

Description of two anaphylaxis phenotypes in children: The utility of a clustering analysis approach

To the Editor,

Anaphylaxis is heterogeneous regarding patients' characteristics, triggers, clinical manifestations, and severity. Clinical anaphylaxis manifestations are various, and their time course is heterogeneous and unpredictable, sometimes life-threatening.¹ The clustering analysis has already been used to identify phenotypes in allergic children, such as atopic dermatitis, asthma, and peanut allergy.^{2,3} Such approach is of interest to better characterize the heterogeneity of allergic diseases and also to provide personalized patient management. Predicting who is the most at risk of severe anaphylaxis reactions would be of a great interest to reduce anaphylaxis morbidity and mortality but remains challenging.

We aimed to approach anaphylaxis heterogeneity by a nonsupervised statistical clustering analysis on a cohort of children (<18 years) admitted to emergency care unit for anaphylaxis.

This study was conducted in a cohort of 482 children (<18 years) admitted in emergency care units for anaphylaxis in three different French regions. The characteristics of these children have been reported before.^{1,4,5} The anaphylaxis was defined according to Sampson's criteria.⁶ The data have been recorded prospectively in one region¹ and retrospectively in the two others.^{4,5} We performed a nonsupervised clustering analysis using 23 variables. The methods and statistical analysis are described (Supplementary Material S1).

Of the 482 children admitted for anaphylaxis to emergency care units, complete information regarding all the variables was available for 224 (48%) children (boys: 62.2%; median age: 6.8 years, IQR: 3.30; 11.8) (Table 1 and Table S2). A history of asthma was reported in 39%, food allergy in 37%, multiple food allergy in 25%, and previous anaphylaxis in 19%. The main anaphylaxis triggers were food (72%; nuts, 24%; peanut, 21%), drugs (7%), and insect venom (5%); 8% of the reactions remained idiopathic. Overall, 28% of children had a ring severity grade 3-4 reaction, 31% received an adrenaline injection, and 24% have been hospitalized in emergency departments for more than six hours.

Using the clustering approach, we described two distinct phenotypes (Table 1) represented in Figure 1. Cluster 1. "Food (mainly peanut and nuts) severe anaphylaxis in highly atopic children": 56 (25%) children (boys, 73%), all with food-induced anaphylaxis reactions, most often related to peanut and nuts (38% and 36%, respectively) and a history of atopy (food allergy, 98%; multiple food allergy, 77%; asthma, 63%; atopic dermatitis, 36%) and more severe anaphylaxis

manifestations (Ring score 3-4, 45%; adrenaline injection, 46%; hospital admission, 36%). Cluster 2. "Mild anaphylaxis with various triggers and few atopic comorbidities": 168 (75%) children by a lower frequency of allergic comorbidities (asthma, 31% food allergy, 16%; atopic dermatitis, 17%), a diversity of anaphylaxis triggers (food, 63%; idiopathic, 11%; iatrogenic, 10%; insect venom, 7%; exercise-induced, 4%) and less severe allergic reactions (Ring 2, 78%; adrenaline injection, 26%; hospital admission, 20%). These children were younger as compared with those of the cluster 1 ($P = .039$). Similar results were observed in the sensitivity analysis (imputed data) except for atopic dermatitis, sex, and age which were no more significant between the two clusters (see Table S3).

This study is the first to explore the patterns of anaphylaxis through a cluster analysis in a cohort of children hospitalized for anaphylaxis. In children, cluster analyses have been used in different allergic diseases to identify phenotypes that may be of interest to personalize patient management and provide targeted treatment.^{4,5}

The link between the severity of allergic reactions and allergic comorbidities confirmed by our results is underscored in various studies. In the 696 patients diagnosed with peanut sensitization in the Mirabel study, 449 were enrolled in a cluster analysis and three phenotypes have been described.⁵ Severity of peanut-induced allergic reactions was associated with allergic multi-morbidity (asthma with atopic dermatitis and/or multiple food allergy).⁵ In addition, the link between multiple allergic comorbidities and severe allergic disease is also reported. In 125 asthmatic children, a "multiple allergies and severe asthma" phenotype has been described using the clustering analysis.⁴ Our results confirm also that peanut and tree nuts, involved in three-quarters of the reactions in the cluster 1 but only one-third of the reactions in the cluster 2, are also associated with more severe reactions. In a cohort of 1094 patients with peanut and tree nut allergies, Summers et al⁷ also demonstrated that severe asthma, severe allergic rhinitis, and severe atopic dermatitis as well were each independently associated with a higher risk of severe anaphylaxis reactions.

Our results also confirmed that children with more severe allergic reactions (cluster 1) were older than those with less severe reaction and allergic disease (cluster 2), as described in the Mirabel study.⁵ However, adolescence was not associated with more severe reaction in our study which is different than previously reported in registries collecting data of severe or fatal cases.⁸ We did not confirm a clear impact of the gender on the severity of food allergic

TABLE 1 Characteristics of 224 children admitted to emergency care units for anaphylaxis selected for the clustering analysis

	Total cohort (n = 224)	Cluster 1 (n = 56)	Cluster 2 (n = 168)	P value
Male sex, n (%)	139 (62)	41 (73)	98 (58)	.047
Age, median [IQR] (y)	6.8 [3.3; 11.8]	8.4 [6.2; 11.3]	6.5 [2.9; 12.8]	.039
Age < 6 y	88 (39)	11 (20)	77 (46)	
Age 6-11 y	82 (37)	35 (62)	47 (28)	
Age ≥ 11 y	54 (24)	10 (18)	44 (26)	
History of atopic disease				
Asthma, n (%)	87 (39)	35 (63)	52 (31)	<.001
Atopic dermatitis, n (%)	48 (21)	20 (36)	28 (17)	.003
Food allergy, n (%)	82 (37)	55 (98)	27 (16)	<.001
Anaphylaxis, n (%)	43 (19)	31 (55)	12 (7)	<.001
Multiple food allergy, n (%)	56 (25)	43 (77)	13 (8)	<.001
Anaphylaxis reaction				
Triggers, n (%)				
Food	161 (72)	56 (100)	105 (63)	<.001
Peanut	47 (21)	21 (38)	26 (16)	<.001
Nuts	53 (24)	20 (36)	33 (20)	.014
Hen's egg	16 (7)	5 (9)	11 (7)	.55
Cow's milk	18 (8)	3 (5)	13 (8)	.77
Other foods	55 (25)	13 (23)	42 (25)	.79
Iatrogenic	16 (7)	0	16 (10)	.014
Insect venom	11 (5)	0	11 (7)	.07
Exercise-induced	6 (3)	0	6 (4)	NC
Idiopathic	18 (8)	0	18 (11)	.008
Cofactors, n (%)	45 (20)	12 (21)	33 (20)	.77
Exercise, n (%)	14 (6)	3 (5)	11 (7)	1.00
Viral infection, n (%)	25 (11)	5 (9)	20 (12)	.54
Ring severity 3-4, n (%)	62 (28)	25 (45)	37 (22)	.001
Adrenaline injection at emergency, n (%)	70 (31)	26 (46)	44 (26)	.005
Prehospital adrenaline injection, n (%)	23 (10)	15 (27)	8 (5)	<.001
Hospital admission, n (%)	53 (24)	20 (36)	33 (20)	.014

reactions. Surprisingly, only two phenotypes have been identified which may be explained by the fact that data were only collected in emergency departments which may underestimate most of drug-induced anaphylaxis cases occurring at hospital.⁹

Despite a multi-center study, our population has a quite small sample size which may affect the results. Due to the large range of variables (23) selected in the clustering analysis and the retrospective data collection in two centers, only 48% of the patients of the initial cohort were finally included, which induce heterogeneity in the results. Comparisons between the characteristics of the children included in the cluster analysis and those not included revealed statistical differences which are another limitation (Table S2). We could not exclude a bias due to the missing data but results after handling

missing data by imputation procedure were nearly similar to the complete cases analysis.

We are aware that the Ring classification is not the most adapted classification to assess the severity of food-induced anaphylaxis in children.¹⁰ This classification was used in the two centers with a retrospective data collection so that no other scoring system could be used.

Our cluster analysis confirms that children with an allergic disease characterized by a history of asthma and food allergy, notably peanut and nuts, share a distinct phenotype with a higher risk of severe anaphylaxis reactions compared to children with less allergic disease. Further and larger studies are required to determine the most at-risk patients who will require a personalized approach and benefit the most of innovative treatments such as food immunotherapy and biologics.

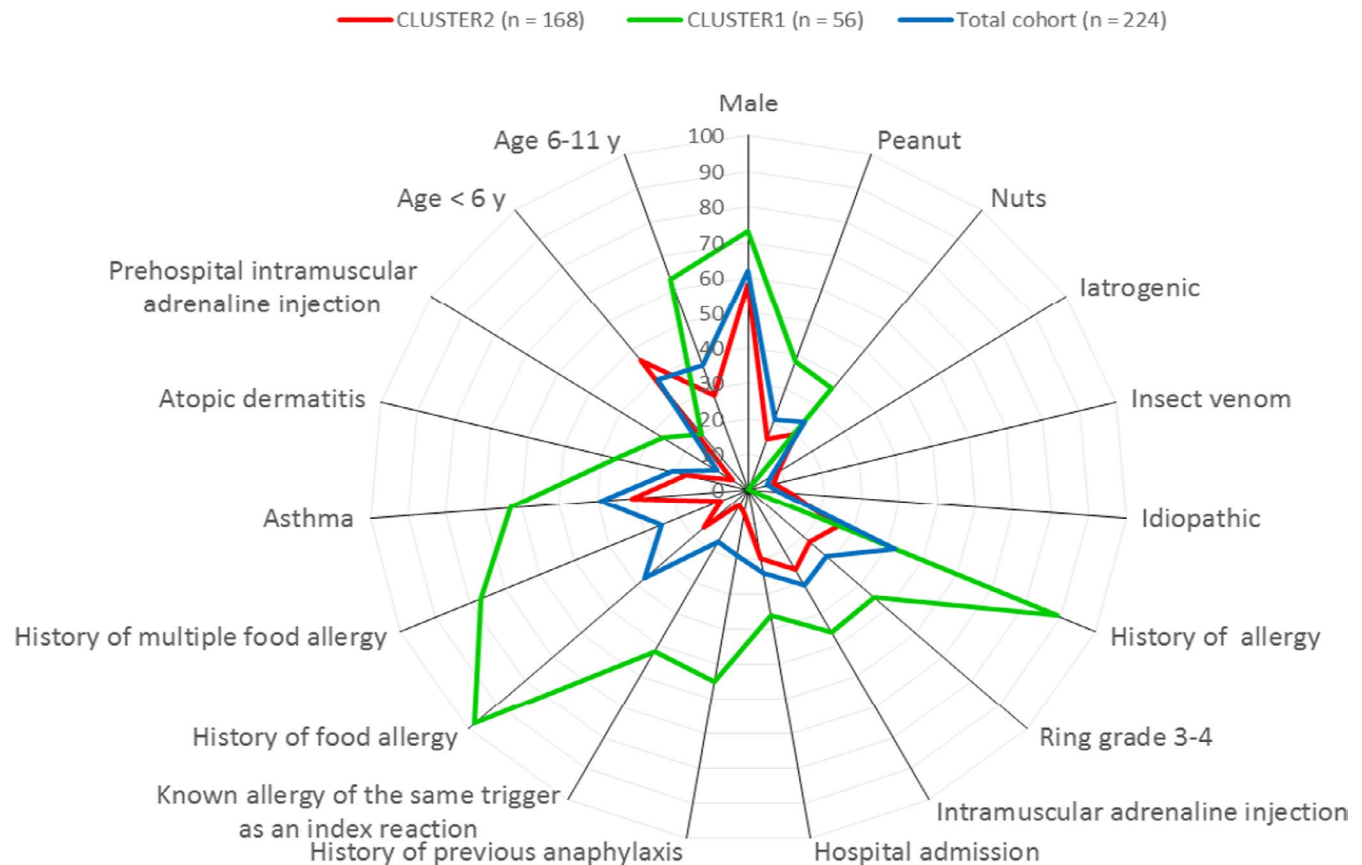


FIGURE 1 Radar graph representing the proportion of each variable significantly different between the two clusters (green line: cluster 1; red line: cluster 2; blue line: total cohort)

KEYWORDS

anaphylaxis, epidemiology, food allergy, pediatrics

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CONFLICTS OF INTEREST

Dr Pouessel reports personal fees and other from Bausch+Lomb, personal fees from Mylan, personal fees from Novartis, grants, personal fees and other from Stallergènes, outside the submitted work. Dr Beaudouin reports personal fees from Mylan, personal fees from ALK, personal fees from Bausch+Lomb, outside the submitted work. Dr Deschildre reports personal fees and other from Novartis, personal fees and other from ALK, personal fees from TEVA, personal fees and other from GSK, grants and personal fees from Stallergenes Greer, personal fees from Almmune, personal fees from Zambon, personal fees and other from CHIESI, personal fees and other from Astra Zeneca, personal fees and other from DBV technologies, personal fees from Boehringer Ingelheim, outside the submitted work. The other authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

S1. Methods and statistical analysis

This study was conducted in a cohort of 482 children (< 18 years) admitted in emergency care units for anaphylaxis in three different French regions: Nord-Pas-de-Calais (n=149; 2015-2017), Lorraine (n=106; 2015), and Provence-Alpes-Côtes d'Azur (Marseille) (n=227; 2010-2015). Approval was obtained from local and national Ethics Committee and parental informed consent to participate was acquired for each case.

Categorical variables were expressed as frequencies and percentages. Age was expressed as median and interquartile range. The characteristics included in the cluster analysis were: gender, age groups (< 6 years, 6-11 years, $\geq$ 12 years), triggers (food, drugs, insect venom, exercise-induced, idiopathic), severity score (Ring and Messmer), adrenaline intramuscular injection before and at admission, hospital admission, history of previous allergy (anaphylaxis, known allergy to the index trigger, single or multiple $\geq$ 2 food allergy), history of asthma diagnosed by a physician, history of atopic dermatitis, cofactors of the current anaphylaxis reaction (exercise, viral infection).

In order to perform a non-supervised clustering analysis, all the variables selected for the analysis were binarized before being transformed by a principal component analysis. The hierarchical clustering analysis (Euclidian metric and Ward's method) was performed on the principal components which explains 80% of inertia. Finally, a hierarchical clustering analysis was carried out aiming to highlight different anaphylaxis phenotypes. The frequency of the used parameters in analysis were compared between the clusters using the Chi-square test or Fisher exact test, except for age which was compared using Mann-Whitney U test. Significant parameters were represented on a radar graph.

A sensitivity analysis was performed using a simple imputation under the missing at random (MAR) assumption. The model of imputation uses a regression switching approach (chained equation method) with predictive mean matching method for continuous variables and logistic regression (binary, ordinal, or polynomial) for qualitative variables. The imputation procedure was performed using all candidate variables for the clustering.

All analyses were done with SAS software (SAS Institute version 9.4) and $p < 0.05$ was considered statistically significant.

32 Table S2. Comparison between children admitted to emergency care unit for anaphylaxis
 33 included or not in the cluster analysis.

	Included (n=224)	Non included (n=258)	P value
Male sex, n (%)	139 (62.1)	143 (55.4)	0.14
Age, mean (SD) (y)	7.9 (5.1)	8.2 (4.3)	0.37
History of atopic disease			
Asthma, n (%)	87 (39)	75/257 (29)	0.03
Atopic dermatitis, n (%)	48 (21)	6/28 (21)	1
Food allergy, n (%)	82 (37)	101/256 (39)	0.52
Anaphylaxis, n (%)	43 (19)	85/202 (42)	< 0.0001
Anaphylaxis reaction			
Triggers, n (%)			
Food	161 (72)	134/258 (52)	< 0.0001
Peanut	47 (21)	25/258 (10)	0.001
Nuts	53 (24)	35/258 (14)	0.004
Iatrogenic	16 (7)	13/258 (5)	0.33
Insect venom	11 (5)	6/258 (2)	0.12
Idiopathic	18 (8)	86/258 (33)	< 0.0001
Ring severity 3-4, n (%)	62 (28)	42/258 (16)	0.002
Adrenaline injection at emergency, n (%)	70 (31)	11/182 (6)	< 0.0001
Prehospital adrenaline injection, n (%)	23 (10)	30/255 (12)	0.60
Hospital admission, n (%)	53 (24)	110/249 (44)	< 0.0001

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36 Table S3. Characteristics of 482 children admitted to emergency care units for anaphylaxis
 37 selected for the clustering analysis (imputed data).

	Total cohort (n=482)	Cluster 1 (n=187)	Cluster 2 (n=295)	P value
Male sex, n (%)	282 (59)	105 (56)	177 (60)	0.40
Age, median [IQR] (y)	7.7 [3.5 ; 12.3]	7.1 [3.2 ; 12.3]	7.8 [3.7 ; 12.3]	0.46
Age < 6 y	189 (39)	72 (39)	117 (40)	
Age 6-11 y	165 (34)	66 (35)	99 (33)	
Age ≥ 11 y	128 (27)	49 (26)	79 (27)	
History of atopic disease				
Asthma, n (%)	162 (34)	79 (42)	83 (28)	0.001
Atopic dermatitis, n (%)	255 (53)	102 (55)	153 (52)	0.57
Food allergy, n (%)	185 (38)	149 (80)	36 (12)	< 0.001
Anaphylaxis, n (%)	137 (28)	90 (48)	47 (16)	< 0.001
Multiple food allergy, n (%)	105 (22)	88 (47)	17 (6)	< 0.001
Anaphylaxis reaction				
Triggers, n (%)				
Food	295 (61)	170 (91)	125 (42)	< 0.001
Peanut	72 (15)	42 (23)	30 (10)	< 0.001
Nuts	88 (18)	49 (26)	39 (13)	< 0.001
Hen's egg	26 (5)	26 (14)	0 (0)	< 0.001
Cow's milk	33 (7)	33 (18)	0 (0)	< 0.001
Other foods	107 (22)	40 (21)	67 (23)	0.73
Iatrogenic	29 (6)	1 (1)	28 (10)	< 0.001
Insect venom	17 (4)	0 (0)	17 (6)	< 0.001
Exercise-induced	11 (2)	0 (0)	11 (4)	< 0.001
Idiopathic	104 (22)	16 (9)	88 (30)	< 0.001
Cofactors, n (%)	108 (22)	31 (17)	77 (26)	0.015
Exercise, n (%)	26 (5)	6 (3)	20 (7)	0.091
Viral infection, n (%)	75 (16)	19 (10)	56 (19)	0.009
Ring severity 3-4, n (%)	104 (33)	122 (65)	37 (12)	<0.001
Adrenaline injection at emergency, n (%)	150 (31)	92 (49)	58 (20)	< 0.001
Prehospital adrenaline injection, n (%)	54 (11)	48 (26)	6 (2)	< 0.001
Hospital admission, n (%)	165 (34)	78 (42)	87 (30)	0.006