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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 LAR[1] (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 AHR[3] 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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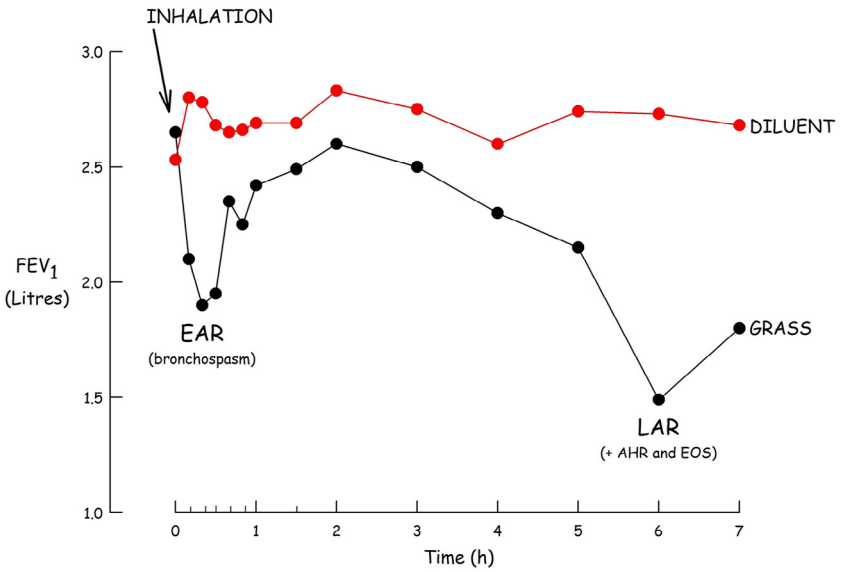

Figure 1. Allergen-induced dual asthmatic response. Forced expiratory volume in 1 second (FEV_1; liters) is on the vertical axis and time (hours) after inhalation challenge is on the horizontal axis. The early asthmatic response (EAR) is maximal at 20 minutes and resolves spontaneously by 2 hours, and 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 deaths[21] 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; *Alternaria* 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.
[a]Google search for "thunderstorm asthma."