

Thunderstorm-triggered asthma: what we know so far

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Abstract: Thunderstorm-triggered asthma (TA) is the occurrence of acute asthma attacks immediately following a thunderstorm. Epidemics have occurred across the world during pollen season and have the capacity to rapidly inundate a health care service, resulting in potentially catastrophic outcomes for patients. TA occurs when specific meteorological and aerobiological factors combine to affect predisposed patients. Thunderstorm outflows can concentrate aeroallergens, most commonly grass pollen in TA, at ground level to release respirable allergenic particles after rupture by osmotic shock related to humidity and rainfall. Inhalation of high concentrations of these aeroallergens by sensitized individuals can induce early asthmatic responses which are followed by a late inflammatory phase. Other environmental factors such as rapid temperature change and agricultural practices contribute to the causation of TA. The most lethal TA event occurred in Melbourne, Australia, in 2016. Studies on the affected individuals found TA to be associated with allergic rhinitis, ryegrass pollen sensitization, pre-existing asthma, poor adherence to inhaled corticosteroid preventer therapy, hospital admission for asthma in the previous year and outdoor location at the time of the storm. Patients without a prior history of asthma were also affected. These factors are important in extending our understanding of the etiology of TA and associated clinical indicators as well as possible biomarkers which may aid in predicting those at risk and thus those who should be targeted in prevention campaigns. Education on the importance of recognizing asthma symptoms, adherence to asthma treatment and controlling seasonal allergic rhinitis is vital in preventing TA. Consideration of allergen immunotherapy in selected patients may also mitigate risk of future TA. Epidemic TA events are predicted to increase in frequency and severity with climate change, and identifying susceptible patients and preventing poor outcomes is a key research and public health policy priority.

Keywords: asthma, thunderstorm, rhinitis, ryegrass

Introduction

Thunderstorm-triggered asthma (TA) is the occurrence of acute asthma attacks immediately following a thunderstorm.¹ TA epidemics are uncommon and are believed to occur when specific meteorological and aerobiological conditions combine to affect predisposed patients. Symptoms such as breathlessness, cough or wheeze occur suddenly in such patients due to bronchospasm and often require emergency medical treatment via a general practitioner or emergency department (ED) presentation and/or hospitalization. Episodes occur typically during storms in pollen season across the world.²

The largest and most devastating epidemic of TA occurred in Melbourne, Australia, in November 2016 where more than 3,400 people sought emergency medical attention and 10 deaths were reported.³⁻⁶ The unprecedented scale and

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severity of the attack and the unexpected nature of the event saw emergency services rapidly overwhelmed.^{3,4} It demanded an urgent and thorough investigation into the phenomenon of TA via coronial inquiry and a rethink on the likely attributable factors and what we can do to prevent such tragic outcomes in the future.

Since the Melbourne 2016 event, there have been a number of publications that have furthered our understanding of TA. In the absence of randomized trial data, we rely on retrospective analyses for potential risk associations as well as data from some case-control studies. Further research using larger cohorts and longer-term studies are required.

Epidemiology

Epidemics of TA have occurred throughout the world and are characterized by a rapid increase in emergency visits for asthma to general practices or hospital EDs following a storm, above what would normally be expected for that area.^{1,5} In Australia, community pharmacies can also be overwhelmed, likely due to the over-the-counter availability of short-acting β_2 -agonist (SABA) medications.³ These epidemics affect large numbers of people and can be potentially fatal, as the Melbourne 2016 epidemic uncovered.⁵

TA epidemics were first described over 30 years ago and have occurred in the UK, North America, Southern Europe and the Middle East during the late spring or early summer pollen seasons (Table 1).^{4,5} Most frequently however, events have occurred in Australia – all during the Spring season and most commonly in November – with at least six discrete events in Melbourne alone since 1984 and elsewhere including rural New South Wales and Canberra.^{3–5} Grass pollen is believed to have triggered all Australian events as well as the majority of events worldwide. Fungal spores and other types of pollen (such as olive) have been implicated in some of the events in the UK, Italy and Canada.^{4,7}

While TA epidemics are considered relatively uncommon, asthma exacerbations following thunderstorms are likely underreported. An observational study in the US analyzed more than 215,832 asthma ED presentations between 1993 and 2004 and reported an increased risk of emergency visits following a thunderstorm of 3%.⁸ A Canadian study found that risk was elevated up to 35% when only summer emergency visits were analyzed.⁹ Concomitant analysis on pollen or air pollution concentrations was not performed in these studies however. A separate study looking at seasonal variation in

asthma admissions in Melbourne from 1991 to 2015 found peaks in hospital admission at the beginning of the school year, in the winter months and during peak pollen season. It suggested that TA could be a semi-regular seasonal occurrence that can go unrecognized and may be responsible for more of the total asthma burden of the disease than originally thought.¹⁰

Prior to the Melbourne 2016 event, deaths from TA were rare.⁵ However, TA events are predicted to increase in frequency and severity.² In the scientific literature, description of epidemics of TA in various geographical areas of the world and climate change scenarios indicate there will be an increase in extremes of weather and intensity of heavy rainfall episodes, including thunderstorms, across the world.^{2,5} It is thus prudent to examine the contributing factors in at-risk regions specifically to identify important or interacting variables that may affect or lead to prevention of such events in the future.

Previous epidemiological studies have identified at-risk populations as those with diagnosed asthma (in particular, individuals with poorly controlled asthma and those not taking regular preventer medication), those with undiagnosed asthma and those with seasonal allergic rhinitis or ryegrass allergy.^{3,6,11,12}

Mechanism

The most current evidence suggests that TA results from a complex interaction of environmental factors and individual susceptibility factors.⁶ TA events occur when a high concentration of aeroallergens (most commonly grass pollen and/or fungal spores) are concentrated at ground level by the thunderstorm outflow tract. Allergens can then reach the lower airways of sensitized individuals by being broken into smaller particles due to osmotic shock related to rainfall and humidity.^{13,14}

The role of ryegrass pollen in TA has been established in the seminal papers by Suphioglu, Knox and colleagues where starchy granules derived from ryegrass pollen particles, observed in pollen trap specimens from a recent TA event, were re-created in the laboratory by soaking pollen particles in water.^{15,16} Intact grass pollen grains (35–40 μm) are usually too large to be respirable to the lower airways. Ruptured pollen grains, however, can release up to 700 starch granules smaller than the maximum 5 μm particle size required to reach the lower airways. These starch particles were demonstrated to contain major ryegrass allergens and were subsequently used to induce striking asthma following bronchial challenge in ryegrass sensitized patients.^{15–17} The

Table I Previously reported thunderstorm-triggered asthma events

Location	Date	Number of TA patients presenting to ED	Proposed allergen trigger
UK, Birmingham ⁴²	1983, July	106	Fungal spores
Australia, Melbourne ⁴³	1984, November	85	NS
UK, Nottingham ⁴⁴	1984, June	19	Fungal spores
Australia, Melbourne ⁴⁵	1987, November	154	NS
UK, Leicester ⁵	1989, July	32	Fungal spores
Australia, Melbourne ⁴⁵	1989, November	277	Grass pollen
Australia, Tamworth ⁴⁶	1990, November	110	Grass pollen
UK, London ^{47,48}	1994, June	640	Grass pollen
Australia, Wagga Wagga ⁴⁹	1997, October	215	Grass pollen
Australia, Newcastle ⁵⁰	1998, October	6	Grass pollen
Canada, Calgary ⁵¹	2000, July	157	Fungal spores Pollen
UK, Cambridge ⁷	2002, July	57	Fungal spores
Saudi Arabia, Al-Khobar ⁵²	2002, November	NS	NS
Australia, Melbourne ⁵³	2003, November	70	Grass pollen
Italy, Naples ⁵⁴	2004, June	7	Pollen
UK, South-East England ⁵⁵	2005, June	0 (none to ED)	NS
Italy, Puglia ⁵⁶	2010, May	20	Olive pollen
Australia, Melbourne ⁵	2010, November	36	Grass pollen
Australia, Melbourne ⁵⁷	2011, November	30	Grass pollen
UK, London ⁵⁸	2013, July	40	NS
Iran, Ahvas ⁵⁹	2013, November	>2,000	NS
Australia, Canberra ⁵	2014, October	15	Grass pollen
Australia, Melbourne ⁶⁰	2016, November	>3,400	Grass pollen

Abbreviations: TA, thunderstorm-triggered asthma; ED, Emergency Department; NS, not specified.

role of ryegrass is further supported by the presence of ryegrass-specific IgE being an almost universal finding in TA sufferers during the Melbourne 2016 event.⁶

The role of molds causing TA events is more contentious. It is evident that mold particles are a trigger for hospitalizations in some environments and that mold spores of many species are frequently detected in pollen traps but are not routinely reported.¹⁸ While increased prevalence of allergic sensitization to molds has been reported in TA sufferers,¹⁹ this has not been uniformly found.¹³ However, fungi can stimulate the innate immune system independently of IgE to cause inflammation, suggesting an alternative immunological pathway to airway inflammation that has yet to be confirmed in TA.²⁰

The rapid onset and offset of symptoms in those affected during TA events have been attributed to allergen-induced early asthmatic responses which are followed by the late inflammatory phase. As classically described in allergic asthma, pollen particles can initiate mast cell degranulation and bronchoconstriction within a few minutes.¹⁵ In predisposed individuals, exposure to ryegrass antigens, for example, can initiate the sensitization

process by activating antigen-presenting cells (including dendritic cells and macrophages), Th2 lymphocytes and trigger heavy-chain class switching in B lymphocytes in favor of IgE production. On allergen re-exposure, cross-linking of IgE to the high-affinity receptor (FcεR1) complex on the surface of mast cells and basophils in these IgE-sensitized individuals initiate the IgE early response. The release of histamine, tryptase, leukotriene and prostaglandin all contribute to mucus secretion, mucosal edema and airways smooth muscle contraction.²¹

The early asthmatic response depends on the degree of sensitization to an allergen, the magnitude of the untreated airway hyperresponsiveness and the dose of allergen inhaled.²² The late asthmatic response follows with Th2 lymphocyte activation, type 2 cytokine formation (IL4, IL-5, IL-9 and IL-13) and an influx of inflammatory cells including eosinophils. This later response is responsive to corticosteroid treatment.²³

IgE responses in murine models showed that exposure to pollen grains or starch particles less than 5 μm resulted in higher eosinophil, lymphocyte and pro-allergy cytokine levels in the lung, linking these inflammatory responses to

asthma-related allergic symptoms.²⁴ Interestingly, after repetitive high-dose and short-interval bronchial allergen challenges, patients who developed late response inflammation were at more risk of developing severe bronchospasm on subsequent allergen challenge.²⁵ This has implications on the future risk and prevention of TA in patients with a prior history of asthma or TA.

These early and late asthmatic responses were also observed in the 2016 Melbourne TA epidemic. Some patients had acute bronchospasm necessitating acute resuscitation in the minutes following the thunderstorm, whilst others self-medicated with short-acting bronchodilators without seeking medical advice, consistent with rapid resolution of bronchospasm in the early asthmatic response. Asthma presentations were also higher in the 24 hrs after the event, with a second peak for ambulance calls 4 hrs after the initial event, suggesting a late response after unsuccessful treatment with bronchodilator alone.³

Contributing factors

Environmental factors

Why TA occurs in some years and not others is incompletely understood. The requirement for both thunderstorm activity to co-exist with high levels of airborne aeroallergens is already known.¹³ In Melbourne, high grass pollen seasons have also been shown to correlate well with high winter rainfall.⁵ In vitro studies show that a cycle of humidifying, wetting and drying of flowering grasses, followed by wind disturbance, releases grass pollen allergen as respirable aerosols directly from the flower.²⁶ Concordantly, ruptured ryegrass was increased by 147% after the passage of the storm in the Melbourne 2016 event.³

Although many TA events in Melbourne follow wet winters, this does not explain all events. In addition, not everyone with grass pollen allergy or allergic rhinitis is at risk of asthma during thunderstorm-triggered asthma epidemics and asthma epidemics can similarly occur without thunderstorms.⁵ Other environmental factors, such as sudden cold, have also been postulated in TA.^{14,27} The 2016 Melbourne event saw a rapid and dramatic fall in temperature and a rise in relative humidity levels as the storm front passed. A similar pattern was seen during the 1994 London TA epidemic.²⁷ Total rainfall was minimal, however, during the Melbourne event.³

The impact of air pollution has been questioned but has not yet been conclusively proven to contribute to causation of TA. The Environment Protection Authority Victoria,

measuring fine particle air pollutants PM_{2.5} and PM₁₀ in Melbourne in 2016, found no increase in PM_{2.5} but elevated levels of PM₁₀ (particles ≤10 μm) after the storm outflow passage. However, elevated PM₁₀ levels are a common finding during high wind events and have not been shown to correlate with previously identified TA days.³

Air pollution can increase airway hyperresponsiveness to aeroallergens in atopic individuals.²⁸ It has been postulated via experimental models that by attaching to the surface of pollen grains, pollutants could modify the allergenic potential of these particles, induce airway inflammation and hence permeability in order to overcome the mucosal barrier of the lung and enhance IgE-mediated responses to aeroallergens. Furthermore, airway mucosal damage and impaired mucociliary clearance due to air pollution has been thought to facilitate the access of inhaled allergens to cells of the immune system and promote airway sensitization.²⁸ Type 2 cytokines are also further increased when pollen is combined with diesel exhaust particles.²⁹

Agricultural activity has also been thought to contribute to TA by releasing high levels of fungal spores and grass pollens. Ryegrass, with widespread pastures to the north of Melbourne, have clearly been implicated in the Australian epidemics. Wheat harvesting has been thought to be implicated in other parts of the world where fungal spores are considered the predominant aeroallergen.⁵

The role of aeroallergens

In the Australian sub-continental region, most patients who suffer from seasonal allergies are sensitized to ryegrass.³⁰ As we know, high levels of aeroallergens in the air are required for TA to occur. Both the Melbourne 2016 and other Australian events occurred on high grass pollen days and ryegrass was implicated. Ryegrass is abundantly grown in Australia and the peak of its pollen season is November which coincides with periods when TA is most likely to occur.³ Other outbreaks around the world have shown fungal spores (such as *Alternaria*, *Cladosporium* and *Didymella* species) to be implicated.⁷

The effect of aeroallergens on an individual depends on their exposure and their allergic sensitization status to that aeroallergen. Prior studies have found that those not allergic to the triggering allergen source and those who stayed indoors seemed to be protected from risk.^{2,12} Thus, there may be some evidence that remaining indoors during and after a thunderstorm is protective. Furthermore, IgE-mediated

responses via skin prick testing or measurement of serum-specific IgE concentrations may give some insight into the degree of sensitization of an individual to an aeroallergen.³¹

Individual susceptibility factors

Vulnerability to TA appears to be linked to an individual's allergic sensitivity and disease status. Individuals need to be either 1) sensitized to the triggering allergen, 2) suffer from allergic rhinitis (hay fever) with or without asthma or 3) be exposed to the open air and not be on preventative asthma treatment.³ There is no clear common allergen globally; however, in the Australian epidemics, there has been almost universal allergic sensitization to ryegrass.¹²

This is also supported by the vulnerability factors found in the individuals who were followed-up after the Melbourne 2016 epidemic. In these individuals, being affected by TA was associated with: allergic rhinitis, ryegrass pollen sensitization, pre-existing asthma, poor adherence to inhaled corticosteroid (ICS) preventer, hospital admission for asthma in the previous year and outdoor location at the time of the storm.⁶

Although most patients in the cohort did not have doctor-diagnosed asthma, all of the 35 critically ill patients admitted to ICU did have a previous diagnosis of asthma, suggesting more severe TA in known asthmatics. Of these, 66% were not on preventer medications, implicating issues with sub-optimal control of asthma and treatment adherence as contributing factors.^{6,22,32}

The ICU patients with TA during the event had a very high mortality (14%) compared to non-TA asthma patients presenting at other times in that year (1%).³² TA patients admitted to the ICU were also more likely to be male (63%). This is in contrast to the largely female predominance of those affected by non-epidemic adult asthma, previously attributed to hormonal differences in gender.³²⁻³⁴

There was also a novel finding of ethnic predominance of Asian ethnicity in affected patients during the Melbourne 2016 event.⁶ In those of Asian ethnicity, those born in Australia had a higher risk of TA than those born overseas. Patients of Asian ethnicity were also over-represented in the ICU admissions and it is interesting that previous studies also found increased prevalence of non-epidemic asthma, hay fever and allergic rhinitis amongst Asian migrants to Australia compared with non-migrant populations.^{6,11,32,35} This may imply further genetic and environmental interactions which are currently poorly understood.

Overall, these findings suggest that not only do factors of ethnicity and gender predispose patients to TA beyond

differences in asthma education and management alone, but that TA patients appear to represent a population that is different to those with non-epidemic asthma. This appears to be supported by literature during the London 1994 TA epidemic which suggested that TA patients appear to be sensitive to different environmental stimuli with non-epidemic asthma being related to air pollution and lightning strikes, for example, which was not found with TA.²⁷

Another concerning statistic in the Melbourne 2016 cohort is that more than 50% of the individuals did not have a previous diagnosis of asthma although a large proportion (26%) had symptoms suggestive of latent asthma.¹¹ This has important implications in prevention of TA by especially targeting those with symptoms of asthma to optimize their asthma control prior to pollen season. This would include advice regarding adherence to preventer treatment and carrying reliever medication in the event of an unexpected asthma attack.

However, this finding also poses a problem in understanding how to best identify those at risk with neither a prior history of asthma nor symptoms of asthma. This unexpectedly large proportion of those experiencing asthma for the first time during a TA epidemic makes predicting those at risk difficult and, currently, there is no evidence-based prevention advice for this group of patients.

It is interesting, however, that 90–100% of those affected with acute breathing difficulties during thunderstorm events both locally and internationally had a history of allergic rhinitis. Thus, targeting this group may be more useful on a population level. However, 15% of Australians suffer from allergic disease and up to two-thirds of those have grass pollen allergy, making the problem widespread and difficult to predict.⁵

The link between allergic rhinitis and asthma is an important one nonetheless. Most patients with asthma have rhinitis (both allergic and non-allergic) and general recommendations are to treat both conditions where they co-exist.⁶ The presence of rhinitis is associated with asthma and increases the risk of emergency visits and hospitalization due to asthma.^{36,37} Interestingly, it appears that TA is primarily an allergic, IgE-mediated airways response in atopic subjects to trigger factors (such as grass pollens) and subjects with non-allergic asthma do not appear to be involved in TA epidemics.² Intranasal corticosteroid sprays, antihistamines, and in some patients, specific allergen immunotherapy directed at controlling rhinitis symptoms are strongly encouraged and may mitigate the risk of TA in these patients.^{23,36,37}

Ryegrass pollen sensitization was found to be universal in those retrospectively examined in the Melbourne 2016 epidemic and previous studies have found that allergen-specific IgE may be a reliable biomarker for allergen-related symptoms.^{12,38,39} The role of biomarkers such as serum-specific IgE and measurement of airway inflammation via exhaled nitric oxide to characterize those at risk of future TA events are uncertain however.

Prevention

Education campaigns aimed at understanding good asthma control and adherence to preventer medications may protect asthmatic patients from experiencing exacerbations during TA epidemics. Adequate control of seasonal rhinitis and advice to seek medical attention if symptoms escalate or symptoms indicative of asthma develop (wheeze, cough, breathlessness) should be promoted in public health messaging.

Predicting patients who will experience symptoms of asthma for the first time or which seasonal rhinitis patients are at risk of TA is difficult. Immunological and genetic biomarkers may be useful and are currently being explored, as are studies investigating whether treating high-risk allergic rhinitis patients with asthma treatments or with allergen immunotherapy will prevent progression to asthma.^{30,38,39}

Development of pollen counters and applications in conjunction with weather forecasting may form the beginnings of an alert system for TA to health services and high-risk individuals. Public health warnings need to be delivered with a timely, targeted and evidence-based approach.¹

The factors that contribute to rapid changes in weather and the ability to understand whether these can be reliably predicted over time remain a priority. The ability to accurately predict thunderstorms and a TA epidemic based on the known requisite factors for such an event would inform a public health warning system. This has been difficult to develop however as prediction models that would be required to integrate multiple information sources are complex and difficult to enact on a large scale. At present, the high false alarm rate for such a warning system would be deemed unacceptable.⁶ Nevertheless, collaboration between health services, governmental departments, biologists, meteorologists, epidemiologists and the community and more effective communication methods between these groups is required.

Perhaps the bigger issue, however, is that of sub-optimally controlled asthma in the community at large. This was uncovered with devastating effect during the Melbourne 2016 epidemic. In Australia, the prevalence of asthma in children is

among the highest in the world (up to 20%) and in 2015, 421 people died of asthma overall.⁴

The risks of even mild asthma can be underestimated by both clinician and patient. Over-reliance on SABA reliever medication and poor adherence to ICS, despite their proven efficacy, can increase risk for exacerbations. Large randomized controlled studies assessing the use of as-required ICS/long-acting β_2 -agonist (LABA) combinations in mild asthma as an alternative to regular low-dose ICS showed prevention of exacerbations and loss of lung function and reduced glucocorticoid exposure however was less effective at symptom control. Nevertheless, as-required ICS/LABA treatment may be a more pragmatic way to address the issues of poor adherence to regular ICS.^{40,41}

TA is not frequent and not the main trigger for allergic respiratory disease overall but can teach us important lessons on the importance of good asthma control.^{2,6,10-12} Government campaigns and public health messaging need to focus on this. General practitioner and ED pathways for asthma management, including provision of asthma action plans, should be optimized as well as emergency response pathways during a TA epidemic.

Conclusion

TA is a sudden and potentially deadly phenomenon that has the capability to rapidly inundate emergency resources and relies on a complex interaction of environmental and individual patient susceptibility factors. As TA events are predicted to increase in frequency, the impact of climate change, changing agricultural practices and air pollution needs careful consideration. Further research on how to predict these events is vital and will require collaboration between health services, governmental departments and the community.

An early warning system based on environmental factors to alert emergency services and allow communication to at-risk individuals is necessary; however, it is difficult to implement given an unacceptably high false alarm rate currently.

The further challenge is to identify those individuals at risk and target prevention strategies efficiently and effectively. Those with known asthma should have treatment optimized and be educated on adherence to preventer treatment. Seasonal rhinitis patients should be evaluated for asthma symptoms also and have rhinitis optimized via nasal corticosteroids. Consideration of grass pollen immunotherapy may offer opportunities to treat both allergic rhinitis and asthma in these circumstances.

Finally, further research into understanding the pathophysiology behind the effects of TA in susceptible individuals is

paramount. Development of potential biomarkers that would signal an at-risk patient would mean these individuals could be pre-emptively treated, thus mitigating risk for future TA attacks in the inevitable event of a repeat TA epidemic.

Disclosure

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