ORIGINAL ARTICLE

Severe Immediate Type Hypersensitivity Reactions in 105 German Adults: When to Diagnose Anaphylaxis

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■ Abstract

Background: There are no epidemiological data available on anaphylaxis in German adults and so far there has been no consensus on when to diagnose anaphylaxis, mainly due to a lack of generally accepted diagnostic criteria. Recently, an international expert group addressed this issue by suggesting new diagnostic criteria for anaphylaxis. We addressed the usefulness of the suggested diagnostic criteria in German adults and attempted to identify putative trigger factors.

Methods: Medical records were reviewed for patients seen in 2006 who had suffered any reaction that led to the suspicion of anaphylaxis. Clinical reaction patterns, eliciting factors, serum tryptase concentrations, and the applicability of diagnostic criteria for anaphylaxis were evaluated.

Results: One hundred five patients (78 women and 27 men, aged 18-77 years) were included in the study. The eliciting factors were as follows: drugs (46%), hymenoptera stings (33%), food (11%), physical factors (4%), or unknown (7%). Ninety-five patients (91%) fulfilled criteria for anaphylaxis currently employed in Germany; 58 (58%) of those patients had grade 2-4 reactions. In contrast, only 53 (51%)—and only 19/48 (40%) of those who reacted to drugs—fulfilled the newly proposed criteria. Recurrent anaphylactic episodes were found in 15% of the patients and elevated serum tryptase was observed in 6%.

Conclusion: The main eliciting factors for anaphylaxis were hymenoptera stings, drugs, and food. The application of the newly proposed diagnostic criteria did not identify as many patients with severe immediate-type reactions as the graded score currently employed for diagnosis of anaphylaxis in Germany. Further efforts are needed to extend and standardize diagnostic criteria for anaphylaxis.

Key words: Anaphylaxis. Diagnosis. Drug allergy. Food allergy. Hymenoptera allergy.

■ Resumen

Antecedentes: No hay información epidemiológica disponible sobre la anafilaxia en adultos alemanes y hasta ahora no se ha alcanzado ningún consenso sobre cuando diagnosticar anafilaxia, principalmente debido a la inexistencia de criterios diagnósticos generalmente aceptados. No hace mucho, un grupo internacional de expertos abordó este asunto, proponiendo nuevos criterios diagnósticos para la anafilaxia. Se estudió la utilidad de los criterios diagnósticos sugeridos para adultos alemanes y se trataron de identificar los posibles factores desencadenantes de la anafilaxia.

Métodos: Se revisó la historia clínica de los pacientes visitados en 2006 que habían padecido alguna reacción que llevó a pensar que podía existir una presunta anafilaxia. Se evaluaron el cuadro clínico de la reacción, los factores desencadenantes, las concentraciones séricas de triptasa y la aplicabilidad de los criterios diagnósticos para la anafilaxia.

Resultados: Participaron en el estudio 105 pacientes (78 mujeres y 27 hombres con edades comprendidas entre los 18-77 años). Los factores desencadenantes fueron los siguientes: fármacos (46%), picadura de himenópteros (33%), alimentos (11%), factores de tipo físico (4%), o desconocidos (7%). Noventa y cinco pacientes (91%) cumplieron los criterios para la anafilaxia que se emplean actualmente en Alemania; 58 de estos pacientes (58%) tuvo reacciones de grado 2-4. Por otro lado, sólo 53 (51%)—y sólo 19 / 48 (40%) de los que tuvieron reacciones a los fármacos—cumplieron los nuevos criterios propuestos. Se observaron episodios anafilácticos recurrentes en el 15% de los pacientes y una elevada concentración sérica de triptasa en el 6%.

Conclusión: Los principales factores desencadenantes de la anafilaxia fueron las picaduras de himenópteros, los fármacos y los alimentos. La aplicación de los nuevos criterios propuestos no identificó a tantos pacientes con reacciones inmediatas graves como el valor gradual que se utiliza actualmente para el diagnóstico de la anafilaxia en Alemania. Por lo tanto, surge la necesidad de llevar a cabo más investigaciones para ampliar y normalizar los criterios diagnósticos para la anafilaxia.

Palabras clave: Anafilaxia. Diagnóstico. Alergia a los fármacos. Alergia alimentaria. Alergia a las picaduras de himenópteros.

Introduction

Although the phenomenon of anaphylaxis was first described in 1902 [1], there is still no consensus on exactly how it should be defined or diagnosed, and consequently, there is considerable disagreement about its prevalence, diagnosis, and management [2-5]. The incidence of severe anaphylactic reactions is said to be 1 to 3 per 10 000 individuals per year, and it seems to be increasing [6,7]. In 2006, an international symposium that included representatives from 16 international organizations from different medical disciplines addressed the important question of definition and management of anaphylaxis [8,9]. This expert group defined anaphylaxis as a "serious allergic reaction that is rapid in onset and may cause death" [8,9]. The following organ systems were indicated as having possible involvement in anaphylaxis: cutaneous/subcutaneous/mucosal, respiratory (laryngeal, pulmonary, nasal), cardiovascular, gastrointestinal, and other (eg, systems involved in uterine contractions and a "sense of doom"). These experts suggested diagnostic criteria that were expected to identify anaphylactic reactions in more than 95% of cases (Table 1) [8,9].

The most commonly reported etiologies of anaphylaxis include allergic—mostly immunoglobulin E-mediated—and nonallergic responses to food, drugs, and hymenoptera stings [2-7]. There are no data available about prevalence and eliciting factors in adults in Germany, where diagnosis and grading of anaphylaxis relies mostly on the criteria proposed by Ring and Messmer [10,11]. In insect allergies, the criteria proposed by Mueller [12] are also in use. Recently, a questionnaire-based survey of anaphylactic reactions in 103 German children was published, detecting mainly food and hymenoptera stings as eliciting factors [13].

The aim of our study was to identify the most important trigger factors of severe immediate-type reactions in a German adult population and to examine the usefulness of the suggested diagnostic criteria in our patients presenting with a history of different patterns of generalized, severe immediate-type reactions.

Methods

A retrospective review of medical records was performed for patients referred by allergologists to our university department for investigation of generalized, severe immediate-type reactions in 2006. The reactions were defined as any reaction having led to the suspicion of anaphylaxis because of symptoms with acute onset, involving at least 1 of the following organ systems: cutaneous, mucosal, or submucosal; respiratory; gastrointestinal; or cardiovascular. We documented age at clinical reaction, sex, eliciting factor, cofactors (infection, exercise, mental stress, and intake of acetylsalicylic acid or alcohol), previous reactions, serum tryptase levels measured by fluorescent enzyme immunoassay (CAP-FEIA, Phadia, Freiburg, Germany; values were considered elevated when they were above the normal value of up to 11.5 ng/mL at 2 different time points), accompanying diseases/drug intake, and use of an emergency kit. The clinical symptoms were then checked for applicability of diagnostic criteria according to the suggestions of Sampson et al [9] or according to Ring and Messmer [10,11].

Results

One hundred five patients (78 women and 27 men) with a mean age of 50 years (range, 18-77 years) presented for investigation of a severe immediate-type reaction that had first appeared a mean of 3.3 years previously (range, 1 day to 36 years). The following eliciting factors were documented (Figure 1): drugs (n=48 [46%], of which 17 were analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), 6 antibiotics, 3

Table 1. Suggested Clinical Criteria for Diagnosing Anaphylaxis (Sampson et al [9])

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

Abbreviations: PEF, peak expiratory flow; BP, blood pressure.
[a]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Table 2. Grading of Anaphylactic Symptoms According to Severity of Symptoms (Ring and Messmer [10,11]).

	Symptoms			
Grade	Dermal	Abdominal	Respiratory	Cardiovascular
1	Pruritus Flushing Urticaria Angioedema			
2	Pruritus Flushing Urticaria Angioedema	Nausea Cramping	Rhinorrhea Hoarseness Dyspnea	Tachycardia (>20 bpm) Blood pressure change (> 20 mm Hg systolic) Arrhythmia
3	Pruritus Flushing Urticaria Angioedema	Vomiting Defecation Diarrhoea	Laryngeal edema Bronchospasm Cyanosis	Shock
4	Pruritus Flush Urticaria Angioedema	Vomiting Defecation Diarrhoea	Respiratory arrest	Cardiac arrest

Abbreviation: bpm, beats per minute.

local anesthetics, 2 cardiovascular drugs, and 2 glucocorticoids), hymenoptera stings (n=35 [33%]: 27 wasp, 5 bee, and 3 hornet or unknown), food (n=12 [11%]: 4 soy milk, 3 fruits, 1 seafood, 1 poppy seed, 1 spices, and 2 unknown), physical factors (n=4 [4%]: cold), or unknown (n=7 [11%]). As cofactors we identified infections (11%), mental stress (8%), exercise (3%), and alcohol (1%). The main accompanying diseases were as follows: cardiovascular (29%), endocrine (16%), respiratory (7%), and depression (4%). Sixteen patients (15%) had already suffered from a previous immediate-type reaction and 15 of them had already been prescribed an emergency kit (consisting of oral antihistamines, glucocorticoids, and epinephrine for self administration), which only 2 had used at the second anaphylactic reaction. Serum tryptase levels were analyzed in all patients and were increased in 8 (6%; mean, 27 ng/mL; range, 14-121 ng/mL), 6 of whom had reacted to insect stings and 2 to NSAIDs. Indolent systemic mastocytosis, as defined by Florian et al [14], was confirmed in 6 of those 8 patients. All of them had suffered from severe grade 3-4 reactions according to Ring and Messmer [10,11].

The following organ systems—either alone or in combination with others—had been involved in the entire group of 105 patients (Figure 2): 86 (82%) mucocutaneous (35 [33%] of whom had isolated mucocutaneous symptoms), 35 (33%) respiratory (2 isolated), 24 (23%) gastrointestinal (3 isolated), and 30 (28%) cardiovascular symptoms (1 isolated). Ten patients exclusively reported symptoms that were too nonspecific to be attributed to a specific organ system (malaise, anxiety, palpitations, and feeling of warmness without clear flush). This could have been either due to a prodromal phase of anaphylaxis or due to a pharmacologic or psychosomatic effect,

and as a result, we did not classify their reaction as anaphylaxis. Thus, 95/105 patients (91%) could be classified according to the criteria of Ring and Messmer [11] (Figure 3). In 57 (60%) of these patients the reactions were classified as grade 2-4, while 38 (40%) had isolated mucocutaneous symptoms.

Importantly, only a subgroup of 53 patients (54% of the 95 patients classified according to the criteria of Ring and Messmer [11]) fulfilled the diagnostic criteria suggested by Sampson et al [9] (36 women and 17 men aged 18-77 years; mean age, 51 years). The eliciting factors in this subgroup were as follows (Figure 1): drugs, 36% (n=19); hymenoptera stings, 43% (n=23); food, 13% (n=7); physical factors, 4% (n=2); and unknown, 4% (n=2). These 53 patients had combined symptoms of the organ systems mentioned above; specifically, 43 (81%) had mucocutaneous symptoms, 32 (60%) respiratory symptoms, 19 (36%) gastrointestinal symptoms, and 28 (53%) blood pressure-related cardiovascular symptoms. All of these 53 patients also met the criteria of Ring and Messmer [11] for a grade 1-4 reaction (Figure 3). Four patients with grade 1 reactions according to Ring and Messmer [11] fulfilled the criteria of Sampson et al [9] because their mucocutaneous symptoms were accompanied by vertigo, which was interpreted as a blood pressure-associated symptom. The complete combination of symptoms in this subgroup is shown in Figure 4.

Forty-six of the 53 patients (88%) fulfilled criterion 1 according to Sampson et al [9] (see Table 1). Two of those 46 patients were diagnosed solely according to criterion 1 because the eliciting factor was not known, while mucocutaneous and either respiratory or blood pressure symptoms were present. The remaining 44 patients also fulfilled criterion 2 according
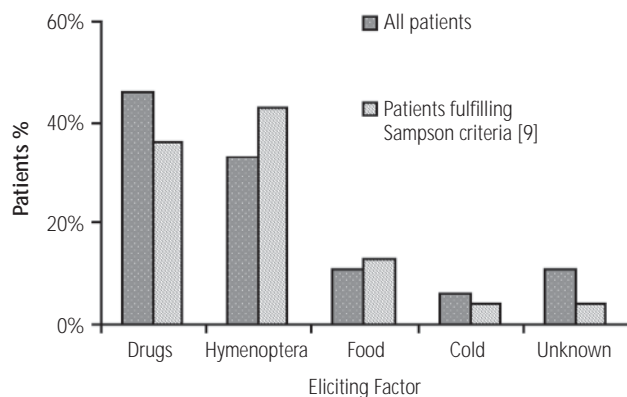
Figure 1. Eliciting factors of anaphylactic reactions in a cohort of German patients (n = 105).
Patients with severe immediate type reactions to drugs fulfilled the diagnostic criteria of Sampson et al [9] less often than those reacting to other allergens. (All patients, n = 105; patients fulfilling the Sampson criteria, n = 53.)
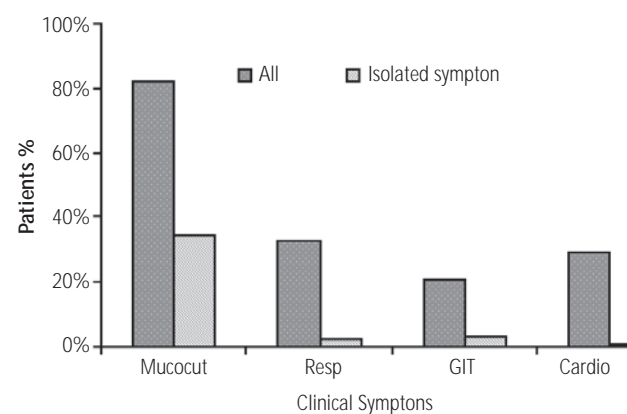

Figure 2. Clinical pattern of organ involvement in a German cohort of patients with suspicion of anaphylaxis (n = 105). The majority of patients (n = 86, 82%) suffered from mucocutaneous symptoms and 35 (33%) had involvement of this organ system alone. Mucocut indicates mucocutaneous; Resp, respiratory; GIT, gastrointestinal; Cardio, cardiovascular.
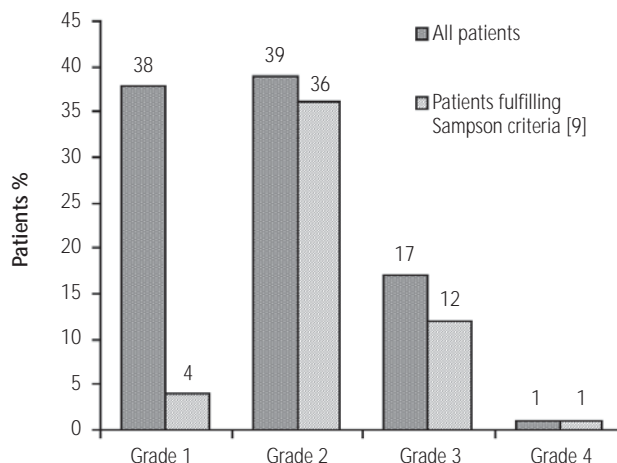

Figure 3. Classification of a German cohort of patients with suspicion of anaphylaxis according to the criteria of Ring and Messmer [11]. The criteria of this graded scale were fulfilled by 95 out of 105 patients (91%). All patients fulfilling the diagnostic criteria of Sampson et al [9] also met the criteria of Ring and Messmer [11]
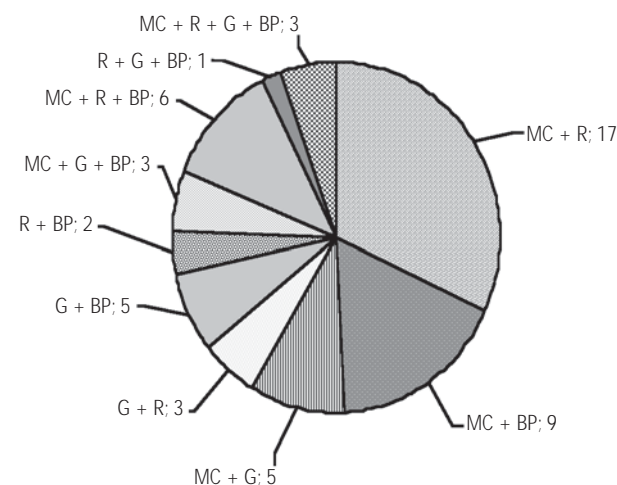

Figure 4. Clinical pattern of combined organ system involvement in 53 German patients with anaphylaxis according to the criteria of Sampson et al [9]. The mucocutaneous system was involved in 43 (81%) of 53 patients diagnosed with anaphylaxis according to Sampson et al. MC indicates mucocutaneous system; R, respiratory system; G, gastrointestinal system; BP, blood pressure-associated symptoms.

to Sampson et al [9] (Table 1). Overall, criterion 2 was fulfilled by 52 patients (98%), mainly because of the combination of mucocutaneous and respiratory symptoms. Seven patients (13%) were diagnosed solely according to criterion 2 because of a lack of mucocutaneous symptoms. Only 8 patients (15%) fulfilled criterion 3 according to Sampson et al [9], but all of them also fulfilled either criterion 1 (n=4) or 2 (all). The applicability of criterion 3 was hampered by the fact that information on blood pressure at clinical reaction was unavailable in the majority of the patients. Moreover, 5 patients who had reacted to unknown allergens (idiopathic anaphylaxis) could not be classified according to Sampson et al [9], although they had combined but not mucocutaneous symptoms. The reason for this was that criteria 2 and 3 ask for "likely" or

"known" allergens, and criterion 1, which does not ask for an allergen, requires mucocutaneous symptoms.

Discussion

In our German cohort of 105 patients with a history of generalized severe immediate-type reactions, we identified

95 (91%) as having had anaphylaxis according to the criteria of Ring and Messmer [10,11]. Of those, 57 (60%) had severe, grade 2-4 reactions. Hymenoptera stings, drugs, and food were the 3 main eliciting factors, consistent with several other reports from developed countries [15-21]. However, when comparing those data, there is a considerable and yet unexplained variability in the particular frequencies of those 3 main eliciting factors (Figure 5). One may speculate that this is either due to specific exposure risks (eg, peanut consumption in the USA) or due to different diagnostic criteria that may, for example, not allow the diagnosis of anaphylaxis in some drug-related immediate type reactions in some countries. Importantly, only 53 (54%) of the 95 patients classified as having suffered anaphylaxis—and only 19 out of 48 (40%) patients who reacted to drugs—fulfilled the diagnostic criteria of Sampson et al [9]. One could argue that this is because we included isolated mucocutaneous symptoms (ie, Ring and Messmer grade 1 [11]), which are not regarded as anaphylaxis by some authors [9,22]. However, even when reanalyzing our cohort and applying the concept that isolated mucocutaneous symptoms are not anaphylaxis, there were still more patients meeting the grade 2 to 4 criteria according to Ring and Messmer [11] (n=57; 60%) than those meeting the criteria of Sampson et al [9] (n=53; 56%).

In our patients, diagnosis according to Sampson et al [9] was mainly hampered by the fact that several of them presented symptoms associated with just 1 organ system, mainly mucocutaneous—ie, classified as grade 1 reactions according to Ring and Messmer [11]. This did not allow sufficient subpoints of either criteria 1 or 2 of the Sampson score to be fulfilled. We feel, however, that patients with such isolated severe immediate-type symptoms should not be excluded from a diagnosis of anaphylaxis, mainly because these reactions have the potential to progress to involvement of other organ systems in a subsequent reaction or would even have progressed to a more severe grade if emergency treatment had not stopped the reaction at an early stage. The observation that deaths typically occur at subsequent reactions in those

patients whose previous reactions had been mild supports the hypothesis that severity of subsequent reactions cannot be predicted from the reaction history [25,26]. We therefore think it is unreasonable to draw a sharp line between patients who had isolated mucocutaneous symptoms—and who would not receive a diagnosis of anaphylaxis according to the criteria of Sampson et al [9]—and those with additional pulmonary, gastrointestinal, or circulatory involvement.

In our cohort, the mucocutaneous system was most frequently involved (82% of patients), and 33% had isolated symptoms associated with this organ system. This percentage of mucocutaneous involvement is comparable to that reported by other authors [15,16,18], thus indicating the clinical patterns in our cohort to be representative of severe immediate-type reactions considered anaphylactic. Involvement of the mucocutaneous and respiratory systems was the most common organ system combination in our cohort (Figure 1), as has been reported by other authors [17,18]. We therefore agree with Sampson et al [9] that mucocutaneous involvement should be one of the main diagnostic criteria for anaphylaxis (Table 1).

Of the 3 different diagnostic criteria proposed by Sampson et al [9], the most applicable criterion in our experience was number 2, asking for any combination of at least 2 organ systems [10,11]. None of our patients were diagnosed solely according to criterion 3. In addition, subanalysis of our data revealed that the criteria proposed by Sampson et al [9] might bear the risk of underdiagnosing severe immediate-type reactions to drugs as anaphylactic. Drugs such as NSAIDs or contrast media often elicit a nonallergic anaphylaxis that can manifest at first application [25], thereby failing to fulfill criterion 3, which indicates the requirement for a known allergen. As immediate-type reactions to drugs, and mainly those to analgesics/NSAIDs, are often reported to be of severe type, such an underestimation could be fatal [23]. Furthermore, in our cohort, patients with unknown allergens, often reported as suffering idiopathic anaphylaxis [24], could not be diagnosed using the criteria proposed by Sampson et al [9] when mucocutaneous symptoms were absent.
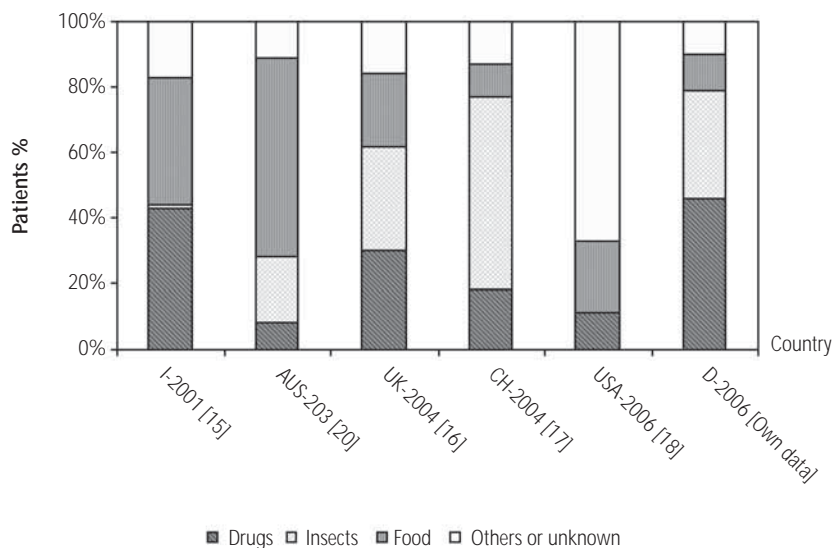

Figure 5. Eliciting factors of anaphylaxis in different developed countries. There is substantial variation in the individual frequencies among the different studies. I indicates Italy; AUS, Australia; USA, United States of America; UK, United Kingdom; CH, Switzerland; D, Germany).

At presentation in our allergy clinic, patients often reported subjective symptoms. As only a subgroup of patients receives emergency treatment with accurate documentation of their objective symptoms, diagnosis of severe immediate-type reactions often has to rely on these subjective symptoms, for instance, on interpretation of vertigo as being possibly the result of blood pressure reduction. Criteria taking into account these symptoms are therefore favourable for clinical use in an allergy clinic. Moreover, based on our own experience, a graded system similar to the ones proposed by Ring and Messmer [10,11], Mueller [12], or Pumphrey and Stanworth [22] seems to be helpful in assessing the severity of immediate-type hypersensitivity reactions [27].

Recurrence rates of anaphylaxis have been reported to vary between 8% and 27% [20,21]. In our own cohort, 16 patients (15%) had suffered from at least 1 previous reaction. Although most of them had been provided with an emergency kit, it was used by only 2 of them at the new incident. Based on our finding that serum tryptase levels were increased in 8 (6%) of our patients, all of whom had suffered from severe reactions, we advocate further studies to test whether this parameter might identify a subpopulation of patients at particular risk for the development of severe generalized immediate-type reactions [28-30].

In conclusion, the 3 most frequent eliciting factors of severe immediate-type hypersensitivity reactions in our cohort of German adults were hymenoptera stings, drugs, and food. The application of diagnostic criteria for anaphylaxis proposed by Sampson et al [9] did not identify as many patients with severe immediate type reactions as the graded score of Ring and Messmer [11]. Thus, additional efforts are needed to further improve our knowledge of anaphylaxis as a potentially life-threatening disorder. Such efforts might also include extension of the diagnostic criteria proposed by Sampson et al [9].

Acknowledgments

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