

*For discussion***Barcelona's asthma epidemics: clinical aspects and intriguing findings**

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Repeated episodes of epidemic asthma occurred in the city of Barcelona, Spain over many years.¹ A collaborative study was undertaken to investigate the possible mechanism or mechanisms,² the research team including physicians, epidemiologists, and meteorologists. The initial study could not find any relation between urban air pollution and asthma attacks but noted that the outbreaks were clustered in time and space and suggested a point source in the harbour district of the city.² Because a link was suspected between atmospheric emissions during the unloading of ships in the harbour and the outbreaks of asthma, the types of cargo moved on epidemic days were determined. The epidemiological data suggested that airborne dust released into the atmosphere during the unloading of soybean was causing the outbreaks of asthma.³ A further study investigated whether the asthmatic patients in the epidemics were in fact allergic to soybean antigens. Sixty four of 86 patients with epidemic asthma, compared with only four of 86 without, proved to have IgE antibodies to a solution of soybean dust,⁴ confirming the link between soybean and the epidemics. The final evidence that Barcelona's epidemics were caused by soybean comes from the fact that no further episodes of epidemic asthma have occurred since filters have been fitted in the exhaust vent of the silos used to store soybean.

Epidemiological studies allow the assessment of a postulated association between an exposure variable and a disease variable. Epidemiological measures such as rate, prevalence, and risk are useful for describing the state of health of a population or for expressing in quantitative terms the consistency of an association; but for any complex medical problem, such as an outbreak of asthma, epidemiological data provide only a partial picture of the outbreak. Few physicians have had the opportunity to attend 30 or more patients with severe asthma, some in extremis, flooding into a crowded emergency room within 30 minutes. Papers describing the epidemiological studies of outbreaks of asthma in Barcelona may not cover some interesting aspects of this phenomenon.

The aim of the present article is to describe some of the clinical aspects of epidemic asthma on the basis of my experience as a member of the clinical committee of the

research team and of close observation of episodes in the emergency room at the hospital where most of the patients in the epidemics attended, with follow up of a group of asthmatic patients who had acute asthma on an epidemic day.

Characteristics of asthmatic attacks

The epidemic attacks of asthma had characteristic features—namely, a sudden onset, an often greater than usual severity, and rapid recovery.

SUDDEN ONSET

The asthma attacks on Barcelona's epidemic days were characteristically explosive in onset in patients who were otherwise clinically stable. The episodes occurred at any time during the day or night and in any place (on the street, at home, or even in the hospital). Although epidemic asthma attacks affected patients with a previous history of persistent asthma, many patients had very mild intermittent asthma, which required only occasional treatment with bronchodilators.

SEVERITY

The severity of the attacks of asthma was greater during epidemic episodes than on non-epidemic days.⁵⁻⁷ A high proportion of the patients were comatose when they reached hospital and many required immediate intubation and assisted ventilation.⁵ The proportion of patients requiring admission to the intensive care unit was higher on epidemic days than on non-epidemic days (7.7% versus 1.1%).⁵ The severity of attacks in epidemics was greater than on non-epidemic days and the number of deaths in the emergency room on epidemic days (1.84%) was 33 times higher than on non-epidemic days (0.06%).⁶

Some patients developed severe attacks despite being treated with oral and inhaled corticosteroids and a combination of bronchodilators included salbutamol, ipratropium bromide, and theophylline.

RAPID RECOVERY

Most patients with severe attacks of epidemic asthma had a very quick recovery and were discharged from the emergency room within three to 12 hours of admission. The proportion of patients in need of hospital admission was lower than during non-epidemic days, and the

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duration of mechanical ventilation was also shorter for patients with severe epidemic asthma than for a control group of asthmatic patients requiring assisted ventilation during non-epidemic episodes. This rapid recovery from the epidemic asthmatic exacerbations mitigated in part the impact of the asthma outbreaks on the emergency service. On admission, a few patients were in extremis and in these cases ventilatory support was started immediately. Some of those who had assisted ventilation could be extubated in the emergency room a few hours later, whereas patients with more severe asthma, persistent and severe airways obstruction, or coma were admitted to the intensive care unit. Patients reaching the emergency department with symptoms and signs (tachypnoea, cyanosis, and tachycardia) of severe asthma were initially treated with oxygen and three or four puffs of a β adrenergic agent every two to three minutes for 10–15 minutes. All were given 60 mg 6-methylprednisolone by the intramuscular route. Patients with extremely severe asthma were often “resuscitated” in a few minutes by these simple measures. If orotracheal intubation and assisted ventilation were unnecessary at admission, patients almost always recovered with pharmacological measures. Most patients were much less distressed within 30–60 minutes. The initial treatment was followed by standard measures, including administration of nebulised salbutamol, corticosteroids, and oxygen. Patients with less severe asthma almost always improved within a few hours. Because on epidemic days the emergency department was completely overwhelmed, the methods normally used to assess and manage exacerbations of asthma on non-epidemic days (measurement of peak expiratory flow and arterial blood gases) were not always performed systematically.

The decision to discharge patients was usually made on the basis of clinical symptoms, a PEF higher than 250 l/m, and a normal or only slightly reduced arterial oxygen tension. Bronchodilators and a short course of oral corticosteroids were given to all patients at discharge. In the following 24–48 hours few patients relapsed and returned to the emergency room. In general, the relapses were mild or moderate and rarely required hospital admission.

Intriguing findings

Barcelona's asthma epidemics showed several intriguing characteristics. Firstly, despite an immunological origin, there was no evidence of a late phase allergic response. Secondly, severe attacks occurred most often in men. Thirdly, children were not affected. Finally, some patients were not residents of Barcelona.

NO EVIDENCE OF A LATE PHASE RESPONSE

To some extent Barcelona's asthma epidemic may be considered as experimental asthma induced by inhalation of an allergen. It is well known that antigen challenge may cause an

early and a late phase reaction.⁸ The intensity of the airway obstruction is usually longer and more severe during the late response than during the immediate response.⁸ Although the reported prevalence of a dual response after antigen challenge has varied widely, the intensity of exposure and the magnitude of the early response are generally believed to affect the presence and severity of the late phase response.⁸ The severe immediate reaction provoked by soybean dust would therefore be expected to have caused a second wave of attacks of severe asthma. This was not the case, however, because the flow of patients to the hospital were clustered very closely in time. On epidemic days referrals for emergency treatment were concentrated in a period of two to three hours. After this “peak period” small numbers of further cases occurred for six to 12 hours, but there was not a second wave of severe asthma attacks.

SEVERE ATTACKS MORE FREQUENT IN MEN

Most of the patients requiring assisted ventilation during the asthma epidemic outbreaks of asthma were men, by contrast with non-epidemic days (83% versus 37%).⁵ Interestingly a female predominance has been found in almost all the published series of severe asthma treated by assisted ventilation.^{5,9} A recent case-control study (J Sunyer and JM Antó, unpublished observation) has shown that men were at higher risk of epidemic asthma than women, the excess risk being explained by smoking. This finding raises the question of whether smoking acts as immunomodulator of the immediate allergic reaction or whether the deleterious effect of smoking on cilia is responsible for this phenomenon.

ASTHMATIC CHILDREN NOT AFFECTED BY EPIDEMIC ASTHMA

Atopic asthma is more prevalent in children, so it could be expected that epidemic asthma arising from allergy to soybean would have affected young patients preferentially. This was not the case, however.

NOT ALL ASTHMATIC PATIENTS AFFECTED IN ASTHMA OUTBREAKS ARE INHABITANTS OF BARCELONA

Not surprisingly, almost all the patients affected in epidemic asthma outbreaks lived in Barcelona. A few patients, however, were not residents of the city. The case of one such patient is described.

A 35 year old female nurse had a 14 year history of asthma. The first attack followed an upper airway infection and necessitated hospital admission. Her asthma then remained moderately well controlled with regular salbutamol and cromoglycate and frequent short courses of oral corticosteroids. She had frequent asthma attacks, some sudden in onset, and had required emergency treatment on 10 occasions. All the exacerbations were of moderate severity and none had required assisted ventilation. Although she was atopic (positive skinprick test response to *Dermatophagoides pteronyssinus*) no clear relation had been established between attacks and any allergen exposure. She lives in Tarragona, a city 100 km from Barcelona. One epidemic day while visiting Barcelona she had a sudden, severe asthma attack, was admitted unconscious, and had a

cardiorespiratory arrest requiring immediate assisted ventilation. With intensive treatment she made a rapid recovery and was extubated two hours later. She showed a positive prick test response to soybean dust and a positive RAST test response (3.5 PRU/ml; Pharmacia Diagnostics, Uppsala) to soybean allergens.

The patient had visited Barcelona only seven times during her life (no more than eight hours on each visit), so sensitisation to soybean could have occurred outside the Barcelona area. Tarragona has a harbour where soybean is unloaded regularly. Some of her sudden asthma attacks in Tarragona may have been caused by soybean allergens. Recent studies have shown that outbreaks of asthma have occurred in other coastal Spanish cities,^{10,11} suggesting that outbreaks induced by soybean are not a problem that affects asthmatic patients in Barcelona only.

Hypothesis to explain Barcelona's peculiar outbreaks

There could be several reasons for the absence of the expected late phase response. Firstly, corticosteroids reduce the late phase response,⁸ and this treatment might have protected the most severely affected patients—who are also the most prone to show this type of reaction—from developing a dual response. Secondly, a late phase response might have occurred immediately after the early response; thus the two different allergic reactions would not be clearly differentiated. Given that Barcelona's outbreaks of asthma were precipitated by a high atmospheric concentration of soybean dust, perhaps late asthmatic reactions were not observed because the late phase response began as soon as the early one had subsided.

Barcelona's epidemic asthma is a fascinating and unusual phenomenon with intriguing findings; might the characteristics of soybean exposure make these episodes so unusual?

Epidemics always occurred on days with high barometric pressure and little wind. On these days soybean dust was released into the city from a silo 70 metres tall with an open top.³ Although the concentration of allergen during epidemic days was undoubtedly very high, the size of allergen particles is probably responsible for the peculiar nature of Barcelona's epidemic. Three observations support this suggestion. Firstly, patients who had epidemic asthma suffered severe attacks while they were indoors with the windows sealed. Secondly, attacks of asthma could not easily be reproduced in the laboratory with the standard methods of antigen challenge. This discordant finding is probably due to differences in the size of allergen particles. During unloading of soybean in the harbour particles of the allergic agent were emitted into the atmosphere in a way that is difficult to reproduce with the methods currently used in antigen challenge. Thirdly, patients with epidemic asthma almost never complained of symptoms of rhinitis during outbreaks of asthma. The tiny soybean particles were so small that they probably bypassed the defence mechanisms of the nose (cilia, mucus) as they did the sealed windows.

Interestingly, no cases of epidemic asthma were detected among workers in the harbour,

perhaps because they were exposed mainly to large particles of soybean dust, which were easily retained by the nose, while the tiny particles were transported by the wind away from the harbour area.

It is generally accepted that most identified aeroallergens (pollens, moulds, animal danders, and mites) are deposited on the nose, oropharynx, and bronchi and that the allergic reaction takes place mainly in the upper airway. The special characteristics of the soybean dust during unloading might have facilitated the deposition of very small particles lower down in the lung, provoking an unusual and severe form of asthma. Might the relatively small size of children's bronchi prevent soybean dust from reaching the most distal part of the lung, where the allergic reaction takes place? Could the fact that men have larger airways than women, together with the deleterious effect of smoking (more prevalent in men) on cilia have meant that soybean dust penetrated further into the distal part of the male lung, thereby precipitating the most severe attacks? Although the influence of airway size on allergic reaction has received little attention, it might be expected to have some influence on the type and severity of the host response.

A predisposition of children to develop more tolerance to new allergens than adults has also been suggested as an explanation of why children were not affected in Barcelona's epidemic.¹² According to this theory, tolerance might account for the tendency to "grow out of asthma" of children. Adults would be less able to develop this tolerance and might therefore be more vulnerable to sensitisation to new allergens. There are no data, however, to sustain this hypothesis. As no studies on soybean sensitisation have been carried out in asthmatic children in Barcelona this argument can be neither substantiated nor refuted.

Barcelona's epidemic asthma is probably the "tip of the iceberg" of a more extensive problem. Thousands of tons of soybean are unloaded daily in many harbours all over the world. Perhaps many "unusual days," with more attacks of asthma than expected seen in the emergency departments, are associated with soybean exposure. Barcelona's experience also suggests that the possible contribution of undetectable atmospheric allergens as precipitating factors in patients with sudden idiopathic asthma attacks must not be overlooked.

The increase in the asthma death rate in recent years is a matter of concern in the industrialised world. Sudden death in both young and adults with asthma is frequently reported in medical journals. Recent studies have shown that those with atopic asthma are more likely than non-atopic patients to develop rapid and fatal asthma attacks.^{13,14} Physicians and patients may detect allergens when the clinical history allows for the establishment of a cause-effect relationship. This is the case for pollens, house dust, animal danders, and occupational asthma. A cause-effect relationship, however, is almost impossible to detect when the presence of allergens in the patient's

surroundings depends on circumstances not detectable in the clinical history. This is the case when the responsible allergens are released into the atmosphere from a source several kilometres from the patient or when the presence or absence of the allergen around the patient is due to changes in climatic conditions (direction and speed of wind). The experience in Barcelona suggests that some attacks usually considered as idiopathic may be due to inhalation of airborne allergens such as soybean dust. Some recent observations suggest that the increase in the prevalence of asthma in industrialised countries may be related to changes in the environment. Detection of new triggers of asthma may be possible, as in the case of the Barcelona epidemics, when the number of patients affected is large enough to call attention to the phenomenon. To date, epidemic asthma has been described only in large cities (New Orleans, Brisbane, Barcelona, Birmingham).¹⁵⁻¹⁷ Less dramatic episodes—merely “unusual days”—could be easily overlooked. Thirty cases of severe asthma occurring in a short period in a big city with one and a half million inhabitants may suggest the existence of an environmental factor. The same phenomenon in a town with 100 000 inhabitants would cause four cases of acute, severe asthma and is unlikely to be considered exceptional by busy physicians on call.

As recent studies have shown that less severe outbreaks of asthma have occurred in other Spanish cities and that thousands of tons of soybean are regularly unloaded in many harbours all over the world, Barcelona's epidemic asthma might represent the extreme of a phenomenon affecting with less intensity other coastal cities.

- 1 Ussetti P, Roca J, Agusti AGN, Montserrat JM, Rodriguez Roisin R, Agusti Vidal A. Asthma outbreaks in Barcelona. *Lancet* 1983;ii:280-1.
- 2 Anto JM, Sunyer J. Asthma Collaborative Group of Barcelona. A point source asthma outbreak. *Lancet* 1986;i:900-3.
- 3 Anto JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. Community outbreaks of asthma associated with inhalation of soybean dust. *N Engl J Med* 1989;320:1097-102.
- 4 Sunyer J, Anto JM, Rodrigo MJ, Morell F. Case-control study of serum immunoglobulin-E antibodies reactive with soybean in epidemic asthma. *Lancet* 1989;ii:179-82.
- 5 Ferrer A, Torres A, Roca J, Sunyer J, Anto JM, Rodriguez-Roisin R. Characteristics of patients with soybean dust-induced acute severe asthma requiring mechanical ventilation. *Eur Respir J* 1990;3:429-33.
- 6 Agusti Vidal A, Anto JM, Ferrer A, Garcia A, Morell F, Rodrigo MJ, et al. *Las epidemias de asma de Barcelona*. Madrid: Ministerio de Sanidad y Consumo, Madrid, Spain. 1990.
- 7 Ussetti P, Roca J, Rodriguez-Roisin R, Agusti AGN, Montserrat JM, Agusti-Vidal A. Urban asthma outbreaks: Barcelona's episodes. *Immunol Allergy Pract* 1985;7:450-7.
- 8 Lemanske RF. Late-phase pulmonary reactions. *J Asthma* 1990;27:69-80.
- 9 Picado C, Montserrat JM, Roca J, Rodriguez-Roisin R, Estopá R, Xaubet A, et al. Mechanical ventilation in severe exacerbation of asthma. Study of 26 cases with 6 deaths. *Eur J Respir Dis* 1983;64:102-7.
- 10 Hernando L, Navarro C, Marquez M, Zapatero L, Galvan F. Asthma epidemics and soybean in Cartagena (Spain). *Lancet* 1989;ii:502.
- 11 Alvarez-Dardet C, Belda J, Peña M, Nolasco A. Outbreak of asthma associated with soybean dust. *Lancet* 1989;ii:1127-8.
- 12 Hendrick DJ. Asthma: epidemics and epidemiology. *Thorax* 1989;44:609-13.
- 13 British Thoracic Society. Comparison of atopic and non-atopic patients dying of asthma. *Br J Dis Chest* 1987;81:30-4.
- 14 Jenkins PF, Mullins J, Davies BH, Williams DA. The possible role of aeroallergens in the epidemic of asthma deaths. *Clin Allergy* 1980;11:611-20.
- 15 Salvaggio J, Seabury J, Schoenhardt EA. New Orleans asthma. V. Relationship between charity hospital asthma admission rates, semiquantitative pollen and fungal spore counts, and total particulate aerometric sampling data. *J Allergy Clin Immunol* 1971;48:96-114.
- 16 Morrison I. It happened one night. *Med J Aust* 1960;ii:850-2.
- 17 Packe GE, Ayres JG. Asthma outbreak during a thunderstorm. *Lancet* 1986;ii:199-204.