

Perspective

Thunderstorm asthma: An allergen-induced early asthmatic response



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Introduction

Thunderstorm asthma is recognized as an allergic phenomenon predominantly to grass pollen. In sensitized individuals, allergen exposure in the laboratory can cause an early asthmatic response (EAR) with or without a late asthmatic response (LAR). The bronchospastic EAR is an infrequent cause of acute asthma presentation. However, we present data to support our hypothesis that individuals with thunderstorm-induced asthma are presenting with acute, often severe, and occasionally fatal allergen-induced EARs.

Allergen Challenge

Allergen challenge in the laboratory results in an EAR followed in many cases by an LAR¹ (Fig 1). The EAR develops within minutes and usually resolves spontaneously over 60 to 120 minutes; the EAR is primarily due to bronchospasm and can be inhibited and rapidly reversed by an inhaled β_2 -agonist.¹ The magnitude of the EAR depends on 3 factors: the dose of the allergen, the degree of atopic sensitization to the allergen, and the underlying level of airway hyperresponsiveness (AHR).² The LAR begins to appear 3 to 4 hours after initial allergen exposure and can last for at least 8 hours; the LAR is inhibited by corticosteroids but not by bronchodilators.¹ The LAR is associated with allergen-induced increase in AHR³ and allergen-induced airway inflammation predominately with eosinophils and metachromatic cells.⁴ The AHR and inflammation can persist for at least several days after a single brief exposure. The LAR and its sequelae resemble naturally occurring allergic asthma and the allergen-induced LAR model in the laboratory has proved of great value in evaluating old and new approaches to asthma pharmacotherapy.⁵ We believe that ongoing or chronic LARs likely

explain most clinical allergen-induced asthma, including exacerbations.

Asthma Exacerbation

Exacerbations of asthma (allergic or otherwise) develop over several days and resolve over a similar timeframe.⁶ This is consistent with the effects of untreated (or inadequately treated) airway inflammation. For the usual allergen-induced asthma exacerbation, this would represent the cumulative or long-term effect of naturally occurring allergen-induced LARs. The inflammatory basis of asthma exacerbations is confirmed by the pathologic features seen in the airways of the large majority of patients with fatal asthma; the airways of such individuals demonstrate a marked inflammatory, usually eosinophilic, exudate with mucous plugging severe enough to lead to fatal respiratory failure.⁷

Although infrequent, acute allergen inhalation exposure (ie, an allergen-induced EAR) in an individual with otherwise well-controlled asthma can cause life-threatening bronchoconstriction,⁸ occasionally requiring intubation and mechanical ventilation.⁹ This is likely more common as a component of a systemic allergic reaction to a sting, bite, food, drug, or allergen injection (ie, to an injected or ingested allergen). The asthma in some of these events can actually be upper airway (primarily laryngeal) obstruction. The pathologic correlate would be the minority of patients who die suddenly from asthma with so-called open airways.¹⁰

Thunderstorm Asthma

Background

There are several reported epidemics of thunderstorm asthma (Table 1), 8 of which have been reported in some detail.^{11–21} Epidemics have occurred primarily in (or been reported from) Australia (n = 6) and the United Kingdom (n = 3) with only 1 in North America (Table 1). The epidemics are characterized by a large number of patients with acute asthma presenting for emergency care over a short

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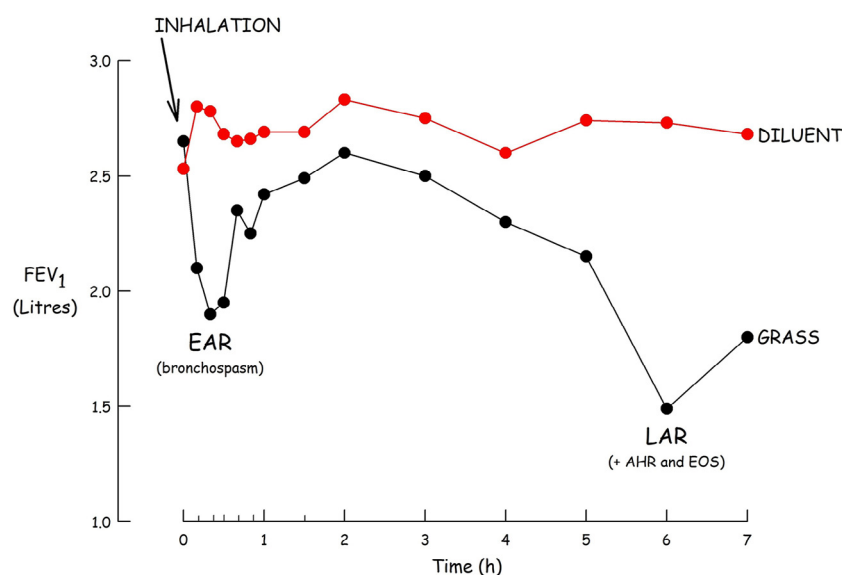


Figure 1. Allergen-induced dual asthmatic response. Forced expiratory volume in 1 second (FEV₁; liters) is on the vertical axis and time (hours) after inhalation challenge is on the horizontal axis. The early asthmatic response (EAR) is maximal at 20 minutes and resolves spontaneously by 2 hours, and the late asthmatic response (LAR) starts at 4 hours and is associated with increases in airway hyperresponsiveness (AHR) and in airway eosinophils (EOS) and metachromatic cells.

period during or shortly after a thunderstorm. The threshold for reporting appears to be 5- to 10-fold greater than the usual numbers of asthma attendances in the emergency department (Table 1). The most severe epidemics, in 1994 in London (640 patients) and in 2016 in Melbourne (>8,500 patients), overwhelmed ambulance and emergency services.^{15,21} Most asthma deaths²¹ were likely due to delay in accessing emergency transport to a hospital. There are references to other, likely less severe, epidemics of thunderstorm asthma that have gone undescribed.¹⁷ The suggested pathogenesis is exposure, in sensitized individuals, to osmotically fragmented allergen particles, predominately grass pollen (rye grass in Melbourne), created by the updrafts, downdrafts, and outflows occurring during severe thunderstorms (Fig 2).¹⁸ Other allergens, alone or in combination, including other pollen and *Alternaria* fungal spores, have occasionally been implicated.²⁰ We analyzed data primarily from

5 reports: Birmingham, United Kingdom in 1983,^{11,12} Melbourne, Australia in 1987 and 1989,¹⁴ London, United Kingdom in 1994,^{15,16} and Wagga Wagga, Australia in 1997.^{17,18} We assessed, where available, the prevalence and degree of (grass pollen) sensitization, the nature of the affected individuals, the magnitude of exposure, the time course from exposure to presentation, and the rate of hospitalization.

Sensitization

Allergen-specific immunoglobulin E (IgE) antibodies were determined by skin prick testing (n = 3)^{12,14,17} or serologic testing (n = 1)¹⁶ in generally small subsets of affected individuals, with the largest cohort being from the Wagga Wagga epidemic (116 of 215).¹⁷ Sensitization to grass pollen was found in 96% to 100% of those tested.

Table 1
Reported Epidemics of Thunderstorm Asthma

Location; date	N	Admit	ICU	Death	Normal number (fold ↑)	Children	Comments	Reference
Birmingham; July 6, 1983	106	36		0	2–20 (>5×)		Grass pollen ↑; positive SPT reactivity to grass in 17 of 18	11,12
Melbourne; November 11, 1984	85			0		"Only 1 child"		13
Melbourne; November 8, 1987	154	26	1	1	26 (6×)	Adults only mentioned		14
Melbourne; November 29, 1989	277	47	3	0	26 (11×)	Adults only mentioned	Marked positive SPT reactivity to grass (mean wheal size 14 mm, n = 12)	14
London; June 24, 1994	640	104	5	0	66 (10×)	13%	PM 2.9 μm = 130,000/m ³ ; grass pollen ↑↑; serum grass specific IgE ↑↑; 488 cases elsewhere	15,16
Wagga Wagga; October 30, 1997	215	41	2	0	~2 (~100×)	12%	Grass pollen ↑↑+ pollen husks; positive SPT reactivity to grass in 111 of 116; outflow 30 min before ambulance	17,18
Calgary; July 31, 2000	157			0	17 (9×)	No increase at children's hospital		19
Cambridge; July 29, 2002	57		3	1 (DOA)	8 (7×)	14%	Additional cases elsewhere; <i>Alternaria</i> spp possibly implicated; positive SPT reactivity to grass in 22 of 26	20
Melbourne; November 25, 2010	~300			0				a
Melbourne; November 21, 2016	>8,500			10	26? (>100×)			21
Kuwait; December 1, 2016	844			5				a

Abbreviations: DOA, dead on arrival; ICU, intensive care unit; IgE, immunoglobulin E; PM, particulate matter; SPT, skin prick test.

^aGoogle search for "thunderstorm asthma."

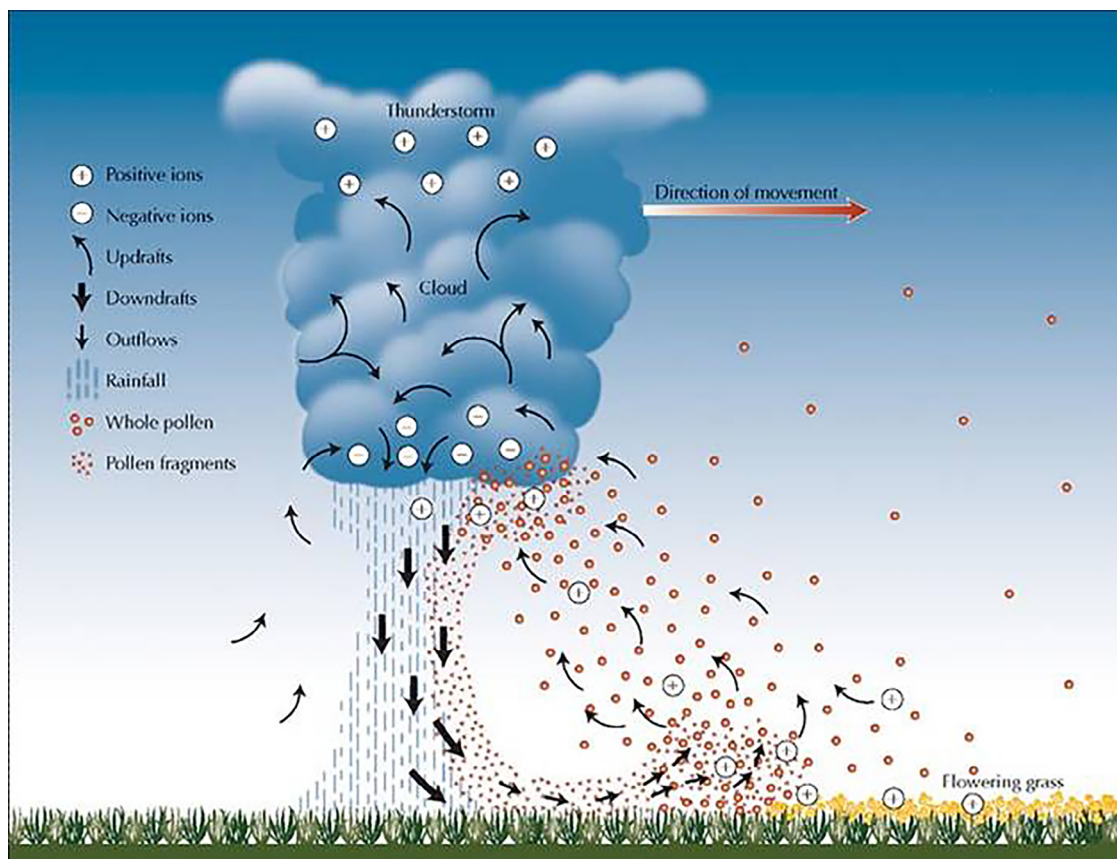


Figure 2. Hypothesized pathogenesis of thunderstorm asthma. Updrafts lift whole grass pollen into moisture-rich clouds, resulting in osmotic fragmentation of pollen. The downdrafts and outflows are allergen rich and the allergen load can increase as the storm moves over grass fields. Reproduced with permission from Taylor PE, Jonsson H. Thunderstorm asthma. *Curr Allergy Asthma Rep.* 2004;4:409–413, Figure 1.

Only 2 reports commented on the magnitude of the sensitization. All 12 tested cases from the Melbourne event in 1989 had skin test positivity to grass pollen.¹⁴ The mean wheal size from the skin prick tests was reported as 150 mm²; this equates to a mean wheal diameter of approximately 14 mm, an exceptionally large average skin prick test size. In 16 patients from the London epidemic, 12 (75%) were noted to have very high levels of serum grass pollen-specific IgE reported as classes 4 to 6 (CAP; Pfizer, New York, New York).¹⁶ These somewhat limited data support a very high prevalence of sensitization to grass pollen in affected individuals and suggest that many (possibly most) individuals have particularly high levels of allergen-specific IgE.

Subjects

The age range of affected individuals appeared different than the usual age range of emergency patients. More than 50% were 20 to 40 years old compared with the normal rate of fewer than 20% (estimated from figure 5.17 of the Australian Institute of Health and Welfare²²). This is an age when total and pollen-specific IgE tends to be at the highest level.²³ Two reports noted (surprisingly) that there was no increased asthma presentations in children,^{13,19} 2 mentioned only adults¹⁴ and 3 others reported that fewer than 15% of affected subjects were children (Table 1)^{15,17,20}; in contrast, children usually represent more than 50% of emergency patients with asthma.^{22,24} Approximately 50% of affected individuals did not have a physician diagnosis of asthma, with many only admitting to allergic rhinitis.^{16,17} In addition, 1 study commented that “asthma

tended to be less severe in the thunderstorm cases ... compared to those attending at other times.”¹⁷ Thus, the affected individuals tended to have otherwise mild, if not unappreciated, asthma with limited use of inhaled corticosteroid and many with no available bronchodilator and were at the age when allergen-specific IgE is at its highest level. Such individuals likely (probably in retrospect) had at least mild and more likely moderate (and untreated) AHR.

Exposure

There are limited data that allow an assessment of the exact magnitude of grass pollen exposure. In 3 events grass pollen levels were noted to be particularly high before the thunderstorm^{11,12,16,18} and low during and/or after the storm.^{16,18} One study noted a marked spike in whole grass pollen grains and what was described as empty pollen husks,¹⁸ presumably pollen grains that had been osmotically ruptured (by the hypotonic cloud or rain water) to release highly allergenic starch granules.²⁵ During the 1994 London epidemic, there was a great spike in small inhalable particulate matter (<2.9 µm) peaking at more than 130,000 particles/m³,¹⁶ approximately 40 times the previous high and nearly 100 times the average. Although not further characterized, it is likely that these small particles would have contained small and inhalable grass pollen fragments, which have been shown to be released under rainy conditions.²⁵ The storm-related updrafts lift pollen into the storm, where the hypotonic moisture causes rupture. The downdrafts and outflows are hypothesized to deliver large doses of fragmented pollen; this allergen load

is likely to increase as the storm moves over allergen-rich grasslands¹⁸ (Fig 2).

Time Course

The difficulty in assessing the time course of presentation is in the uncertainty as to when the exposure began. There is no doubt that the asthma appeared suddenly and overwhelmed ambulance and emergency department services.^{15,18,21} The best data come from the 1997 Wagga Wagga epidemic. The thunderstorm outflow commenced at 9:42 PM¹⁸; this is presumed to be the beginning of the peak intensity exposure. The first ambulance call was less than half an hour later at 10:08 PM,¹⁸ and it was reported that 183 patients presented to the emergency department that day¹⁷ (ie, within a 2-hour timeframe). Although the data are limited, there is a likelihood that, in many of these individuals, there was a short interval from exposure to the development of asthma significantly severe enough to result in the requirement for emergency treatment.

Admissions

The admission rate for these 5 epidemics was 254 of 1,392 or approximately 18% (Table 1).^{11,14,15,17} This was compared with data from Australia for approximately the same period.²² The 18% admission rate was less than half that seen in emergency department asthma presentations in New South Wales (42%). When children were excluded, this was still significantly less than the 32% admission rate.²² These data suggest that a smaller proportion of patients with thunderstorm-induced asthma require hospitalization and implies a more rapid recovery, on average, compared with the usual patient with asthma in the emergency department.

Conclusion

These data give strong support to the hypothesis that individuals afflicted by thunderstorm asthma are experiencing allergen-induced EARs, which are primarily acute bronchoconstriction events. The features supporting this contention are the high degree of grass pollen allergy, the high allergen exposure, the prevalence of (probable) moderate and untreated AHR, the short interval from exposure to presentation, and the apparent (average) relative rapidity of recovery. We believe acute EARs are otherwise relatively infrequent explanations for asthma exacerbations requiring emergency treatment. This has more mechanistic than clinical relevance. Acute treatment of such patients should not be affected, because they will require a bronchodilator for the (predominant) bronchoconstriction and corticosteroids to treat or prevent the subsequent LAR. The latter is of particular importance; there is a possibility that those who recover very rapidly might be (inappropriately) judged not to require corticosteroid. These data also suggest that patients with mild, even very mild, asthma, if they can be identified, should have immediate ambulatory access to asthma therapy; such highly sensitized individuals also should be advised, by way of prevention, to remain indoors with closed windows during severe thunderstorms.

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