ORIGINAL ARTICLE

How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland

C F Macdougall, A J Cant, A F Colver

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See end of article for authors' affiliations

Correspondence to: Dr A Colver, Senior Lecturer in Community Child Health, Northumbria Health Care Trust and University of Newcastle upon Tyne, Donald Court House, 13 Walker Terrace, Gateshead NE8 1EB, UK; allan.colver@ncl.ac.uk

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Aims: To discover the incidence of fatal and severe allergic reactions to food in a large population of children.

Methods: A retrospective search for fatalities in children 0–15 years from 1990 to February 1998, primarily of death certification at offices of national statistics. A prospective survey of fatal and severe reactions from March 1998 to February 2000, primarily through the British Paediatric Surveillance Unit. Main outcome measures were deaths and severe reactions. A case was deemed severe if one or more of the following criteria was met: cardiorespiratory arrest; need for inotropic support; fluid bolus >20 ml/kg; more than one dose of epinephrine; more than one dose of nebulised bronchodilator. A case was deemed near fatal if intubation was necessary.

Results: The UK under 16 population is 13 million. Over the past 10 years, eight children died (incidence of 0.006 deaths per 100 000 children 0–15 years per year). Milk caused four of the deaths. No child under 13 died from peanut allergy. Two children died despite receiving early epinephrine before admission to hospital; one child with a mild food allergic reaction died from epinephrine overdose. Over the past two years, there were six near fatal reactions (none caused by peanut) and 49 severe ones (10 caused by peanut), yielding incidences of 0.02 and 0.19 per 100 000 children 0–15 years per year respectively. Coexisting asthma is more strongly associated with a severe reaction than the severity of previous reactions.

Conclusions: If 5% of the child population have food allergy, the risk that a food allergic child will die from a food allergic reaction is about 1 in 800 000 per year. The food allergic child with asthma may be at higher risk. Prescribing an epinephrine autoinjector requires a careful balance of advantages and disadvantages.

Severe food allergic reactions are characterised by angioedema, hypotensive shock, and wheeze. The phrase "severe food allergic reaction" is preferable to "anaphylaxis", which sometimes describes a severe reaction and sometimes an allergic mechanism. There is professional[1–3] and public[4 5] concern that the number of severe and fatal childhood food allergic reactions is increasing dramatically, leading to increased prescription of epinephrine (adrenaline) autoinjectors,[6] anxiety for schools,[7 8] costly actions by food manufacturers,[9] and significant parental concern.

Food allergy in childhood is common with a prevalence of between 0.3% and 8%.[3 10] Fatal and severe food allergic reactions are well documented in children.[11–13] Although their incidence is not known, some claim the incidence in adults and children is increasing,[1 2 12 14] while others suggest there is no evidence of this in children.[15] We conducted a prospective survey of fatal and severe allergic reactions to food in children from March 1998 to February 2000; together with a retrospective search for fatal allergic reactions from 1990 to February 1998.

METHODS

The British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health studies the epidemiology of uncommon childhood disorders in the UK and Ireland.[16] All consultant paediatricians receive a card every month for reporting any of the 10 to 12 conditions currently under surveillance. The overall response rate was 93.4% in 1999.[17]

The offices of national statistics for England and Wales, Scotland, Northern Ireland, and the Republic of Ireland record details of all death certificates. Before 1993, search for cause of death is limited to the International Classification of Disease (ICD9) code. Since 1993 the office for England and Wales can also search on the text entry using "wild cards" (e.g. allerg* = allergy, allergen, etc).

The five ICD9 codes used for the initial searches for England and Wales were 995.0 anaphylactic shock, 995.3 allergy unspecified, 988 toxic effect—noxious food, E865 accidental poisoning—food and plants, 6931 dermatitis caused by food ingestion. When text searches were then performed for allerg*, anap*, food, egg, milk, *nut*, etc to identify further cases and their assigned ICD code, no additional cases or ICD9 codes were revealed. Therefore searches in the other countries and pre 1993 in England and Wales were undertaken using the five codes already mentioned.

Definitions

Paediatricians were asked to report patients under 16 who died or were admitted to hospital for a food allergic reaction or reaction to an unknown allergen. Children spending a few hours under observation without treatment were excluded, as were children whose only symptoms were asthmatic and the allergen unknown.

A case was deemed "severe" if one or more of the following criteria was met: cardiorespiratory arrest; need for inotropic support; fluid bolus of more than 20 ml/kg; more than one dose of epinephrine by any route; more than one dose of nebulised bronchodilator. Cases where intubation was necessary were deemed "near fatal".

The allergen was recorded as "mixed food" if multiple foods were ingested; and recorded "? food" if the allergen was

uncertain or other processes such as an exercise induced reaction were more likely to have been responsible. The severity of previous reactions was classified as mild (rash, only needed advice and antihistamine), moderate (distressed breathing, dizziness, and anxiety), or severe (needing urgent treatment and assessment in hospital).

Ascertainment of fatal reactions: 1990 to February 2000

Notifications of deaths were sought from the offices of national statistics as described above. However, we could not be certain that these offices recorded all deaths, and it is important to examine the extent to which other sources yield the same or additional cases. The following sources were also used:

- BPSU 1998–2000
- Database of allergy deaths as a result of all types of allergy in all age groups held by Dr R Pumphrey,[18] an immunologist in Manchester
- Anaphylaxis Campaign—a voluntary organisation with nationwide contacts
- Personal letters to 10 experts in paediatric allergy in the UK
- Asthma and Allergy Information Research,[14] a web based information service for the public, whose director contacted the study
- *Daily Telegraph* and *The Times* stored on CD-ROM.

Paediatricians have shown great interest in the study, and possible cases they recall over the past 10 years have been mentioned to us informally on six occasions. We have followed up such details and all six were already known to us.

Ascertainment of severe reactions: March 1998 to February 2000

After cases were notified to the BPSU, additional information was sought from the notifying consultant by means of a questionnaire about severity, management, associations, previous reactions, and outcomes.

RESULTS

There were three deaths in the prospective period March 1998 to February 2000 and five in the retrospective period 1990 to February 1998 (table 1). Four cases arose in the searches by offices of national statistics and appeared in at least one of the other sources. There were also two cases from Dr Pumphrey, one from BPSU, and one from Asthma and Allergy Information Research, for which there was no other source. The under 16 population in 1999 was 13 028 933, based on data from the offices of national statistics. Thus, the period 1990–2000 yields an incidence of 0.006 deaths per 100 000 children 0–15 years per year (95% CI 0.002 to 0.01).

A total of 295 cases were reported in the prospective period by 176 consultants from 133 departments. Complete data were not obtainable in eight cases but none was a fatal or near fatal case. A total of 56 cases were duplicate reports or reported in error. Complete data were therefore available on 231 cases; 58 of these met the severity criteria.

There were 55 severe non-fatal reactions (21 female, 34 male) in the prospective period, six requiring intubation (near fatal). This yields an incidence of severe non-fatal events of 0.2 per 100 000 children per year. Table 2 shows the provoking allergens. Table 3 shows the association of the notified cases with a history of asthma. The more severe the reaction, the greater the chance the patient had coexisting asthma. Although the cases with non-severe reactions represent an unknown proportion of comparable reactions not admitted to hospital, we included them because coexisting asthma was so much less common. The fatal cases appeared to have especially troublesome asthma but we cannot be any more precise because historical accounts of antiasthma medication do not satisfactorily define severity. Table 4 shows the association with the severity of previous reactions. In 53% there had been a previous reaction and in 33% of these it was reported to be

Table 1 Deaths 1990–2000

Year	Case	Age	Allergen
1991	1	13 years	Milk
1992	2	15 years	Peanut
1994	3	3 months	Egg white
1994	4	9 years	Milk (in ice cream)
1995	5	13 years	Peanut
1998	6	13 years	Milk
1999	7	15 years	Milk
1999	8	5 years	Mixed food

Table 2 Provoking allergens in the severe non-fatal food allergic reactions, 1998–2000

	Reported reaction	
Allergen	Severe	Near fatal
? Food	3	
Mixed food	9	2
Cows' milk—includes ice cream, yoghurt, formula milk	5	1
Egg	3	1
Peanut	10	
Yeast extract (Marmite)	2	
Soya	1	
Sesame seed	1	
Potato	1	
Wheat	1	
Lentil		1
Mixed nuts	2	
Walnut	1	1
Brazil nut	2	
Cashew nut	7	
Macadamia nut	1	

Table 3 Association of asthma with severity of food allergic reaction, 1998–2000

Reported reaction	Cases without asthma	Cases with asthma (%)
Non-severe	109	64 (37)
Severe	21	28 (57)
Near fatal	1	5 (83)
Fatal	0	3 (100)

χ^2 for trend 14.4, df=1, p=0.0002.

Table 4 Association of severity of previous reaction with severity of food allergic reaction, 1998–2000

	Previous reaction			
Reported reaction	Uncertain	None	Mild/ moderate	Hospitalised
Non-severe	11	77	74	11
Severe	4	15	22	8
Near fatal	1	1	3	1
Fatal	0	0	2	1

χ^2 for trend comparing mild/moderate with hospitalised: p>0.05.

to the same allergen, although the allergen judged responsible after a meal of mixed foods may be influenced by the previous history.

DISCUSSION

This first large child population based study of fatal and severe reactions to food covered a 0–15 years childhood population of 13 million and yielded a low incidence of 0.006 fatal events per 100 000 children per year over the period 1990–2000. Such deaths are much less common than sudden unexpected non-violent deaths from any cause in childhood which are about 3 per 100 000 per year.[19] If 5% of the child population have food allergy, the risk that a food allergic child will die from a food allergic reaction is 1 in 800 000 per year.

The accuracy of death certificates pertaining to food allergy has been criticised.[20] Furthermore, a postmortem diagnosis of allergy may be difficult,[18] and a diagnosis of asthma (a "natural cause") may be easier for a family to cope with than a diagnosis of allergy (an "unnatural cause" requiring an inquest). Nevertheless, we think cases are likely to have been identified because of the multiple sources we have used and the fact that the tragedy of a child's death always leads to careful inquiry.

The finding that peanut was the cause of two of eight fatal reactions and no near fatal reactions differs from studies that report peanut to be the most common cause of fatal reactions to food in children in the United Kingdom and United States.[9 12] Additionally, there were no deaths from peanut allergy in children under 13. Milk caused the greatest number of fatal reactions (four of eight); this is in line with reports of both the frequency[21] and severity[22] of reactions to milk.

In the prospective period, the reason for notification was that the child was admitted to hospital. The referring physician was not asked to assess severity. The severity criteria, deliberately set so that all children meeting the criteria would have had to be admitted to hospital, were based on clear treatment decisions that would always be recorded. The criteria were applied by us, based on the answers in the questionnaire completed by the notifying physician. Any inaccuracy in the number of severe reactions so classified will be an overestimate because initial under treatment demands further treatment, whereas initial over treatment would not be noticed.

The incidence of non-fatal severe events was 0.2 per 100 000 children per year. The allergens responsible were similar to those reported in other series, the commonest being peanut (18%), albeit less common than previously reported.[13]

Those suffering the most severe reactions tended to have had severe previous reactions, but it is notable that in two of the three fatal reactions and five of the six near fatal reactions, the previous event had not required urgent hospital treatment. This challenges the view that a previous mild reaction makes a fatal reaction less likely.[12 13 23]

All fatal cases, and all but one near fatal case, had a clear history of asthma; the excepted case was only 7 months old, so may have been too young to have asthma diagnosed. The relation between severe reactions and asthma has been suggested previously,[12 23] but we encountered the same difficulty as Sampson and colleagues[12] in judging the adequacy of asthma control based on medication history. The child with food allergy, who also has poorly controlled asthma, may be at particular risk as it is reasonable to suppose that bronchoconstriction will be more severe when asthmatic and food allergic triggers to bronchoconstriction combine.

Is it asthma or food allergy?

There were three further fatalities reported to us as being food allergic. All three children had eaten food shortly before the reaction. In one, the allergen to which the child was known to be allergic was not ingested; in the second, although milk protein may have been ingested, there was a concurrent and intense exposure to grass pollen; and in the third there was concurrent direct contact with a stuffed animal and the only previous reaction had been to an unknown allergen. These cases illustrate a group of asthmatic deaths where food may be initially implicated but subsequently shown to be unlikely.

On the other hand, could an apparently idiopathic attack of asthma be a manifestation of an unrecognised food allergic reaction? Our definition of a case excluded children whose only symptoms were asthmatic (no rash or oedema) and the allergen unknown because there is no means for attributing such reactions to food or for knowing if a causal link exists.

Children who received a single dose of epinephrine

Our criteria for a severe reaction excluded children who received only one dose of epinephrine and fulfilled none of the other criteria. There were 78 such excluded children but they cannot be all such cases, as some may not be admitted to hospital as recommended for observation for late or biphasic reactions.[24] In 27 of the 78 (34%), no respiratory symptoms were noted before epinephrine administration; in 14 of these cases only mild cutaneous signs were seen. This suggests that some epinephrine is being administered unnecessarily. However, in the other instances, there were worrying symptoms that required urgent referral to hospital. Our study cannot determine whether epinephrine prevented potentially fatal occurrences in some of these.

Two of the three children in the prospective period who died received epinephrine before hospital. All the children who died had asthma and the precipitation of a severe asthmatic attack may have led to death. Administration of salbutamol by inhalation, together with intramuscular epinephrine and rapid transfer to hospital, might then be better emergency treatment than epinephrine alone.

Treatment with epinephrine carries some risk of cardiac arrhythmia, even when given in recommended doses,[25] and can cause death if given inadvertently in overdose. One fatality reported to us, which we have not classified as a food allergic death, was in a child with a mild food allergic reaction who died from overdose of intravenous epinephrine (coroner's verdict).

Conclusion

The finding of so few deaths in such a large population should reassure parents and doctors that the risk of death is small. The findings are especially relevant to children under 10, in whom the risk of severe or fatal reaction is even smaller than in the 10–15 year old group, especially as there is increasing evidence that some young children grow out of their allergy by age 10.[26 27]

The child with food allergy and troublesome asthma may be at particular risk, and their asthma should be kept under optimal control. While a previous mild reaction may not be as reassuring as has been thought, absence of asthma may be. Early administration of epinephrine may not prevent death and concomitant treatment for the asthmatic component of an allergic reaction may be very important.

We emphasise that our findings relate to children, not adults; and to food, not other allergens.

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Authors' affiliations
C F Macdougall, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK
A J Cant, Paediatric Immunology and Infectious Diseases Unit, Newcastle General Hospital
A F Colver, Northumbria Health Care Trust and University of Newcastle upon Tyne, Donald Court House, 13 Walker Terrace, Gateshead NE8 1EB, UK

AC had the original idea for the study, and with CM, coordinated the study. All three authors were involved in study design, analysis, and writing of the paper.

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