Anaphylaxis in children and adolescents: The European Anaphylaxis Registry

Linus B. Grabenhenrich, MD, MPH,[a] Sabine Dölle, PhD,[b] Anne Moneret-Vautrin, MD,[c] Alice Köhli, MD,[d] Lars Lange, MD,[e] Thomas Spindler, MD,[f] Franziska Ruëff, MD,[g] Katja Nemat, MD,[h] Ioana Maris, MD,[i] Eirini Roumpedaki, MD,[j] Kathrin Scherer, MD,[k] Hagen Ott, MD,[l] Thomas Reese, MD,[m] Tihomir Mustakov, MD,[n] Roland Lang, PhD,[o] Montserrat Fernandez-Rivas, MD,[p] Marek L. Kowalski, MD, PhD,[q] Maria B. Bilò, MD,[r] Jonathan O'B. Hourihane, MD,[i] Nikolaos G. Papadopoulos, MD,[j] Kirsten Beyer, MD,[s,t] Antonella Muraro, MD,[u] and Margitta Worm, MD[b] *Berlin, Bonn, Wangen, Munich, Hannover, Rheine, and Dresden, Germany, Nancy, France, Zurich and Basel, Switzerland, Cork, Ireland, Athens, Greece, Sofia, Bulgaria, Salzburg, Austria, Madrid, Spain, Lodz, Poland, Ancona and Padua, Italy, and New York, NY*

Background: Anaphylaxis in children and adolescents is a potentially life-threatening condition. Its heterogeneous clinical presentation and sudden occurrence in virtually any setting without warning have impeded a comprehensive description.
Objective: We sought to characterize severe allergic reactions in terms of elicitors, symptoms, emergency treatment, and long-term management in European children and adolescents.
Methods: The European Anaphylaxis Registry recorded details of anaphylaxis after referral for in-depth diagnosis and counseling to 1 of 90 tertiary allergy centers in 10 European countries, aiming to oversample the most severe reactions. Data were retrieved from medical records by using a multilanguage online form.
Results: Between July 2007 and March 2015, anaphylaxis was identified in 1970 patients younger than 18 years. Most incidents occurred in private homes (46%) and outdoors (19%). One third of the patients had experienced anaphylaxis previously. Food items were the most frequent trigger (66%), followed by insect venom (19%). Cow's milk and hen's egg were prevalent elicitors in the first 2 years, hazelnut and cashew in preschool-aged children, and peanut at all ages. There was a continuous shift from food- to insect venom– and drug-induced anaphylaxis up to age 10 years, and there were few changes thereafter. Vomiting and cough were prevalent symptoms in the first decade of life, and subjective symptoms (nausea, throat tightness, and dizziness) were prevalent later in life. Thirty percent of cases were lay treated, of which 10% were treated with an epinephrine autoinjector. The fraction of intramuscular epinephrine in professional emergency treatment increased from 12% in 2011 to 25% in 2014. Twenty-six (1.3%) patients were either admitted to the intensive care unit or had grade IV/fatal reactions.
Conclusions: The European Anaphylaxis Registry confirmed food as the major elicitor of anaphylaxis in children, specifically hen's egg, cow's milk, and nuts. Reactions to insect venom were seen more in young adulthood. Intensive care unit admissions and grade IV/fatal reactions were rare. The registry will serve as a systematic foundation for a continuous description of this multiform condition. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

From [a]the Institute for Social Medicine, Epidemiology and Health Economics, [b]the Department of Dermatology and Allergy, and [s]the Department of Pediatric Pneumology and Immunology, Charité - Universitätsmedizin Berlin; [c]the Allergy Vigilance Network, University Hospital Nancy; [d]the Division of Allergology, University Children's Hospital Zurich; [e]the Department of Pediatrics, St Marien-Hospital, Bonn; [f]Pediatric Pneumology and Allergology, Lungenzentrum Süd-West, Wangen; [g]the Department of Dermatology and Allergology, Ludwig-Maximilian-Universität, Munich; [h]Pediatric Pneumology and Allergology, Kinderzentrum Dresden-Friedrichstadt, Dresden; [i]the Department of Paediatrics and Child Health, University College Cork; [j]the Allergy Department, University of Athens; [k]the Department of Dermatology, University Hospital Basel; [l]Pediatric Dermatology and Allergology, Children's Hospital Auf der Bult, Hannover; [m]Rheine Kinderklinik, Mathias-Spital, Rheine; [n]the Clinical Centre of Allergology, University Hospital Alexandrovska/Medical University Sofia; [o]the Department of Dermatology, Paracelsus Medizinische Privatuniversität Salzburg; [p]the Allergy Department, Hospital Clinico San Carlos IdISSC, Madrid; [q]the Department of Immunology, Rheumatology and Allergy, Medical University of Lodz; [r]the Department of Internal Medicine/Allergy Unit, University Hospital Ospedali Riuniti, Ancona; [t]the Icahn School of Medicine at Mount Sinai, New York; and [u]the Department of Mother and Child Health, Padua General University Hospital.

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Corresponding author: Margitta Worm, MD, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: margitta.worm@charite.de.

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As the most severe course of an acute allergic reaction, anaphylaxis occurs in patients of all ages, but most research and guidelines are focused on adults.[1-3] Typical elicitors and the clinical presentation of anaphylaxis in children and adolescents were shown to be different from those in adults,[4] calling for specific research and targeted guideline development for a pediatric population.[5,6]

Increasing frequencies of allergic diseases have been observed over recent decades, but there is considerable uncertainty in whether this reflects true variations in disease frequency or differences in perception, labeling, and diagnostic habits.[7] Little is known about the occurrence of severe allergic reactions and time trends on a population level,[8-10] and even less is known for pediatric anaphylaxis.[11,12]

Food items are the most common triggers of severe allergic reactions in childhood, with some allergens, such as cow's milk and hen's egg, specific to young ages. However, age-dependent distributions have not been published for adequately large populations to account for less frequent causes. The clinical picture of anaphylaxis in children, especially that in infants, is different from that in adults.[4,13] This varied clinical picture reflects differences in allergen absorption, a developing immune system, and lack of preschoolers' ability to talk about subjective symptoms. Interpretation of diagnostic tests (eg, tryptase measurement) is valid only in light of age-dependent reference values and experience in pediatric allergology. Confirming the causal role of a suspected elicitor can become a tedious venture, even more so in children.

Emergency treatment, long-term management, and counseling are supported by current guidelines[2,14] but are only partly adapted to pediatric settings.[15] For example, there is a long-standing debate about the application and dose of epinephrine as the first-line treatment for anaphylaxis.[16] Reactions initially treated by a layperson rely on epinephrine autoinjectors, which are also available for younger patients but not for infants.[17] Implementation of treatment recommendations has been assessed in the general population,[18] but data on emergency management in children and adolescents are lacking. Counseling to reduce the risk of recurrent reactions and emergency drug prescriptions could be tailored based on age-specific distributions of comorbidities and cofactors, such as asthma or physical exercise.

Based on data collected in the European Anaphylaxis Registry from 2007 to 2015,[19] the aim of this analysis was to show data on the most severe allergic reactions occurring in children and adolescents. This large-scale survey comprises data on elicitors, symptoms, emergency treatment, and long-term management from 10 countries. The survey allows guideline adherence to be traced by comparing treatment habits over 8 consecutive years. The overall goal was to improve the timely recognition, emergency management, and prevention of recurrent reactions by disseminating knowledge of age-dependent distributions of pediatric anaphylaxis.

METHODS

Setting and design

The European Anaphylaxis Registry collected information on anaphylactic reactions through a Web-based data entry system. Data for the current analysis were provided by tertiary referral centers specialized in pediatric allergology, dermatology, or both in Germany, France, Switzerland, Ireland, Greece, Austria, Spain, Bulgaria, Italy, and Poland. The study was approved by the Ethics Committee at Charité - Universitätsmedizin Berlin (the coordinating center) and by the local ethics committees in all participating countries.

Participants

Children who experienced anaphylaxis were referred to the participating specialized clinics for in-depth diagnosis, counseling, and, if possible, specific immunotherapy. On their first visit, parents were asked to provide written informed consent to allow registration of the child's medical history and reaction details in the database after completion of the diagnostic workup. The study centers were asked to enter their most severe cases, usually with circulatory or respiratory symptoms, but milder anaphylaxis could be recorded as well. Fatal anaphylaxis, known from either counseling of previous reactions in the referral center or from an emergency physician's notification, could be recorded with the parents' consent as well. Database entries were included if the sex of the child and the year of reaction were specified and the age at reaction was less than 18 years.

Data source and handling

The online data entry system comprised a German questionnaire for Germany, Austria, and Switzerland; a French version for centers in France; and an English version for all other participating countries. The questionnaire was initially developed and piloted in the German Anaphylaxis Registry[20,21] and translated/back-translated for international use. The questionnaire was refined through yearly updates, with new items introduced based on expert judgment. Interrater reliability was assessed by using repeated data entry by 2 independent professionals. Data collected through questionnaire versions 2 to 6 (n = 134, 219, 167, 689, and 761) with entry dates from July 2007 to March 2015 were used. Trained professionals in each study center retrieved data retrospectively from the medical records, including laboratory measures and emergency protocols. Raw study data were stored with pseudonyms on a server at Charité - Universitätsmedizin Berlin.

Variables

Specific areas covered have been reported earlier,[22] and the online version can be accessed through www.anaphylaxie.net. Age at reaction was categorized in 3 strata: preschoolers (0-5 years), schoolchildren (6-12 years), and adolescents (13-17 years). Assuming primary documentation habits to differ randomly, most variables were reported as a fraction of valid answers by item (comorbidities, cofactors, details of previous reactions, symptoms and severity, emergency treatment, and long-term management). Therefore the denominator used for calculating percentages might slightly vary from the column totals shown. The location of reaction was reported as a fraction of all cases, assuming missing answers to represent categories not presented as default. Elicitors were assessed by using a comprehensive list of typical foods, insect venoms, drugs, and other less frequently expected causes of allergic reaction, such as latex or allergen immunotherapy. Rare food items specified as free text entries were reported within the group of food elicitors. The diagnostic certainty of the causal agent was documented at the 2 levels *known* versus *suspected* based on the local allergy specialist's individual appraisal, without specifying reasons for their decision. Symptoms documented through free text were manually assigned to default answer categories, where reasonable. Severity was graded retrospectively based on the 4 levels of symptom profiles proposed by Ring and Messmer[23]: grade II with involvement of at least 2 organ systems, grade III with signs of circulatory and/or respiratory failure/shock, and grade IV with circulatory or respiratory arrest. The criteria for selection of the most severe cases were (1) a known elicitor with grade III symptoms admitted to an intensive care unit, (2) grade IV symptoms, or (3) fatal reactions.

Statistics

Cleaning and analysis of data were carried out by using the SAS 9.4 system (SAS Institute, Cary, NC). Stratified analysis of frequencies was used to