Severe food anaphylaxis :

107 cases registered in 2002 by the Allergy Vigilance Network

DAnne Moneret-Vautrin, MD, Gisèle Kanny, MD, PhD, Martine Morisset, MD, Marie-Françoise Fardeau, MD, Etienne Beaudouin, MD, Ludivine Parisot and the members of allergovigilance network

Alquier MC, Arnoult-Coudroux E, Baaset-Stheme D, Banoun L, Bataille A, Blonde-Vincent F, Bosse I, Boulegue M, Bourrain JL, Breuil K, Carme S, Chappard C, Château-Waquet J, Chatziantoniou K, Croizier A, Lepeltier, Deblay F, Denis A, Deluze C, Dron-Gonzales M, Dubreil Y, Durand-Perdrieu, Dzviga C, El Gueddari Y, Flabbée J, Fontaine JF Frentz P, Gallen C, Ghassan H, Gosselin-Decker, Grand JL, Guerra M, Hallet JL, Jacson F, Jacquier JPA, Jonathan AM, Le Pabic F, Mathelier-Fusade P, Meyer JP, Molle I, Mouton-Faivre C, Muller D, Omarjee B, Paty E, Petit N, Pirson F, Pouvreau H, Queron-Rabier F, Rance F, Scherer P, Sullerot I, Talhouarn G, Vodoff MV, Wallaert B.

Department of Internal Medicine, Clinical Immunology and Allergology
University Hospital
Avenue de Lattre de Tassigny – 54035 NANCY cedex – France

E-mail : l.parisot@chu-nancy.fr

Address of the corresponding author and for reprint request:

Gisèle Kanny

Internal medicine, Clinical immunology and Allergology

University Hospital - Hôpital Central

29 avenue de Latre de Tassigny

54035 Nancy France

Telephone: (33) 03.83.85.28.63

Fax: (33) 03.83.85.28.64

e-mail: g.kanny@chu-nancy.fr

Abstract

Background: The prevalence of food allergies increases, relating to diet modifications. The consumption of new foods - exotic foods or foods originally used for animal feed, new proteins, neo allergens due to the use of new technologies and soon, Genetically Modified Foods - are in the spotlight.

Objective: It is essential to develop a system of food allergy vigilance encompassing the full range of foods being consumed. Understanding this imperative leads logically to the suggestion of developing an allergy vigilance network taking advantage of the ongoing experience of allergists "on the ground".

Methods: The French Allergy Vigilance Network is subscribed to by 260 allergologists (232 of whom are French). The aims of the Network are to record cases of severe anaphylaxis, to establish an epidemiological data bank from prospective multicenter studies, and to monitor the allergic risk from novel foods.

Results: In 2002, 107 cases of severe anaphylaxis were recorded: anaphylactic shock - 59.8% (one fatal), systemic reaction - 18.7 %, laryngeal angio-edema - 15.9 %, acute severe asthma - 5.6 % (one fatal). The main allergens identified were peanuts, nuts, shellfish, lupine flour and wheat flour. Action has been taken as a result: information by industry on inadequate labeling, withdrawal of wrongly labeled batches, and university hospital centers have been encouraged to establish the allergenic safety of their catering services.

Conclusion: Setting up such a network in other countries would lead to a significant advance in knowledge of the peculiarities of allergies relating to a wide variety of eating habits.

Key words: food allergies – allergic risk – novel foods – allergy vigilance – food safety - network

Introduction

The prevalence of food allergies has been increasing continually over the last years [1]. A study of a population of 33,110 in a representative French sample of 1/1000° people aged fewer than sixty has revealed an estimate of 3.24 % [2]. Consequently, serious forms such as anaphylactic shock, laryngeal angio-edema, and acute serious asthma are growing in number [3]. A documented study showed a five-fold increase over the last twenty years [4]. Some allergies, to peanuts and nuts in general, are long-lasting [5-8]. Data from the CICBAA shows that the relative prevalence of serious forms of allergy increases with age, such that it is in no way an exaggeration to state that food allergies are now a Public Health problem.

Current knowledge of food allergies is viewed in an environmental context. Many factors foster food allergies: taking medication (beta-blockers, non-steroidal anti inflammatory drugs, angiotensin converting enzyme inhibitors, generally prescribed medicines whose consumption increases with age) [9-11], tobacco [12], and technological processes of food industries. Neoallergens can be induced by new processes of agriculture and food industries: long term storage of grain and fruit, ethylene oxide radiation, the use of insecticides and anti-bacterial chemical products such as salicylic acid and ethophon on vegetable cultivation [13-15]. The increasing use of isolated food proteins (lysozyme, casein, gliadin, soya protein etc.) is at risk of modified allergenicity by production processes [16-18]. Finally, the allergenicity of residual proteins in staple food vegetable oils (peanut, sunflower, sesame and soya oil) seems higher than believed [19-23].

Within this complex environment, an additional problem comes from novel foods. These are either exotic proteins that appear in societies where they were not previously consumed (kangaroo meat, quinoa, nangai nut etc.), or indigenous proteins only used until now as animal feed (some Leguminosae such as lupine flour and white peas). Studies have confirmed the risk of sensitization and allergies from crossing nangai nut with other nuts, and lupine flour with peanuts [24, 25]. The imminent marketing of

genetically modified foods requires a policy of evaluation before the submission of a commercialisation request [26-28].

The current situation is therefore assessed as follows. There is a lack of data on the incidence of these severe forms of food allergy. The suggested figure of one death in 800,000 children is contested [29, 30]. The financial cost cannot therefore be assessed. The incidence of allergens is in part the outcome of eating habits, which are in turn affected by food industry initiatives. No method exists at present either for assessing the progression in the incidence rate of these allergens or for monitoring the risk arising from new technologies.An international consensus has been established that all risks to health from the environment must be examined, controlled and avoided as far as possible. The complexity of the food environment means that no food allergy risk can be completely avoided before being marketed, and secondly, previously unknown food allergy risk factors are constantly occurring. This leads therefore to the necessity for food allergy vigilance which, taking its example from pharmaco-vigilance, would specifically monitor the allergic risk in foods consumed. This merits a development advocated for genetically modified foods [27] but which must be extended to all food consumption [31, 32].

The organization that could ensure food allergy-vigilance would depend progressively on the food health safety agents of each country and should be set up moreover at the international level. No matter what the attributions, the privileged information, the means of action, the allergological expertise will be the outcome of precise data, notified by allergologists experienced in detecting, diagnosis and taking responsibility for food allergies. The French Allergy Vigilance Network presents the cases of severe anaphylaxis reported in 2002 by its members.

Methodology

The Allergy vigilance Network

The French Allergy Vigilance Network was set up in 2001. Its aim is to collect data, with three concerns:

1. Recording cases of lethal and near-lethal anaphylaxis for patients benefiting from an allergological assessment.

2. Collecting epidemiological data on specific points by short-term (one month) prospective studies.

3. Assessing new allergies arising from newly marketed foods or ingredients, or from new allergic risks.

The Network is open to any French or foreign allergologist on request. Communication is by Email: l.parisot@chu-nancy.fr. The medical co-ordinators are internists and allergists, with the help of a clinical research assistant. Their role is to disseminate information on food allergology, to respond to requests for information from Network members, to check accident reports, and to analyze the data from prospective studies.

In 2003 the Network became linked to the following national agencies: AFSSA and DGCCRF[1]. The network is composed of 262 allergists, of whom 232 are French. The other countries represented are Belgium (11), Algeria (6), Luxembourg (2), Poland (2), Chili (2) Morocco (1), Finland (1), Greece (1), Italy (1), Portugal (1), Switzerland (1) and the USA (1). Of French Departments (including overseas territories "*DOM-TOM*") 79% are covered. The panel comprises 64.6% allergists, 13.5% pediatric allergists, 10.7% pneumo-allergists, 4.2% dermato-allergists, 2.7% internists allergists and 4.3% other.

This report is on the first study carried out by the Network and examines point 1 of the above aims.

[3] DGCCRF : Direction Générale de la Consommation et Répression des Fraudes

Cases of severe anaphylaxis reported by the Allergy-Vigilance Network

The cases reported meet two conditions - precise information on the accident prior to the consultation with the allergist, including the exact clinical characteristics, **AND** on the management of the clinical acute reaction, compatible with the diagnosis of severity. The allergen must be formally identified except where the accident follows from a novel food or food product. The conjunction of possibly worsening factors is reported. Any unusual detail is sought.

Four clinical states are considered as severe. Anaphylactic shock is defined by cardiovascular collapse, no matter what the associated symptoms. Laryngeal angioedema is defined by an acute respiratory problem accompanied by hoarseness or voice loss. Serious acute asthma is defined subsequently by recourse to hospitalization in an intensive care or respiratory diseases unit, or by the medical diagnosis established at the time of the accident. Systemic serious reaction is defined by an association of symptoms in two or more organs.

For inclusion the case must involve the need for an injection of epinephrine, or recourse to emergency services or hospitalization.

The report by the allergist includes details of the means of diagnosis used. In the majority of cases this concerns the food-anaphylaxis relationship established by case history, completed by the demonstration of sensitization by prick-test or RAST or another specific IgE identification technique, and in some cases oral or labial provocation.

Case validation is carried out by the Network co-ordinators as necessary after telephone discussion with the reporting allergist. Each case is given a reference incorporating the allergist's initials and the name of the town and the Department where it occurred. The case is brought to the notice of the whole Network within seven days of reporting by Email, in French and English. It is published in the specialized food allergy review, "Alim'Inter".

Results

In 2002, 107 cases were reported of which 59.8 % were cases of anaphylactic shock (one being fatal), 18.7% systemic reaction, 15.9% laryngeal angio-edema, 5.6% serious acute asthma (one fatal). Adults represented 69% of cases (74 cases). Recourse to emergency service was noted in 89.7% of cases (96 cases). Hospitalization was necessary in 69% of cases of which 31% in an intensive care unit in 31%. Definite use of adrenaline was recorded in 55% of cases. On examination the anaphylactic risk was underestimated in 5.6% of patients and therapeutic delay occurred.

The most frequent causal allergens (Table 1) were peanut (14), nuts (16), shellfish (9) latex group fruit (9 patients), and most often in-patients allergic to latex: avocado (4), kiwi (2), fig (2), and banana (1). Next came lupine flour (7), wheat flour (7), celery (5) and snails (5), etc. Isolated observations included sulfites, quinine (an additive in a tonic drink), mustard, lentils, kidneys, pork, melon, grapes, pears, chicory, artichokes, oranges and *Anisakis simplex.* Four patients had an immediate post-prandial shock and the in-depth examination did not discern any food or other etiology. These were reported as idiopathic shock.

A co-factor was present only in adults, in 25.6% of cases (21 cases). Two risk factors were reported in 4 cases. Exercise is a major risk factor, most often linked to wheat flour. Concomitant consumption of alcohol (4), aspirin or NSAIDs (5) and beta-blockers (4) was established.

The allergen was present in a masked form in 13% of cases: peanut (6 - with one fatal), lupine (4), sesame (3), and hazelnut (1).

In 4 cases of which one lethal a severe anaphylactic reaction occurred after consumption of macaroon in which the almonds have been replaced by peanuts paste without an adequate labeling. Two cases of anaphylactic shocks in hospitalized children were due to chocolate drink containing lupine flour. Both children were allergic to peanuts and AS occurred by cross allergy. A case of food allergy to hazelnuts is due to a mislabeling on chocolate packaging at Halloween.

Two cases of severe anaphylaxis by proxy are reported: the incriminated allergenic peanuts. The patient presented the allergic reaction by contact with another person eating peanuts.

Discussion

While food allergy is 3.6 times more prevalent in children than in adults (data bank of the Circle of Clinical and Biological Investigations of Food Allergy: CICBAA), this report confirms the preponderance of severe forms in adults. However, one of the fatal cases occurred in a child allergic to soy, having presented an acute lethal asthma after eating a bar of tofu chocolate while expending energy (basket ball) (D Denis, Caen). The fatal anaphylactic shock was caused by a hidden allergen (peanut in a man 21 y.o) (M. Dron-Gonzales, Martigues). A state of apparent death with flat EEG was observed on arrival at hospital. In both these cases, the allergic risk was underrated and the subjects had neither benefited from an examination nor from specialist advice on allergies, even though they had previously presented allergic reactions. Moreover, the fact that epinephrine was only administered in 55% of cases confirms the observation of various authors: the gravity of anaphylaxis is frequently underestimated [3, 33-35]. Serious acute asthma cases (reported by pneumo-allergists) are mainly due to the snail in patients allergic to dust mites [36].

The incidence of causal allergens shows that in France as in the USA and the United Kingdom, peanuts and nuts are preponderant, above all among children [5, 7]. It also reflects French eating habits - snails, kidneys, wheat flour and lupine flour (an ingredient that is currently used in certain types of biscuit pastry and in pizzas, pâtés and pastries since 1997). This indicates the validity of operating a Network of this type per country. Useful additional information can be obtained by a direct survey of patients [5, 37].

Some 13% of severe accidents are due to hidden allergens: peanut paste in macaroons stated to be almonds, hazelnut in chocolate with mislabeling, lupine flour in chocolate powder and so on. The scale of this problem is a definite factor [38-42]. Leguminosae (soy, lupine and white pea flours) are a particular danger as they are currently used in a great variety of food products (sausages and bakery products). These ingredients are not declared on the label when the produce is manufactured, and some of these products are unlabelled anyway e.g. sausages and cheese [43].

Reporting the above-mentioned cases has enabled several public interest measures to be taken. Lack of labeling and errors in labeling have been targeted. The report that four severe cases of anaphylaxis, one of which was fatal, were linked to eating macaroons said to be "almond" but actually made with peanut paste with an artificial almond flavoring, resulted in this case of non-labeling being notified to the DGCCRF and the food industry being informed. A second report, completed by information supplied by the business concerned, revealed a labeling error, and the DGCCRF was informed of the relevant batch number and was able to have it withdrawn from sale within three weeks (a work of the Food Anaphylaxis Network, USA, regularly informed of contaminated batches of products by the industries).

The two cases of anaphylactic shocks in hospitalized children were observed in two children allergic to peanuts: anaphylactic shock occurred by cross allergy after intake of a chocolate drink containing lupine flour. These cases were communicated to all university hospital centers so as they review the allergenic safety of hospital catering services. Dieticians responsible for hospital catering units set up advised procedures [44].

The effective involvement of Network members may be a concern. In 2002 the level of active involvement was 23%. Hopefully, this level of interest will increase since in the first five months of 2003 a similar number of allergists declaring cases have been already obtained. Comparing the same period, over 2002 and 2003 an increase of 46% of the records is noticed. Information collected shows the value of an additional "food allergy alert" network that will shortly be developed by the French Agency for Safety of Food in connection with food industries. Through the intermediary of this organization, allergist members of the Allergy Vigilance Network will have access to prompt information where novel foods are concerned. Having food materials available at short notice for realistic prick tests will be possible once the two Networks are able to work together. Their co-operation will in turn enable the alert to be given of the danger of new cross sensitization or cross allergy.

Conclusions

Atopic diseases rely on genetic factors inducing a polarization of responses directed towards Th2. However the role of environmental factors is essential since they could exercise a sufficient pressure on the immune system of the individual to direct the naïve T lymphocytes to a Th2 profile [45, 46]. Food allergy is a typical topic illustrating the importance of environmental factors linked to the extraordinary transformation of foodstuffs. While food proteins are potential allergens, the technologies of the modern industrial foods could represent this pressure element, spreading the allergic danger to a growing proportion of the community. A food allergy vigilance policy is therefore a vital element for protection. The Allergy Vigilance Network is a first line approach in this development.

References

1. Sampson H. Food hypersensitivity: manifestations, diagnosis, and natural history. Food Technol 1992; 46:141-4.
2. Kanny G, Moneret-Vautrin D, Flabbee J, Beaudouin E, Morisset M, Thévenin F. Population study of food allergy in France. J Allergy Clin Immunol 2001; 108:133-40.
3. Sampson H, Mendelsohn L, Rosen J. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992; 327:380-4.
4. Moneret-Vautrin D, Kanny G. L'anaphylaxie alimentaire. Nouvelle enquête multicentrique. Bull Acad Natl Méd 1995; 179:161-84.
5. Sicherer S, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Cin Immunol 1999; 103:559-63.
6. Skolnick H, Conover-Walker MK, Koerner CB, Sampson HA, Burks AW, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol 2001; 107:367-74.
7. Ewan P. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. Br Med J 1996; 312:1074-8.
8. Moneret-Vautrin D, Rance F, Kanny G, Olsewski A, Guéant J, Dutau G, et al. Food allergy to peanuts in France-evaluation of 142 observations. Clin Exp Allergy 1998; 28:1113-9.
9. Moneret-Vautrin D, Blain H, Kanny G, Bloch Y. Anaphylaxis to walnuts and pine nuts induced by ACE. Allergy 1998; 53:1233-4.
10. Morisset M, Moneret-Vautrin D. Food anaphylaxis induced by aspirin. Allerg Immunol 2001; 33:147-9.
11. Moneret-Vautrin D, Kanny G, Faller J, Levan D, Kohler C. Choc anaphylactique grave avec arrêt cardiaque au café et à la gomme arabique, potetntialisé par un collyre bêta-bloquant. Rev Med Int 1993; 14:107-11.
12. Kulig M, Luck W, Lau S, Niggemann B, Bergmann L, Kelttke U. Effect of pre and post-natal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first three years of life. Allergy 1999; 54:220-8.
13. Hanninen AR, Mikkola JH, Kalkinnen N, Turjanmaa K, Ylitalo L, Reunala T, et al. Increased allergen production in turnip (Brassica rapa) by treatments activating defense mechanisms. J Allergy Cin Immunol 1999; 104:194-201.
14. Hsieh LS, Moos M, Lin Y. Characterizationof apple 18 and 31 kd allergens by microsequencing and evaluation of their content during stokage and ripening. J Allergy Cin Immunol 1995; 96:960-70.
15. Malanin K, Lundberg M, Johansson S. Anaphylactic reaction caused by neoallergens in heated pecan nut. Allergy 1995; 50:988-91.
16. Leduc V, Moneret-Vautrin D, A, Guérin L, Morisset M, Kanny G. Anaphylaxis to wheat isolates: immunochemical study of a case proved by means of double-blind, placebo-controlled food challenge. J Allergy Clin Immunol 2003; 111:897-9.
17. Franck P, Moneret-Vautrin D, A, Dousset B, Kanny G, Nabet P, Guenard-Bilbault L, et al. The allergenicity of soybean-Based products is modified by food technologies. Int Arch Allergy Immunol 2002; 128:212-9.
18. Korhonen H, Pihlanto-Leppala A, Rntamaki P, Tupasela T. Impact of processing on bioactive proteins and peptides. Trends Food Sci Technol 1998; 9:307-19.

19. Zitouni N, Errahali Y, Metche M, Kanny G, Moneret-Vautrin D, Nicolas J, et al. Influence of refining steps on trace allergenic protein content in sunflower oil. J Allergy Clin Immunol 2000; 106:962-7.
20. Moneret-Vautrin D, Hatahet R, Kanny G, Ait-Djafer z. Allergenic peanut oil in milk formulas. Lancet 1991; 338:1149.
21. Kanny G, De Hauteclocque C, Moneret-Vautrin D. Sesame seed and sesame seed oil contain masked allergens of growing importance. Allergy 1996; 51:952-7.
22. Errahali Y, Morisset m, Moneret-Vautrin DA, Metche M, Nicolas JP, Frémont S. Allergen in soy oils. Allergy 2002; 57:648-9.
23. Olszewski A, Pons L, Moutete F, Aimone-Gastin I, Kanny G, Moneret-Vautrin D, et al. Isolation and characterization of proteic allergens in refined peanut oil. Clin Exp Allergy 1998; 28:850-9.
24. Sten E, Stahl Skov P, Andersen SB, Torp AM, Olesen A, Bindslev-Jensen U, et al. Allergenic components of a novel food, Micronesian nut Nangai (Canarium indicum), shows IgE cross-reactivity in pollen allergic patients. Allergy 2002; 57:398-404.
25. Moneret-Vautrin D, Guérin L, Kanny G, Flabbee J, Frémont S, Morisset M. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. J Allergy Clin Immunol 1999; 104:883-8.
26. Lack G. Clinical risk assessment of GM foods. Toxicol Lett 2002; 127:337-40.
27. Joint FAO/WHO expert consultation on allergenicity of food derived from biotechnology. 2001.
28. Taylor S, Hefle S. Will genetically modified foods be allergenic? J Allergy Cin Immunol 2001; 107:765-71.
29. Warner JO. How dangerous is food allergy in childhood? Pediatr Allergy Immunol 2002; 13:149-50.
30. Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Arch Dis Child 2002; 86:236-.
31. Hourihane JOB. Prevalence and severity of food allergy - need for control. Allergy 1998; 53:84-8.
32. Moneret-Vautrin D. Aspects actuels des allergies alimentaires: nécessité d'une allergovigilance. Bull Acad Natl Méd 2001; 185:943-62.
33. Wuthrich B. Lethal or life-threatening allergic reactions to food. Invest Allergol Clin Immunol 2000; 10:59-65.
34. Pumphrey R. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30:1144-50.
35. Bock S, Munoz-Furlong A, Sampson H. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001; 107:191-3.
36. Guilloux L, Vuitton DA, Delbourg M, Lagier A, Adessi B, Marchand CR, et al. Cross-reactivity between terestrial snails (Helix species) and house-dust mite (dermatophagoides pteronyssinus. Allergy 1998; 53:151-8.
37. Eigenmann P, Pastore F, Zamora S. An Internet-based survey of anaphylactic reactions to foods. Allergy 2001; 56:540-3.
38. Borelli S, Anliker MD. Peanut anaphylaxis: the problem of hidden allergens. Dtsch Med Wochenschr 1999; 124:1197-200.
39. Wensing M, Koppelman S, Penninks SJ, C.A B-K, Knulst AC. Hidden hazelnut is a threat to allergic patients. Allergy 2001; 56:191-2.
40. Vidal C, Perrez-Carral C, al e. Unexpected sources of soybean exposure. Ann Allergy, Asthma, Immunol 1997; 79:350-2.
41. Foucard T, Edberg U, Malmheden-Yman I. Severe, even fatal reaction to foodstufs:peanuts and soya underestimated allergen. J Swe Med Assoc 1997; 95:2635-8.

42. Malmheden-Yman I, Eriksson IA. Analysis of food proteins for verification of contamination or mislabelling. Food Agric Immunol 1994; 6:167-72.
43. Taylor SL, Hefle SL. Ingredient and labelling issues associated with allergenic foods. Allergy 2001; 56:64-9.
44. Sergeant P, Kanny G, Morisset M, Waguet JC, Bastien C, Moneret-Vautrin D, A. Food safety of allergic patients in hospitals : implementation of a quality strategy to ensure correct management. Eur Ann Allergy Clin immunol 2003; 35:120-3.
45. Gennery AR, Cant AJ. Developpement of allergy post-bone marrow transplantation. Clin Exp Allergy 2002; 32:1677-8.
46. Okudaira H. Why atopic diseases prevail in developed countries. Allergy Clin Immunol Intern 1998; 10:110-5.

Table 1: Incidence of allergens responsible for near-lethal or lethal anaphylaxis in 2002, according to the reports of the French Allergy Vigilance Network

Allergen	Children - 37	Adults - 70
Peanut	10	4
Hard-shelled nut	10	6
Shellfish	3	8
Latex group fruit - avocado, kiwi, fig, banana	0	9
Leguminosae (lupine included) and peanut excluded	6 (4)	4 (3)
Wheat flour	0	7
Celery	1	4
Snail	2	3
Sesame	0	4
Milk	3	0
Buckwheat	0	3
Fish	0	3
Peaches	0	2
Poultry	1	1
Isolated cases	1 (pork)	10 (melon, pear, chicory, artichoke, orange, mustard, kidney, quinine, sulfites, anisakis)
Idiopathic anaphylaxis	0	2