



Severe food allergies: can they be considered rare diseases?

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Food allergy is a very frequent disease, but its clinical spectrum is various. Differently from asthma and allergic rhinitis, an official definition of severe food allergy does not exist [1,2]: one can expect that such definition differs among each of the multifaceted aspects of food allergy. Surely, the severe manifestations are only a small part of the spectrum of food allergy. As examples, Food Protein-Induced Enterocolitis Syndrome (FPIES) is severe by definition [3], but only the patients sensitive to a large number of offending foods and/or with severe characteristics of the reaction can be considered with severe FPIES. Anaphylaxis is also an example of a generalized food-allergic manifestation, which can in some cases be life threatening and thus be considered a severe food allergy.

The definition of severity is precisely what is required to indicate when food allergic diseases can be considered rare. Using such definition, existing epidemiological studies can be read back for the exact identification of the prevalence of severe food allergy, and new studies could be targeted to this goal. Despite variation in the terminology and prevalence thresholds used to define rare diseases among different jurisdictions and organizations, the prevalence threshold is precisely what is most commonly requested to be able to define a rare disease.

In general, this term identifies conditions whose prevalence is less than 50 cases/100 000 persons [4]. In some countries, as the United States (US) and Japan, the prevalence threshold is not explicitly considered [5]. However, a disease prevalence of 64 cases/100 000 people is implied in the US definition [6]. If so, anaphylaxis used to be a rare disease, as its prevalence in general populations between 1999 and 2010 ranged among 6.7 and 49.8 per 100 000 (Fig. 1) [7,8]. More recent studies reported higher prevalences, but methodological constraints (use of surveys) limit these reports [9]. In any case, food-induced anaphylaxis is only a fraction of all cases of anaphylaxis, and is indubitably rare by prevalence definition. Even rarer is food-induced life-threatening anaphylaxis. As not rarely 'rare diseases' are defined by qualitative terminologies, 'life-threatening' may be part of the definition of a rare

disease. In our case, if we use the admission rate to emergency departments during an anaphylactic attack as a proxy measure, we get a precise idea of the prevalence of life-threatening anaphylaxis. In US, the overall admission rates for food-induced anaphylaxis per 100 000 insured patients were 3.8 in 2005 and 7.7 in 2014 [10]. Previous retrospective reports from Denmark, Germany, Italy, USA, and UK reported rates among 3.2 and 90 per 100 000 [11]. More recent data reported hospitalization rates among 2.1 and 32.7/100 000 in Italy, USA, and UK [12–16].

We also have an idea of fatal anaphylaxis rates: they range among 0.03 and 0.1 per 100 000, and it has been calculated that 12 deaths from food-induced anaphylaxis occur in the US every year [17]. Ebisawa *et al.* (pp. 212–219) provide an article on food labeling issues in patients with severe food allergies and on OIT in severe food allergy. Agostoni *et al.* (pp. 220–226) provide an article on impact of elimination diets on nutrition and growth in children with severe food allergies. People at risk include children with severe multiple-food anaphylaxis, whose quality of life (QOL) is curtailed by emotional, social, nutritional, and financial burdens [18, Mennini *et al.* (pp. 204–211), Ebisawa *et al.* (pp. 212–219), Agostoni *et al.* (pp. 220–226)].

Similar considerations may apply to other food-allergic conditions, again severely affecting the quality of life [19] and for which epidemiologic studies are lacking. The FPIES guidelines state that 'it is debatable if it is a rare syndrome, as opposed to a syndrome rarely recognized', but an Australian

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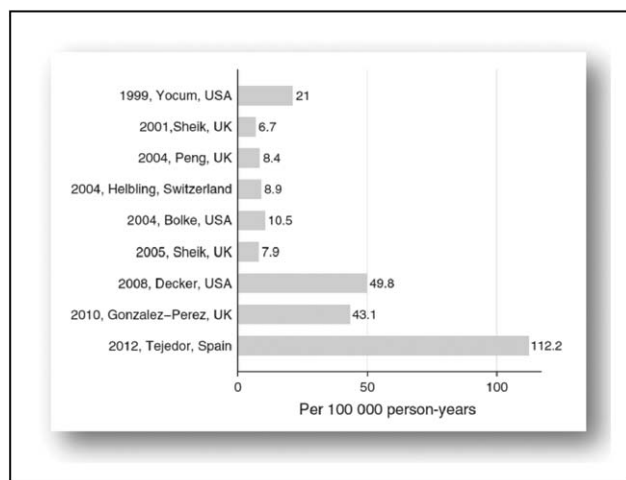


FIGURE 1. Incidence of anaphylaxis (per 100 000 persons/year) in the general population (data from Ref. 7).

report indicates a frequency of 10:100 000 infants less than 2 years of age, closely corresponding to the Australian reported incidence of eosinophilic esophagitis in children, of 9 per 100 000 [20,21]. In Euro-preval birth cohorts, including 12 000 infants, no case of FPIES was reported [22,23], indicating that FPIES prevalence in Europe in 2005–2007 was less than 10 per 100 000.

Thus, technically speaking, some forms of food allergy met the epidemiologic criteria to be included in the lists of rare diseases. Yet, these lists include today few food-allergic manifestation. The NIH Genetic And Rare Disease information center includes Eosinophilic enteropathy [24]. The European organization on orphan drugs and rare diseases, Orphanet [25], includes the same (Eosinophilic colitis, ORPHA:402035, and Eosinophilic enteritis, ORPHA:2070), plus Eosinophilic Oesophagitis, ORPHA:73247. Food allergy may also be present in Severe dermatitis-multiple allergies-metabolic wasting syndrome (ORPHA:369992), in PLCG2-associated antibody deficiency and immune dysregulation (ORPHA:300359), and in autosomal dominant hyper-IgE syndrome (ORPHA:2314). In Asia, much progress has been made in Japan, South Korea, and Taiwan, with the enactment of legislation and accompanying regulation of rare diseases and orphan drugs, but food allergy is poorly represented. China is also actively promoting the regulation of rare diseases and orphan drugs [26].

As rare diseases make for the highest health-system costs, specific strategies are being developed by governments worldwide to manage their service needs and the research in the field. As it is well known that severe respiratory allergies are associated with the greatest costs of morbidity and

economic expenditure, we can argue that severe food allergies are also responsible for the highest medical and human shares. A precise definition of severe food allergy and its classification among the rare diseases would be essential to promote research on these conditions. Dahdah *et al.* (pp. 227–231) provide an article on apheresis in severe food allergies. Fiocchi *et al.* (pp. 232–238) provide an article on use of biologics in severe food allergies. Within this framework, specific legislations could be adopted to encourage research on advanced therapies and the development of orphan drugs, and to establish a common approach to the treatment of these forms with biologics.

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REFERENCES

- Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *Nutr Res* 2011; 31:61–75.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, *et al.* EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014; 69:1008–1025.
- Nowak-Węgrzyn A, Chehade M, Groetch M, *et al.* International consensus guidelines for the diagnosis and management of Food Protein-induced Enterocolitis Syndrome. *J Allergy Clin Immunol* 2017. [Epub ahead of print]
- Richtan T, Nestler-Parr S, Babela R, *et al.*, International Society for Pharmacoeconomics and Outcomes Research Rare Disease Special Interest Group. Rare disease terminology and definitions—a systematic global review: report of the ISPOR Rare Disease Special Interest Group. *Value Health* 2015; 18:906–914.
- Liu B, He L, He G, He Y. A cross-national comparative study of orphan drug policies in the United States, the European Union, and Japan: towards a made-in-China orphan drug policy. *J Public Health Policy* 2010; 31:407–420; discussion 420–1.
- Orphan Drug Act. 2049–2066. Available from: <http://www.gpo.gov/fdsys/granule/STATUTE-96/STATUTE-96-Pg2049/content-detail.htm>. [Accessed 20 March 2017].
- Tejedor-Alonso MA, Moro-Moro M, Múgica-García MV. Epidemiology of anaphylaxis: contributions from the last 10 years. *J Investig Allergol Clin Immunol* 2015; 25:163–175.
- Panesar SS, Javad S, de Silva D, *et al.*, EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013; 68:1353–1361.
- Wood RA, Camargo CA Jr, Lieberman P, *et al.* Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol* 2014; 133:461–467.
- Motosue MS, Bellolio MF, Van Houten HK, *et al.* Increasing emergency department visits for anaphylaxis, 2005–2014. *J Allergy Clin Immunol Pract* 2017; 5:171–175.
- Lieberman P. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006; 97:596–602.
- Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000–2009. *J Allergy Clin Immunol* 2014; 134:960–962; e3.
- Nocerino R, Leone L, Cosenza L, Canani RB. Increasing rate of hospitalizations for food-induced anaphylaxis in Italian children: an analysis of the Italian Ministry of Health database. *J Allergy Clin Immunol* 2015; 135:833–835; e3.

14. Mullins RJ, Dear KBG, Tang MLK. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol* 2015; 136:367–375.
15. Turner PJ, Gowland MH, Sharma V, *et al.* Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol* 2015; 135:956–963; e1.
16. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014; 133:1075–1083.
17. Jerschow E. Fatal anaphylaxis in the United States. 1999–2010: temporal patterns and demographic associations. *J Allergy Clin Immunol* 2014; 134:1318–1328.
18. Patel N, Herbert L, Green TD. The emotional, social, and financial burden of food allergies on children and their families. *Allergy Asthma Proc* 2017; 38:88–91.
19. Meyer R, Godwin H, Dziubak R, *et al.* The impact on quality of life on families of children on an elimination diet for nonimmunoglobulin E mediated gastrointestinal food allergies. *World Allergy Organ J* 2017; 10:8.
20. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014; 14:208–216.
21. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006; 91:1000–1004.
22. Schoemaker AA, Sprickelman AB, Grimshaw KE, *et al.* Incidence and natural history of challenge-proven cow's milk allergy in European children—EuroPrevall birth cohort. *Allergy* 2015; 70:963–972.
23. Xepapadaki P, Fiocchi A, Grabenhenrich L, *et al.* Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study. *Allergy* 2016; 71:350–357.
24. <https://rarediseases.info.nih.gov/diseases/9142/eosinophilic-gastritis>. [Accessed 20 March 2017].
25. <http://www.orpha.net/consor/cgi-bin/index.php>. [Accessed 14 March 2017].
26. Song P, Gao J, Inagaki Y, *et al.* Rare diseases, orphan drugs, and their regulation in Asia: current status and future perspectives. *Intractable Rare Dis Res* 2012; 1:3–9.