_1/FVC \), 0.68. When patients were symptom-free, the mean of the highest FVC was 99% predicted; \( FEV_1 \), 98% predicted; and \( FEV_1/FVC \), 0.79. Seventeen patients had their lung function normalized. The remaining patient had a persistent mild airway obstruction.

Discussion

We studied 18 patients who had two or more prolonged episodes of unexplained, persistent asthma to investigate the clinical features of these asthma episodes. All but one patient had the onset of their first such episode in adulthood, including the subject who had her first prolonged episode before the study period. We observe that these prolonged episodes of unexplained asthma have several characteristic features. The onset of the episodes often occurs between September and March. The majority of patients have symptoms suggestive of an infection of the upper respiratory tract at the onset of the episodes. These episodes of persistent asthma may last for years. During the asthma episodes, the severity of asthma decreases over time and eventually recovers. The severity of the asthma at the initial part of the episodes correlates positively with the duration of the episodes. And finally, these episodes can be separated by long and relatively asthma-free intervals that last months to years.

This kind of unexplained persistent asthma that is episodic in nature and lasts months to years has not been described previously. In studies of the natural history of asthma in adults and children, asthma is characterized with remission and relapse in many patients.\(^4\)–\(^{7,8\)–\(^{15}\)

The majority of our patients were atopic, but allergen exposure did not have an obvious correlation with these prolonged persistent asthma episodes. Nine patients had a dust mite allergy. They had 18 prolonged persistent asthma episodes ranging from 2 to 46 months, but did well during relatively asthma-free intervals that lasted 1.5 to 63 months.
without changes of their environment. Ten patients had positive skin tests to seasonal allergens of trees, grass, weeds, and molds, and 2 patients had mildly increased asthma in the grass season. However, their prolonged episodes of persistent asthma were unrelated to the seasonal occurrence of asthma in spring-summer-fall, with symptom-free periods in winter. Their prolonged episodes lasted 2 to 65 months (median, 6), with intervals between the episodes lasting 1.5 to 63 months (median, 20). Thirteen patients had positive skin tests to dog or cat allergens. Seven patients had a dog and/or cat in their home throughout the study period. Five patients removed the dog or cat from their home soon after the appearance of the first prolonged episodes. However, the subsequent episodes occurred despite the absence of dogs or cats in their homes. The remaining cat-allergic patient had no cats in her home throughout the study period. Two patients received allergy immunotherapy during the study period. One patient developed a prolonged episode of persistent asthma 6 months after the initiation of immunotherapy, when the immunotherapy just reached maintenance schedule. Another patient recovered from a prolonged episode of persistent asthma 1 month after the initiation of immunotherapy, which was still at the beginning stage of our immunotherapy schedule. In both instances, the recovery of the prolonged episode of persistent asthma could not be attributed to the effect of immunotherapy.

Thirty-four of the 39 episodes had the onset between September and March, which coincided with respiratory viral infection season, such as respiratory syncytial virus, parainfluenza virus, influenza virus, and adenovirus. The majority of these patients had symptoms suggestive of an infection of the upper respiratory tract at the onset of these episodes. These clinical features suggest that upper respiratory infections may be pivotal in the initiation of these episodes. Without microbiological data, however, this association cannot be certain.

In a review of 625 cases of asthma, Pearson noticed that following a respiratory infection, some patients developed a “subacute type of asthma” that often persisted for weeks or sometimes months. Recently, adenoviral and \textit{Chlamydia pneumoniae} infections have been associated with the onset of chronic persistent asthma in children and adults, and \textit{Mycoplasma pneumoniae} was found to be present in the lower airways of chronic, stable asthmatics with greater frequency than control subjects. Furthermore, adenovirus, \textit{M pneumoniae}, and \textit{C pneumoniae} have been shown to cause persistent infection or colonization in the airways. Whether the persistent infection/colonization of these microbial organisms and the persistence of asthma are causally related remains to be answered.

In this study, all prolonged episodes of persistent asthma had a similar course, being more severe at the beginning, becoming milder later, and finally recovering. Another observation is that the duration of the asthma episodes was positively correlated with the severity of the asthma measured at the initial part of the illness (Fig 1).

We investigated only those patients who had no asthma or intermittent asthma before and after the prolonged episodes of persistent asthma. Clinically, we have observed a similar pattern of prolonged exacerbations of asthma in patients with long-term, persistent symptoms. These latter patients were excluded from this analysis.

The study population in this study was limited to the practice of one author (KCC) between from 1977 to 1989. Those patients who had only one prolonged episode of persistent asthma during the study period or those who had prolonged exacerbations of asthma with long-term, persistent asthma were not included in the analysis. There were approximately several hundred patients under the care of the author during this period; hence, this pattern of prolonged episodes of persistent asthma is not uncommon.

The patients under our care were referred to us by primary care physicians from a large nonacademic prepaid health plan system. While patients under allergist care tend to be somewhat more severe and atopic than those under generalist care, they still reflect a broad spectrum of disease. We therefore feel that our results are generalizable to the larger community-based population with asthma.

In this series of patients, we are unable to determine the proportion of patients who had a prolonged sinusitis as a possible contributing factor to their prolonged asthma episodes. Thirty-five episodes were associated with yellowish or greenish nasal discharge/postnasal drainage at the onset of the episodes. In six episodes, the yellowish or greenish nasal discharge/postnasal drainage persisted for 1.5 to 3 months, which suggested the presence of a prolonged sinusitis. In the remaining episodes, the colored nasal discharge or postnasal drainage lasted < 10 days. Without microbiological data, however, the diagnosis of sinusitis could not be certain.

The observations learned in this study are useful for clinicians. When treating a patient with an acute asthma exacerbation occurring in September through March, and with symptoms suggestive of an infection of the upper respiratory tract, the clinicians should be aware that in some of these patients persistent asthma may develop and may persist for months to years. The clinicians also may predict that these asthma episodes may be more severe at the begin-
ning, becoming milder later, and may lead to full recovery. Furthermore, since the duration of a prolonged episode of persistent asthma can be as long as 6 years, when evaluating a patient who gives a history of persistent asthma for a few years, the treating clinician cannot be certain whether this patient is in the midst of a prolonged persistent asthma episode, or is destined to have a persistent asthma for the rest of his life.

The Expert Panel Report 2 of the National Asthma Education and Prevention Program recommended that appropriate step-down in pharmacologic therapy be carried out during follow-up visits. Our findings lend support to this recommendation because persistent asthma in some patients becomes milder and finally recovers. Because the median symptom-free interval is 13 months, the treating physician may consider stopping maintenance anti-inflammatory medications in those patients who have a prolonged remission. This would avoid unnecessary medical care cost as well as medication side effects. This practice is also compatible with the current Expert Panel Report 2 recommendation, since during the relative symptom-free intervals, these patients either had no asthma clinically or had intermittent asthma, and no controller medications are required. However, one should also consider that since the timing of the next episode cannot be predicted, continuing maintenance anti-inflammatory medications maybe preferable in order to prevent the occurrence or reduce the severity of the next episode. Another useful implication from our data is that the treating physicians should adjust the patient’s asthma severity classification when the asthma becomes milder or recovers.

Our findings also have significant implications for clinical research. Because the prolonged episodes of persistent asthma usually become milder over time, the favorable outcome comparing before and after an intervention or treatment may reflect the natural course of the disease in these patients who have this kind of prolonged persistent asthma episodes. An appropriate control group is needed for conducting proper investigations.

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