

Epidemiology of anaphylaxis

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Purpose of review

The purpose of this article is not only to review the epidemiology of anaphylaxis and factors that affect the epidemiology but also to help us understand underlying mechanisms and predisposing factors. This, in turn, has a bearing on efforts related to prevention and management.

Recent findings

The purpose of this review is to assess the incidence of anaphylaxis and to review the factors that affect this incidence, with special reference to the most common causes, drugs and foods. Factors affecting the incidence are geographic location, sex, atopy, and socioeconomic status. Although no exact incidence, based upon available data, can be established, it is reasonable to assume that 1–2% of the population may be affected. Also, clearly, there is underreporting of episodes. Finally, the incidence of anaphylaxis appears to be increasing.

Summary

The exact incidence of anaphylaxis is unknown, but appears to be increasing. Foods and drugs are the most common causes. The incidence is affected by geographical location, sex, atopy, and socioeconomic factors.

Keywords

anaphylaxis, drug reactions, epidemiology, food allergy

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Introduction

The intent of this study is to review the incidence and epidemiology of anaphylactic reactions with special emphasis on the factors, which affect this incidence and on reactions to the two most common causes of anaphylaxis, foods and drugs.

Sources of information on the epidemiology of anaphylaxis

Unfortunately, there is no single comprehensive source of information regarding the epidemiology of anaphylaxis. We obtain information on this subject from several sources including analysis of hospital and emergency department admissions and emergency medical service data [1–7,8^{••},9–11], visits to allergists' offices [12,13], surveys of various databases and patient populations [14,15,16^{••},17^{••},18–30], and analyses of automatic epinephrine injector (AEI) prescriptions [31[•],32–34].

For the purpose of this review, references, for the most part, will be limited to those published after 2000. For a detailed analysis of those articles published before 2000, the reader is referred to two previous reviews [35,36].

In addition, there have been a number of excellent reviews of this topic [37^{••},38^{••},39[•],40–42,43^{••}] from

which information was gleaned for the preparation of this article.

Problems encountered in establishing the true incidence of anaphylaxis

The clear conclusion drawn from reviewing data regarding the incidence of anaphylaxis is that the true incidence has not been established. Recognizing this, the American College of Allergy, Asthma, and Immunology formed an international working group to review the incidence of anaphylaxis. The conclusion of this group was that data on anaphylaxis incidence and prevalence are sparse, and often imprecise. As noted above, findings are based on diverse study designs, and these findings are often not comparable. Thus, there have been widely varying estimates of the frequency of this condition.

The problems that have led to this conclusion are numerous. First of all, there has been no universal consensus as to the definition of anaphylaxis. There still are inadequate International Classification of Diseases (ICD) codes allowing physicians to accurately record diagnostic episodes. The literature is replete with problems of terminology. Prevalence and incidence are often used interchangeably or incorrectly [37^{••}]. Available data probably underestimate the true incidence

because of underreporting and the aforementioned lack of proper ICD codes.

The panel convened by the American College of Allergy, Asthma, and Immunology, reviewing the sources and considering these problems, felt that the best data probably come from real-time prescription information for AEIs [32–34]. To illustrate difficulties in assessing these data, however, one can compare studies looking at prescription data obtained from Canada [32,33] versus Wales [34]. In Canada, AEIs were given to approximately 1% of the population of Manitoba, whereas in Wales, AEIs were given to 0.2 per 1000 population [34]. Thus, there can be an extremely variable rate of AEI prescriptions per population numbers written in countries of similar socioeconomic status and ethnicity.

Thus, no definitive conclusion can be made regarding the overall incidence or prevalence of anaphylaxis. However, taking all of these problems into consideration, an estimation can be made of the frequency of occurrence of anaphylactic episodes. The panel convened by the college estimated that there are approximately 50–2000 episodes per 100 000 persons, or a lifetime prevalence of 0.05–2%. Anaphylactic episodes affect perhaps up to 2% of the population.

A review of articles dealing with the epidemiology of anaphylaxis in contrast to defining the overall incidence, does offer reliable insight into the factors that affect incidence. An analysis of these factors is of particular importance, as it may offer revelations regarding the pathogenesis of this condition.

Factors affecting the epidemiology and incidence

Numerous factors affect the incidence of anaphylaxis.

Atopy

That atopic individuals are predisposed to anaphylactic episodes is clear. This certainly is expected, as a significant percentage of such reactions are immunoglobulin E (IgE) mediated. However, this phenomenon extends beyond IgE-mediated anaphylaxis, as atopic individuals are at increased risk for idiopathic anaphylaxis, exercise-induced anaphylaxis, and anaphylactic reactions of the non-IgE-mediated variety such as those to radiocontrast media [35,36].

As to why atopic individuals are so predisposed, but there are several possibilities is unclear. The most intriguing of these is perhaps the concept of basophil/mast cell 'hyper-releasability'. Atopic individuals have demonstrated lower thresholds for the release of histamine from baso-

phils in patients with food allergy, atopic dermatitis, asthma, and bronchial aspergillosis [35,36].

In addition, atopic individuals dominate series of all causes of anaphylaxis [12]. It has been postulated that the extracellular cytokine milieu associated with atopic disease [increased interleukin (IL)4 and IL13] might account for the predisposition of atopic individuals to anaphylactic episodes [43^{••}].

Geography

There are at least two studies indicating that there is a distinct effect of geographical location on the incidence of anaphylaxis. One study looked at emergency admissions for anaphylaxis in England [9], and the other assessed AEI prescriptions in the United States [31[•]]. Both studies found a distinct north–south gradient for anaphylactic episodes. In the south of England, there were 22–25 emergency anaphylaxis admissions per 100 000 emergency admissions, whereas in the north of England, for the most part, the rate was less than 15 admissions for anaphylaxis per 100 000 emergency admissions [9]. In the United States, prescriptions for AEI were far more common in the north than in the south of the country. For example, the highest rate of prescriptions was in the northern state of Massachusetts where there were 11.81 prescriptions per 1000 persons. In the southern United States, there were approximately three prescriptions per 1000 persons [31[•]].

In neither study could these findings be accounted for by access to medical care or other factors. It is interesting to note that at least in the United States study, the rate of prescriptions was inversely related to sunlight exposure, and therefore it was postulated that relative vitamin D deficiency may play a role in increasing the incidence of anaphylactic episodes.

Socioeconomic factors

Socioeconomic factors also seem to play a role in the incidence of anaphylaxis with areas of higher socioeconomic status seemingly being related to an increased number of episodes [9,32–34]. In a survey of emergency department admissions for anaphylaxis in England, geographical areas with higher socioeconomic environments had an increased incidence of admissions. In addition, both in Canada [32,33] and Wales [34], prescriptions for AEIs were higher in populations of relative wealth. Once again, these findings could not be explained by access to medical care or other factors.

Sex

A number of studies have clearly demonstrated that the overall incidence of anaphylaxis is significantly higher in women than men [9,12,35,36]. This is certainly true for the incidence overall and for the incidence in adults.

However, in children, in some series males predominate [33]. Yet, when all patients are considered (both children and adults), the overall incidence is highest in women. There seems to be a reversal of this when children only are reviewed. It has been shown in animal models that progesterone increases target organ sensitivity to mediators and can enhance histamine release *in vitro* [35,36].

Regardless of the vicissitudes related to obtaining valid data establishing a true incidence of anaphylaxis, it appears clear that the incidence of anaphylactic episodes is increasing [8^{••},9,21,22,34,39[•],43^{••}]. In Wales, between 1994 and 1999, there was a five-fold increase in anaphylaxis causing a 20-fold rise in AEI prescriptions [34]. In England, hospital admissions for anaphylaxis have increased as well [21]. Between January 1990 and January 2000, admissions increased from six to 41 per million. Simultaneously, food allergy rates rose from five to 28 per million [21]. The prevalence of anaphylaxis in France has also risen over the last decade [22]. National statistics in France recorded 2575 cases in 2005 – 22% more than in 2003 [22]. In Australia, there have been distinct increases in hospitalizations for anaphylaxis [8^{••}].

There has been a sharp increment in the incidence of hospitalizations for food-related anaphylaxis among children less than 5 years of age. Admissions for nonfood-related anaphylaxis (which occurred predominantly in adults) also increased. These increases were greater than that seen for angioedema and urticaria – although the rates for these conditions were also up [8^{••}]. For example, between 1994–1995 and 2004–2005, in Australia, admissions for anaphylaxis produced by food had an average annual increase of 13.2%. The rate increased across all age groups, but was much greater in ages 0–4 years. In this age group, there was a 5.5-fold increase in the rate of admissions between these time periods. In the same study, the rate of hospital admissions for anaphylaxis due to nonfood causes was highest in those 35 years and older. Overall, anaphylactic admissions for nonfood triggers had an annual increase of 8.5% between 1994–1995 and 2004–2005 [8^{••}].

The trends noted between 1990 and 2000 seem to be continuing. For example, in the United Kingdom, admission rates for anaphylaxis have increased between 1991 and 2004 [44] and the percentage of emergency department admissions for allergic reactions has also increased in the United Kingdom in the last decade [39[•]].

Foods and drugs: the most common culprits

Foods and drugs are the most common causes of anaphylaxis.

Epidemiology of food allergy

Although food allergies are common at any age, they are particular prevalent in children. When one reviews a series of anaphylactic episodes in adults, recurrent idiopathic anaphylaxis occurs with frequencies similar to that of foods [12]. However, in episodes occurring in children, foods clearly predominate [13].

The exact incidence and prevalence of food allergy is unknown and clearly varies according to the stringency of the diagnostic criteria applied, the geographic location, and age. On the Isle of Wight, United Kingdom, cumulative incidence of food allergy reported by parents was 25.8%, and 2.2% of those tested were sensitized to at least one food [38^{••}]. When these children were evaluated by food challenge, approximately one-eighth of those receiving challenges had a confirmed diagnosis. Thus, the reported incidence is dependent on the stringency of the criteria applied. The authors estimated that 2.2–5.5% of infants had food hypersensitivity during the first year of life [45,46].

In France [18], the prevalence of food allergy has been estimated to be 3.2% (range 3.04–3.44%) [18]. Also in France, in 2002, there were 107 cases of severe anaphylaxis to foods. The major allergens found were peanuts, nuts, shellfish, lupin flour, and wheat flour [26].

Data from the Canadian Pediatric Surveillance Program found peanuts, tree nuts, cow's milk, egg, fish/shellfish, and fruits/vegetables were the most common triggers. In this survey, 2350 Canadian physicians reported anaphylactic episodes. The surveillance was carried out over 18 consecutive months [29].

In Germany [25], pediatricians, assessed by questionnaire, reported 103 cases of anaphylaxis, and foods were the most common agents. In this investigation, 57% of the cases were due to foods, with the most common culprits being peanuts and tree nuts.

From the above studies, we can conclude that foods are the most common cause of anaphylaxis in the world today; clearly so in children. Although the exact incidence is unknown, and rates have varied from as low as 1% to greater than 5%, perhaps 2% of the population suffers or has suffered from food allergy.

That the incidence of food allergy is increasing is highly probable. This is particularly true for peanuts [43^{••}]. In the United Kingdom, prevalence rates for peanut allergy are in excess of 1% [43^{••}]. In population-based United States studies, self-reported peanut allergy in children rose from 0.4% in 1997 to 0.8% in 2002. In the Isle of Wight there was a two-fold increase in reported peanut allergy (0.5–1%) between 1989 and 1994 [43^{••}].

The frequency of shellfish allergy increases with age. Only about 0.1% of children age 0–5 years, and 0.8% of children age 6–17 are reported to have shellfish allergy. However, in adults age 18–40, the reported rate is 2.6%, and in 41–60-year olds, it is 3.3% [15].

Although tree nut allergy is probably less frequent as a whole than peanut and shellfish allergy, its importance lies in the fact that it accounts for an inordinately large percentage of severe and fatal reactions [16^{••},19].

Epidemiology of drug allergy

Drug allergies rival food allergies in terms of frequency and importance. For example, in a population-based study of incidence and severity of anaphylaxis in the United Kingdom encompassing approximately 8 million person years, based on the UK General Practice Research Database conducted between January 1, 1994, and December 31, 1999, drug-induced episodes exceeded those due to foods. In addition, drug reactions were slightly more severe as a whole than those due to foods [24].

In one series [11], insect sting was the most common cause of anaphylactic episodes, and drugs the second most frequent culprit. As in many previous investigations [35,36], antibiotics were the most common drugs incriminated, followed by nonsteroidal antiinflammatory agents (NSAID). Penicillin was the most common antibiotic to cause events.

In a survey of data obtained from a study population consisting of children and adolescents enrolled in a health maintenance organization, as expected, because of the age group evaluated, food was the most common cause of events. Medication-associated anaphylaxis, however, occurred as well, and, as in other studies, antibiotics and NSAID were common causes.

Other series have noted the prominence of radiocontrast and various agents administered during the perioperative period as being common causes. In Australia [8^{••}], the rate of hospital admissions for nonfood causes was highest for age 35 and older. When angioedema as well as anaphylaxis was included in their surveys, ACE inhibitors as well as aspirin became major offenders [8^{••}].

In an evaluation of severe anaphylactic episodes, all with circulatory symptoms, performed in Switzerland, the frequency of drug reactions almost doubled that of reactions due to foods. It was second in frequency to hymenoptera stings. This investigation was performed in an emergency department over a 3-year period. Approximately half of the reactions to drugs were to NSAID. Antibiotics were the second most frequent drug offender [11].

A similar investigation performed in Hong Kong [4] also found that drugs, next to foods, were the most frequent causes. Once again, NSAID followed by antibiotics were the most common causes. In an emergency department series in Australia [1], antibiotics (β lactams being the most frequent) were followed by NSAID in terms of frequency.

From the above, it can be seen that the vast majority of outpatient episodes of anaphylaxis due to drugs are caused by antibiotics and NSAID. It can also be seen, in series of outpatients who experience episodes, drugs rival foods in terms of frequency, and are the most common causes in adults [12].

Conclusion

Because of the vagaries aforementioned, the exact incidence of anaphylaxis cannot be established based on available data. However, the best estimate for overall incidence places it near 1–2% of the population. Clearly the incidence seems to be increasing and may well be underestimated because of underreporting. The two most frequent offenders are foods, followed closely by drugs. The most frequent foods to cause reactions are peanuts, shellfish, and tree nuts. The incidence to foods, especially peanuts, appears to be increasing. The most commonly incriminated drugs on an outpatient basis are antibiotics and NSAID.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 364).

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