Continued loss of asthma control following epidemic thunderstorm asthma

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ABSTRACT

Background: Epidemic thunderstorm asthma (ETSA) severely affected Melbourne, Australia in November 2016. There is scant literature on the natural history of individuals affected by ETSA.

Objective: A multicentre 12-month prospective observational study was conducted assessing symptomatology and behaviors of ETSA-affected individuals.

Methods: We used a structured phone questionnaire to assess asthma symptom frequency, inhaled preventer use, asthma action plan ownership and healthcare utilization over 12 months since the ETSA. Analysis of results included subgroup analyses of the “current,” “past,” “probable,” and “no asthma” subgroups defined according to their original 2016 survey responses.

Results: Four hundred forty-two questionnaires were analyzed. Eighty percent of individuals reported ongoing asthma symptoms at follow-up, of which 28% were affected by asthma symptoms at least once a week. Risk of persistent asthma symptoms was significantly higher in those with prior asthma diagnosis, current asthma, and probable undiagnosed asthma (all \( p < 0.01 \)). Of 442 respondents, 53% were prescribed inhaled preventers, of which 51% were adherent at least 5 days a week. Forty-two percent had a written asthma action plan and 16% had sought urgent medical attention for asthma in the preceding year.

Conclusions: Following an episode of ETSA, patients experience a pivotal change in asthma trajectory with both loss of asthma control and persistence of de novo asthma. Suboptimal rates of inhaled preventer adherence and asthma action plan ownership may contribute to asthma exacerbation risk and susceptibility to future ETSA episodes. Longer-term follow-up is needed to determine the extent and severity of this apparent change.

Keywords: Asthma; Environmental exposure; Physiopathology; Public health; Weather
INTRODUCTION

Epidemic thunderstorm asthma (ETSA) has been defined as an observed increase in acute cases of bronchospasm following thunderstorms in the local vicinity [1]. Thunderstorm asthma was first described in the United Kingdom in 1983 [2]. Since then similar episodes have been reported across the world including in Australia, Europe, the Middle East and the United States of America [1, 3].

ETSA events in Australia have been described since 1984, with the majority of them occurring in Melbourne [4]. On 21st November 2016, Melbourne was struck by the world’s largest and most catastrophic ETSA event with in excess of 3500 Emergency Department (ED) presentations and 35 intensive care unit admissions recorded over a 30-hour period. This event was also associated with 10 deaths, the highest ever recorded from an ETSA event [5]. While the characteristics of this and other such populations have been previously described, the natural history of asthma symptoms after such catastrophic events has not been systematically examined [6-8].

We undertook a multicentre prospective observational study assessing the symptomatology, behaviors and healthcare utilization of affected individuals 12 months after the 2016 thunderstorm asthma event.

MATERIALS AND METHODS

In December 2016, individuals who presented to EDs across 8 Melbourne health services with a clinical diagnosis of ETSA were contacted and administered a standardized telephone questionnaire using methodology previously described [5]. Individuals who indicated their willingness to participate in future research were contacted again in December 2017. A structured telephone questionnaire (Supplementary material) was utilized. Specific questions regarding frequency of asthma symptoms, use of inhaled preventer, asthma action plan ownership and need for urgent healthcare utilization in the preceding 12 months were included. Questionnaires with reply-paid envelopes were mailed to individuals who were uncontactable by phone. Questionnaires were directed at the parents of individuals less than 18 years old. Patients who declined to consent, were uncontactable, or did not respond to the mailed questionnaire were excluded.

Asthma symptoms (wheezing, coughing, shortness of breath, and chest tightness) were categorized into “persistent,” “frequent episodic,” “infrequent episodic,” or “asymptomatic” based on their average frequency over the last 12 months. “Persistent” was defined as having symptoms ≥ once a week; “frequent episodic” as having symptoms > once a month but < once a week; “infrequent episodic” as having symptoms ≤ once a month, with “asymptomatic” reporting no symptoms.

The asthma status of an individual was determined from questionnaire responses obtained in the first survey round in December 2016 [5, 6]. “Prior asthma” was defined as any previous doctor-diagnosis of asthma, and within this category, “current asthma” was defined as those with symptoms in the 12 months leading up to November 2016, and “past asthma” as those without. Individuals who did not have a prior doctor-diagnosis of asthma were further classified into those with “probable asthma” or “no asthma,” based on whether they reported...
having experienced symptoms suggestive of asthma (wheeze, chest tightness, or shortness of breath) that either disrupted their sleep, or occurred with colds, hayfever or exercise.

Data were summarized using mean ± standard deviation or number (%) as appropriate, and compared using χ² test, Mann-Whitney U test and analysis of variance where applicable. A p value of less than 0.05 was considered statistically significant.

There was no funding source for this study. The corresponding author had full access to all data collected by each health service. The study was approved by the institutional review board of each centre.

RESULTS

Response rate and demographics
Of the initial 8 health services involved in the 2016 ETSA study [5], 2 services declined to participate in the follow-up study. This left 772 individuals (out of the original 1,435) across the remaining 6 health services available for inclusion. Of this group, 330 were nonresponders with reasons for nonresponse including: 41 who declined, 278 uncontactable despite multiple attempts or due to resource limitation, 8 with incomplete questionnaires and 3 deceased due to nonasthma causes, leaving 442 individuals (57%) with completed follow-up questionnaires (Fig. 1).

The mean age of respondents was 35 ± 16 years, and 56% were males. This group was similar in age and gender to the original 2016 cohort (Table 1), and was not statistically different from the nonrespondents.

Fig. 1. Consort diagram. Follow-up of patients 12 months after the Melbourne November 21, 2016 epidemic thunderstorm asthma event.
Symptomatology

Almost 80% (n = 349) of respondents reported at least one episode of asthma symptoms in the 12 months following the ETSA event. Of these, 57% (n = 201) reported “infrequent episodic” symptoms and 15% (n = 52) “frequent episodic” symptoms. Importantly, 28% (n = 96) described “persistent” symptoms.

Preventer prescription and adherence, asthma action plan ownership, and healthcare utilization

Overall inhaled corticosteroid preventer prescription rate in this cohort was 53% (n = 232). In those with “persistent” symptoms, 66% (n = 63) had an inhaled corticosteroid preventer, 60% (n = 39) of whom reported good adherence (usage ≥5 days/wk). Preventer and adherence rates were lower in the other groups with overall preventer adherence just over 50%.

Forty percent (n = 38) of individuals with “persistent” symptoms had an asthma action plan. By comparison 56% (n = 29) of those reporting “frequent episodic” and 46% (n = 93) of those reporting “infrequent episodic” symptoms possessed an asthma action plan.

Healthcare utilisation was defined as any urgent visit to a general practitioner’s clinic, ED or hospital admission for asthma. This varied from 4% in those reporting no asthma symptoms on follow-up, to 26% in those with “persistent” symptoms.

Subgroup analysis

Of the 442 individuals who completed the follow-up questionnaire, 43% (n = 189) had “prior asthma.” This comprised of 62% (n = 118) with “current asthma” and 38% (n = 71) with “past asthma.” Notably, 82% (n = 58) of those who had reported “past asthma,” that is no asthma symptoms in the 12 months preceding the 2016 ETSA event, reported asthma symptoms on follow-up. Although the majority of this cohort experienced “infrequent episodic” symptoms, 22% (n = 13) had “persistent” symptoms. Among those with “current asthma,” only 11% were asymptomatic, with 89% reporting ongoing asthma symptoms on follow-up (Fig. 2).

Out of the remaining 57% (n = 253) with no doctor-diagnosis of asthma prior to November 2016, 55% (n = 138) had “probable asthma” and 45% (n = 115) “no asthma.” Interestingly, 63%

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Table 1. Patient characteristics

| Characteristic | Respondents (n = 442) | Nonrespondents (n = 330) | 2016 Cohort (n = 1,435) | p value |
|---------------|------------------------|--------------------------|-------------------------|---------|
| Age (yr)      | 35.2 ± 16.1            | 33.7 ± 19.6              | 34.0 ± 18.6             | NS      |
| Male sex      | 249 (56)               | 193 (58)                 | 799 (56)                | NS      |
| Asthma status |                        |                          |                         |         |
| Ever been diagnosed with asthma |                      |                          |                         |         |
| Current asthma | 118 (62)               | 78 (57)                  | 395 (64)                | NS      |
| Past asthma   | 71 (38)                | 57 (41)                  | 210 (34)                | NS      |
| Total         | 189 (43)               | 138 (42)                 | 616 (43)                | NS      |
| Never been diagnosed with asthma |                      |                          |                         |         |
| Probable asthma | 138 (55)              | 83 (44)                  | 369 (46)                | 0.04*   |
| No asthma     | 115 (45)               | 106 (56)                 | 424 (52)                | -       |
| Total         | 253 (57)               | 189 (57)                 | 809 (56)                | NS      |
| Missing data  | 0 (0)                  | 3 (1)                    | 10 (1)                  | -       |

Values are presented as mean ± standard deviation or number (%). NS, not significant. χ² test.
(n = 73) of those in the “no asthma” group reported asthma symptoms on follow-up — 70% of them (n = 51) experienced “infrequent episodic” symptoms, 9% (n = 7) “frequent episodic” symptoms, and 21% (n = 15) “persistent” symptoms. In contrast, 82% (n = 113) of those in the “probable asthma” group were symptomatic on follow-up (Fig. 2).

Individuals with “prior asthma” were significantly more likely to report asthma symptoms on follow-up than those with no prior doctor-diagnosis of asthma (p = 0.0001). Amongst those with “prior asthma,” individuals with “current asthma” in 2016 were significantly more likely to report asthma symptoms than those with “past asthma” on follow-up (p = 0.008). Similarly, individuals with probable undiagnosed asthma prior to ETSA 2016 reported significantly more asthma symptoms on follow-up than those with no suggestive symptoms of asthma (p = 0.0002).

**DISCUSSION**

This is the first 12-month follow-up study assessing symptomatology and behaviors of individuals affected by ETSA. Our study shows that the vast majority of individuals affected by 2016 ETSA had ongoing asthma symptoms on follow-up. Moreover, there were low rates of inhaled preventer use and asthma action plan ownership among the group, even in those reporting “persistent” symptoms. Importantly, our data suggests a loss of asthma control in those with previously well-controlled asthma, and the development of symptoms suggestive of *de novo* asthma in those with no history or symptoms suggestive of prior asthma. Each of the above has potential impact on the understanding and optimal management of individuals affected by ETSA.

High reported rates of asthma symptoms on follow-up suggest ongoing poor asthma control which increases individual vulnerability to acute triggers. Inhaled preventers are also underprescribed and underused, with only slightly more than 25% of this cohort being adherent to their prescribed preventer. While poor adherence in asthma management is a known issue [9-11], efforts to rectify this are paramount as inhaled preventers not only form the cornerstone of asthma treatment, but have also been shown in other studies to be protective against acute ETSA presentations in those with pre-existing asthma [12].
Low asthma action plan ownership rates found in our study provides further evidence of a significantly undermanaged cohort.

Subgroup analysis of this follow-up cohort showed that 82% of individuals with a known doctor-diagnosis of asthma who were asymptomatic in the 12 months leading up to 2016 ETSA reported asthma symptoms on follow-up. Moreover, 63% of individuals who had neither a prior doctor-diagnosis of asthma nor any prior symptoms suggestive of undiagnosed asthma described asthma symptoms on follow-up. Of concern is that in both of these groups, approximately 20% of individuals experienced at least weekly symptoms. Apart from individual case reports, these observations have not been previously described to this scale, and require confirmation by other studies. However, they appear to suggest that an episode of ETSA may alter the natural history of allergic airways disease resulting in either a persistent loss of asthma control, or the development of de novo asthma. It has been postulated that the acute bronchospasm in thunderstorm asthma is an allergen-induced early allergic response [13]. After allergen challenge, many subjects may develop a late asthmatic response, associated with persistent airway inflammation and symptoms less responsive to bronchodilator. It is also known that a higher inhaled allergen dose is more likely to induce a late asthmatic response with associated increase in nonspecific bronchial responsiveness [14]. From our data, we hypothesize that ETSA constitutes a massive small airways allergen challenge inducing persistent airway inflammation with nonspecific bronchial hyperresponsiveness. However, this is speculative and requires further evaluation of the persistence of airway inflammation with measures such as fractional exhaled nitric oxide and other tests of nonspecific bronchial hyperresponsiveness. What remains clear is the need for further research and ongoing follow-up of this unique cohort to better understand their natural history.

From our initial cohorts, we have identified a trifecta that predicts development of ETSA including Lolium perenne sensitization, clinical history of seasonal allergic rhinitis (SAR) and exposure to the environment during a thunderstorm [7]. Our pilot study of sublingual immunotherapy with a 5-grass mix tablet that protected such patients from ETSA suggests that allergen-specific immunotherapy should be considered for patients with SAR controlled by pharmacotherapy who are at risk of ETSA [15]. Allergen immunotherapy should be considered in even moderate SAR, particularly (but not necessarily only) in patients experiencing asthma exacerbations during the grass pollen season who live in a geographically at-risk region [16].

This study has several limitations. Firstly, due to the rare, unpredictable and fleeting nature of ETSA events, there was no comparative control group in the initial or this follow-up study. An appropriate control group would have been subjects of a similar age, sex, and allergic profile (particularly of allergic rhinitis), with or without diagnosed asthma, living in metropolitan Melbourne at the time of the event who did not present to ED with acute ETSA. However, as these are unique events, recruiting such a control group who remained asymptomatic has been challenging. Furthermore, there is evidence of a large cohort of sufferers during the Melbourne 2016 ETSA event who did not come to the attention of medical services, implying a potentially hidden and significant susceptible population [17]. Nevertheless, the data we have presented of a pivotal change in new onset and reactivation of asthma symptoms in this cohort compared to their own historical control is of significance and relevance.

Secondly, inherent to the use of questionnaire surveys, the possibility of recall bias cannot be excluded. It may be that following the ETSA event, those affected may be more aware and
have sharper recall of asthma symptoms. However, the questions in the follow-up study were structured identically (in recalling asthma symptoms in the prior 12 months) to the original study immediately after the ETSA event, and recall bias should be minimal.

Thirdly, a large proportion of potential respondents were lost to follow-up. Nonetheless we believe that our 57% response rate is acceptable with age and gender distribution, as well as prior asthma diagnosis of this follow-up cohort being similar to the 2016 original cohort. It should also be noted that the vast majority of nonresponders were due either to follow-up resource limitation or being uncontactable (85%), rather than "declined to participate" (12%). However, subgroup analysis showed those without asthma diagnosis prior to ETSA 2016, who had "probable asthma" i.e., reported ever having experienced symptoms suggestive of asthma (wheeze, chest tightness, or shortness of breath) that either disrupted their sleep, or occurred with colds, hayfever or exercise, were more likely to respond to this follow-up survey compared to those in the same subgroup who had never experienced those symptoms (p = 0.04). Nevertheless, our data show that even amongst those without an asthma diagnosis and who had never experienced asthma symptoms prior to ETSA 2016, 63% reported asthma symptoms in the following year, with 13% overall having symptoms ≥ once per week. While responder bias of the more symptomatic individuals may be inherent to the nature of follow-up questionnaire surveys, the proportion reporting frequent persistent symptoms in this subgroup is of public health concern, and significant in understanding the clinical persistence of allergic airways disease.

In summary, our study provides fresh insights into the natural history of individuals affected by ETSA, highlighting the need for improved recognition, diagnosis and management of asthma. The pivotal change in asthma trajectory with both loss of asthma control and persistence of de novo asthma highlights the importance of ongoing research in this unique group of individuals.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://www.apallergy.org/src/sm/apallergy-9-e35-s001.pdf.

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