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Cluster analysis of 505 real-life food-induced anaphylaxis in children reveals two stable clinical phenotypes

To the Editor,

Food-induced anaphylaxis (FIA) should be considered potentially fatal, and the reaction outcome is unpredictable.^{1,2} FIA's clinical picture is highly heterogeneous, and the severity varies between episodes, even within the same individual.³ Currently, there are no clinically useful predictors of FIA severity.⁴ Some⁵ believe that in FIA, stereotypical reaction phenotypes exist, which affect the severity.

This study aims to identify clinical phenotypes of real-life FIA in a large homogenous children population.

We conducted a longitudinal, prospective study on the clinical course of 677 acute food-induced allergic reactions in 417 children aged 0–18 years treated as inpatients at the Allergy Department straight after their first food-induced acute allergy episode. Due to mild symptoms limited to one organ system classified as a systemic allergic reaction (SAR), 172 events did not meet the anaphylaxis criteria and were excluded. After verification, 505 FIA in 325 children were included in the analysis. The diagnosis of anaphylaxis was established according to published definition criteria (Supplementary Methods) upon an in-depth analysis of medical history by investigators, including one anaphylaxis expert. All subsequent anaphylactic episodes were verified by the investigators during scheduled visits over six-month intervals. Searching anaphylaxis trigger, skin prick tests, and measure of serum specific immunoglobulin E for 114 allergen components were performed in every child. When justified, prick-to-prick tests with fresh food were performed.

Based on the coexistence of the first FIA episode's clinical symptoms, we performed a non-supervised statistical cluster analysis that enabled us to stratify the data set of FIA's clinical manifestation without any previously defined hypothesis. All single or first of the multiple FIA episodes in 325 children were assigned to the *discovery cohort*, and baseline clustering was done (Supplementary Results). All 30 clinical symptoms (Table 1) of FIA were included as dichotomous variables. One hundred thirty-eight patients with more than one FIA were assigned to the *validation cohort*, and the cluster membership prediction was made. Finally, clustering stability was calculated. The clinical characteristics of cohorts are shown in Table S1.

Clustering of all 30 symptoms of the first anaphylaxis episode (Figure S1A,B) revealed two clinically distinct phenotypes

SUPPORTING INFORMATION

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(Figure 1A) with significantly different symptoms predominance, as indicate *p*-values (Holm-Bonferroni sequential adjustment) in Table 1. Cluster 1, defined as *skin/non-severe respiratory* phenotype, included 81% of the *discovery cohort*, with mild-to-moderate allergic reactions and no cardiovascular, life-threatening respiratory and severe symptoms of the central nervous system (CNS). Cluster 2, defined as *severe respiratory/cardiovascular* phenotype, four times less frequent, with predominant severe to life-threatening manifestations, contained all the cardiovascular symptoms, severe respiratory, and CNS symptoms. The green area in the radar graph (Figure 1A) indicates symptoms more characteristic for Cluster 1, while the red area indicates symptoms more characteristic for Cluster 2.

Between-cluster comparison is shown in Table S2. The most severe reactions, Muraro grade 3, were significantly more frequent in Cluster 2 than in Cluster 1 (85.2% vs. 10.6%, $p < .0001$). Among children from Cluster 1, mild atopic dermatitis ($p = .0185$) and clinically relevant allergy to three or more food allergens ($p = .0344$) were more often than in Cluster 2. In children from Cluster 2, older age ($p = .0171$), lower incidence of atopic dermatitis ($p = .0222$), allergy to only one food allergen ($p = .0344$), food-dependent exercise-induced anaphylaxis ($p < .0001$), and adrenaline administration ($p = .0001$) were observed significantly more frequently than in Cluster 1. No significant differences between phenotypes were found depending on sex, presence or severity of asthma, and anaphylaxis trigger at the allergen component level (Table S3).

Clinical characteristics of children with more than one FIA episode are shown in Table S4. The median observation time of each patient in this cohort was 48 months and did not differ between clusters (Table S5).

The clustering of the pattern of coexisting symptoms of the first FIA episode in 138 children from the validation cohort served as a baseline comparison for 180 subsequent FIA episodes in this cohort (Table S6). Both clusters were characterized by relatively high stability over time (Figure 1B). In the *skin/non-severe respiratory* phenotype, the next anaphylaxis episode was mild to moderate in 90%; PPV = 0.9 (95%CI: 0.84 to 0.93). In the *severe respiratory/cardiovascular* phenotype, the following reaction was severe in 70%; PPV = 0.7 (95%CI: 0.52 to 0.83). There were no significant differences of FIA triggers

TABLE 1 Between-clusters comparisons of clinical manifestation of the first episode of anaphylaxis in the discovery cohort

Clinical manifestations	Cluster 1 Skin non-severe respiratory, n = 264	Cluster 2 Severe respiratory cardiovascular, n = 61	Total n = 325	p-value	p-value*
<i>Clinical manifestations, no. (%)</i>					
Sudden relevant hypotension	0 (0)	47 (77.0)	47 (14.5)	<.0001	<.0001
Presyncope (dizziness/weakness)	0 (0)	25 (41.0)	25 (7.7)	<.0001	<.0001
Pale and floppy child	0 (0)	12 (19.7)	12 (3.7)	<.0001	<.0001
Short episode of collapse/syncope	0 (0)	10 (16.4)	10 (3.1)	<.0001	<.0001
Confusion/somnolence	0 (0)	9 (14.8)	9 (2.8)	<.0001	<.0001
Chest tightness/dyspnoea	6 (2.3)	4 (6.6)	10 (3.1)	<.0001	<.0001
Cardiovascular failure	0 (0)	5 (8.2)	5 (1.5)	<.0001	.0002
Mild-to-moderate bronchospasm	79 (29.9)	4 (6.6)	83 (25.5)	<.0001	.0009
Sudden change in activity level	12 (4.5)	13 (21.3)	25 (7.7)	.0001	.0012
Angioedema (not laryngeal)	147 (55.7)	23 (37.7)	170 (52.3)	.0009	.0198
Severe bronchospasm	27 (10.2)	14 (23.0)	41 (12.6)	.0018	.0365
Repetitive vomiting	67 (25.4)	24 (39.3)	91 (28.0)	.0048	.0907
Crampy abdominal pain	31 (11.7)	14 (23.0)	45 (13.8)	.0076	.1369
Nasal/eye symptoms	39 (14.8)	2 (3.3)	41 (12.6)	.0077	.1369
Sudden repetitive cough	43 (16.3)	3 (4.9)	46 (14.2)	.0108	.1722
Nausea/drooling	7 (2.7)	3 (4.9)	10 (3.1)	.0196	.2946
Loss of consciousness	2 (0.8)	3 (4.9)	5 (1.5)	.0282	.3954
Mouth tingling/oral pruritus	6 (2.3)	2 (3.3)	8 (2.5)	.0375	.4875
Generalized pruritus	32 (12.1)	15 (24.6)	47 (14.5)	.0384	.4875
Respiratory failure	0 (0)	1 (1.6)	1 (0.3)	.0494	.5431
Respiratory arrest	0 (0)	1 (1.6)	1 (0.3)	.0494	.5431
Hoarseness	11 (4.2)	0 (0)	11 (3.4)	.0855	.7697
Diarrhea	12 (4.5)	4 (6.6)	16 (4.9)	.0869	.7697
Upper airways angioedema	32 (12.1)	11 (18.0)	43 (13.2)	.2045	1
Feeling of impending doom	1 (0.4)	1 (1.6)	2 (0.6)	.3028	1
Generalized urticaria	134 (50.8)	29 (47.5)	163 (50.2)	.3231	1
Dyspnoea (upper airways)	29 (11.0)	5 (8.2)	34 (10.5)	.3680	1
Throat pruritus	28 (10.6)	4 (6.6)	32 (9.8)	.4624	1
Stridor/"barky" cough	25 (9.5)	5 (8.2)	30 (9.2)	.5747	1
Generalized flushing	32 (12.1)	10 (16.4)	42 (12.9)	.5834	1

Note: Data are presented as number and percentage of observations.

*Holm-Bonferroni sequential adjustment.

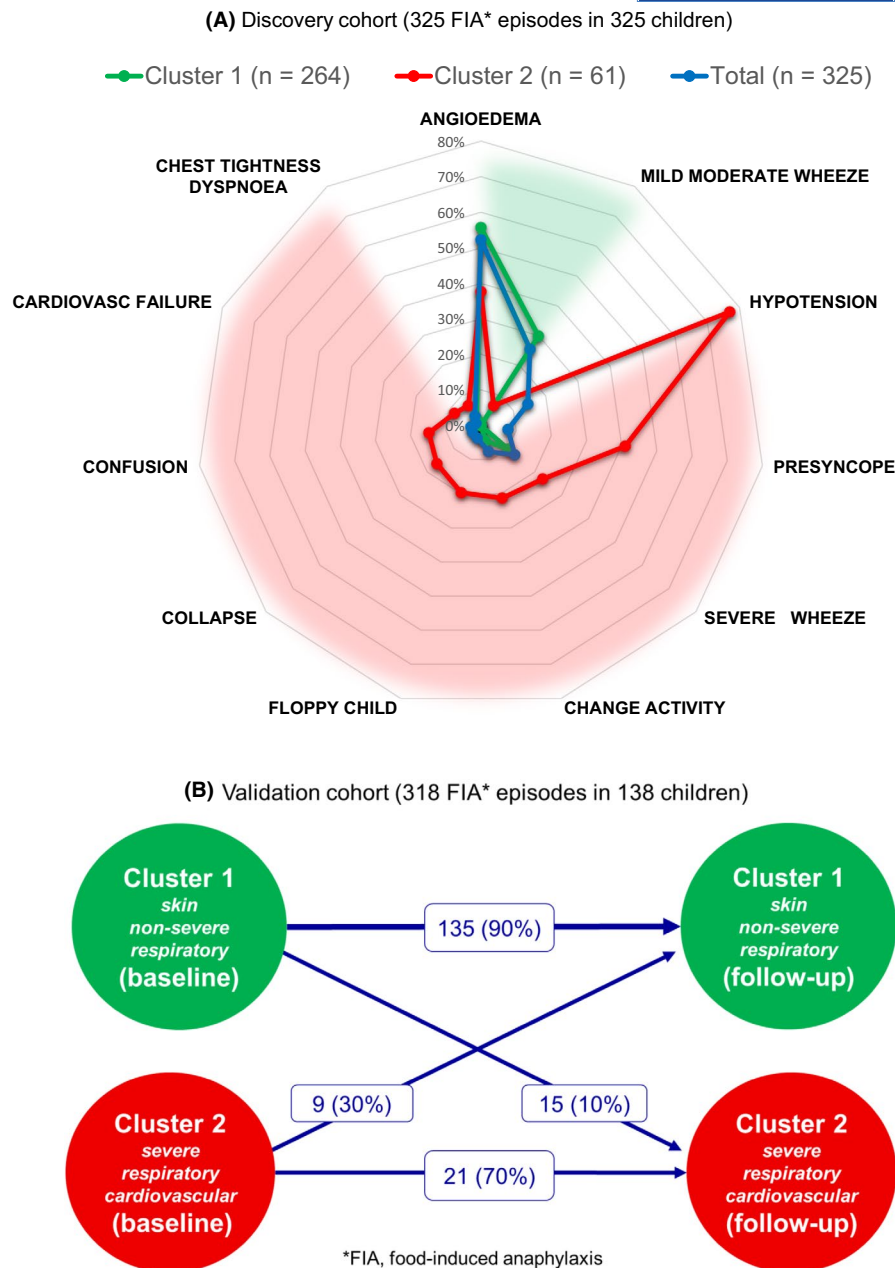


FIGURE 1 (A) Radar graph representing the proportion of each symptom significantly different between the two clusters in the discovery cohort. The red area indicates symptoms more characteristic for Cluster 2, and the green area indicates symptoms more characteristic for Cluster 1. (B) Visualization of long-term stability of clusters in the validation cohort

in subsequent anaphylaxis episodes between Cluster 1 and Cluster 2 (Table S7). Children with unstable clustering compared to children with stable clustering had significantly more than two FIA episodes ($p = .0218$) (Table S8).

To conclude, the present study showed that real-life FIA in children could be naturally grouped into two clinical phenotypes of different severity. In our study, most reactions were mild and not life-threatening, as previously was shown.⁶ We found that both phenotypes were characterized by remarkable stability over time. Others⁵ also observed a similar pattern of symptoms and

organ involvement in most patients during consecutive challenges. Although the total number of children with more than one FIA in our study was relatively low, the results, for the first time, point out that the pattern of coexisting symptoms of the first episode may determine the clinical picture of the next anaphylaxis reaction. However, since anaphylaxis course is unpredictable, all cases of anaphylaxis, regardless of severity, should be treated with adrenaline, according to guidelines.^{1,7}

Extensive population-based studies should be conducted to confirm these results.

KEYWORDS

anaphylaxis, children, cluster analysis, food, phenotypes

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

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The roadmap for allergology in Europe: The European training requirements for the specialty of allergology

To the Editor,

The development of the European training requirements (ETR) for medical specialties in Europe is regulated by the Union Européenne

des Médecins Spécialistes (UEMS), a non-governmental organization representing national associations of medical specialists at European Level.

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