Lessons of Component Resolved Diagnosis in anaphylaxis: Analysis of a case series of the International Anaphylaxis Registry

Arroabarren E[1], García BE[1,2,3], Anda M[1], Pesántez C[1], Zavala MJ[1], Olaguíbel JM[1,2]

[1]Servicio de Alergología. Hospital Universitario de Navarra (HUN), Spain

[2]CIBER de Enfermedades Respiratorias (CIBERES), Spain

[3]Health Research Institute (IDISNA, Instituto de Investigación Sanitaria de Navarra), Pamplona, Spain

Corresponding author:

Esozia Arroabarren

Servicio de Alergología. Hospital Universitario de Navarra (HUN).

C/Irunlarrea, s/n. 31008 Pamplona, Spain

E-mail: **esoziaa@yahoo.es;** earroaba@navarra.es

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0912

Key words: Anaphylaxis. Lipid transfer protein. Component-resolved diagnosis (CRD). Cofactor enhanced anaphylaxis. Idiopathic anaphylaxis.

Palabras clave: Anafilaxia. Proteína transportadora de lípidos (LTP). Diagnóstico por componentes. Anafilaxia aumentada por cofactores. Anafilaxia idiopática.

Allergy diagnosis´ aims in anaphylaxis are: triggers´ identification, minimizing recurrence risk, providing prognosis information and, in some cases of hymenoptera anaphylaxis (HA) and food allergies, etiological treatment. Component resolved diagnosis (CRD) may be essential to accomplish such goals. Its current purposes include: immunotherapy prescription assistance, food-allergy risk assessment, idiopathic anaphylaxis (IA) and pollen-food syndromes [1-3] evaluation. Proposed CRD uses in anaphylaxis include [2-3]: multiple foods´ exposure, cofactor-enhanced food allergy, latex, idiopathic, hymenoptera and red meat induced anaphylaxis. These proposals need to be confronted with real cases´ evaluation [4]. Our aim was to evaluate CRD usefulness in a series of cases included by our Department in the International Registry of Anaphylaxis (IAR) supported by The Network for Online Registration of Anaphylaxis (NORA) between 2012 and 2021 [5]. IAR consists in standardized data collection by structured online questionnaires including clinical data (demographics, severity, elicitors, cofactors…) and performed allergy work-up [5]. We additionally analysed complete CRD results of our cases.

Available determinations included skin prick tests (SPT) with purified profilin (Pho d 2) (ALK®), lipid transfer protein (LTP) (Pru p 3) (Roxall®), tropomyosin (Pen m 1)

doi: 10.18176/jiaci.0912

(Leti®), Ovomucoid-Gal d 1-, Ovalbumin-Gal d 2-, Lisozyme-Gal d 4 (Leti®), Alfa-lactoalbumin-Bos d 4-, Beta-lactoglobulin-Bos d 5-, Casein-Bos d 8- (Roxall®), performed according to EAACI Guidelines [6]. Specific IgE determinations included uniplex (ImmunoCAP, ThermoFisher; cutoff: 0.35 kU/L) and/or multiplex (ImmunoCAP ISAC, ThermoFisher; cutoff: 0.3 ISU) assays [1]. Tests were ordered on individual basis, according to clinician´s judgment and current practice.

Cases were split per elicitor group as categorized in IAR. Allergens were divided between causative and co-sensitizations per clinical judgment. Cofactors´ distribution according to patients´ allergen profiles was also described. We used the statistical software SPSS 22.0 for Windows, BMDP Statistical Software release 7, Star Xact (Cytel Software Corp) for analysis.

CRD usefulness was categorized as:

a. Not performed: cases without determinations despite CRD availability for suspected biological source (eg: Hake anaphylaxis without parvalbumin determinations).
b. Unnecessary, according to suspected elicitor and clinician´s judgment (eg: Amoxicillin anaphylaxis).
c. Unavailable: without CRD availability for suspected biological source at inclusion in IAR (eg: venom allergens, at first years of IAR).
d. Inconclusive: cases with negative results for current available allergens (eg: idiophatic anaphylaxis, banana anaphylaxis with negative ImmunoCAP ISAC determinations).
e. Diagnostic: culprit allergens, biological source and clinical picture concurred.

doi: 10.18176/jiaci.0912

We included 116 cases. Patients´ characteristics (age, severity, cofactors´ presence, individual culprit) are detailed in Supplementary files 2 and 3. Elicitor groups included foods (62.1%), drugs (22.4%), hymenoptera (7.8%), idiopathic (3.4%), other culprits (royal jelly and Anisakis simplex) (2.6%) and associated to simultaneous exposure to different elicitor groups (tick bites plus food intake) in 1.7% cases.

Performed CRD determinations included (number of cases/%) SPT (82/70.7%), uniplex ImmunoCAP (64/55%) and multiplex ISAC determinations (22/19%).

Per elicitor groups (Table)

CRD usefulness varied depending on elicitor groups and according to specific culprits. SPT with purified allergens performed in 27% of drug anaphylaxis cases were negative and considered inconclusive. CRD was considered unnecessary in other drug anaphylaxis. CRD was diagnostic in 68.1% of food anaphylaxis (FA) cases. Usefulness was maximum assessing plant FA and multiple simultaneous food groups´ exposure. Within the 13 shellfish registered cases, only 2 patients tested positive to tropomyosin. These results suggest considering other allergens such as arginine kinase and sarcoplasmic protein, as well as diagnostic tests´ choices to optimize subsequent advice in shellfish allergy [7]. Besides, it reflects current limitations in allergen availability regarding this food.

CRD was diagnostic in HA when it became available. CRD was useful in 2 cases involving mixed-group allergens, but insufficient in suspected IA or cases involving "other elicitors".

Per culprit allergens

doi: 10.18176/jiaci.0912

nsLTPs were the most frequent elicitors in fruits, nuts and after simultaneous exposure to several food groups in this group. They were considered the only responsible in 27 cases. Other profiles, including co-sensitization or monosensitization to other allergens were less frequent. Recently, a case previously attributed to LTP was reassessed and sensitization to peamaclein [1] (GRP) confirmed. Among animal foods, shellfish was the most frequent culprit. Besides tropomyosin, other animal origin allergens included galactose-α-1,3-galactose, milk and/or egg allergens.

Hymenoptera, "others" and mixed groups´ exposure included less patients. Their results show the difference made by the availability of venom allergens and galactose-α-1,3-galactose over the Registry years.

Per clinical scenario [3]

CRD usefulness in FA has been addressed.

We observed high rates of potential cofactors (according to IAR) in most elicitor groups ($p=0.003$; Chi^2 test, Supplementary files 1,2). Considering allergen profiles´ sensitization (Supplementary File 1), highest percentage of cofactors was observed in patients sensitized to galactose-α-1,3-galactose. Cofactors were present in half of LTP induced anaphylaxis, but high rates of cofactors were also present in cases in which culprit allergens were not identified.

Four patients with IA were included. IA assessment by CRD includes several options: negative ImmunoCAP ISAC results would exclude sensitization to multiple major allergens and that would be an important outcome itself. Negative results might also suggest sensitization to allergens absent in current assays or mechanisms different to IgE.

Differential diagnosis of IA includes hidden allergens´ exposure, Anisakis, mast cell activation and alpha-gal syndromes [8]. These cases have been included during a 9-year time lapse, with important changes in available tests, such as hymenoptera allergens, galactose-α-1,3-galactose and its association to IA description [3,8] and recently, GRPs. We wonder if our IA figures would have been the same before these additions. Amongst "others" group, usefulness may be hampered by the multiple allergens included in royal jelly [9].

Negative CRD results may be helpful to assess some drug anaphylaxis cases (eg: FA with Non-steroidal anti-inflammatory drugs (NSAID) as cofactor versus NSAID induced anaphylaxis), a surmountable obstacle in certain FA if we have enough clinical data regarding biological sources, but they make diagnostic challenges for complex allergen sources´ and IA evaluation.

CRD usefulness in anaphylaxis varies according to elicitor group and between triggers within the same group. An increase in its usefulness is expected over time, as the description and availability of allergens increases. Cases of IA persist despite new allergens and alpha-gal syndrome identification.

Meetings: Preliminary results of this work have been presented in poster sessions at the 2022 EAACI Hybrid Congress held in Prague, Czech Republic, July 2022 and at the American Academy of Allergy Asthma and Immunology Meeting, held in San Antonio, Texas, 2023th February

doi: 10.18176/jiaci.0912

Funding

The project leading to these results has received funding from “la Caixa/Caja Navarra” Foundation (ID 100010434), under agreement.

Conflict of interest

The authors have no conflict of interest to declare in relation with this report.

References

1. Luengo O, Labrador-Horrillo M. Molecular Allergy Diagnosis in Clinical Practice: Frequently Asked Questions. J Investig Allergol Clin Immunol. 2022;32(1):1-12.
2. Cardona V, Ansotegui IJ. Component-resolved diagnosis in anaphylaxis. Curr Opin Allergy Clin Immunol. 2016;16(3):244-9.
3. Cardona V, Guilarte M, Labrador-Horrillo M. Molecular diagnosis usefulness for idiopathic anaphylaxis. Curr Opin Allergy Clin Immunol. 2020;20(3):248-52.
4. Dubiela P, Dölle-Bierke S, Aurich S, Worm M, Hoffmann-Sommergruber K. Component-resolved diagnosis in adult patients with food-dependent anaphylaxis. World Allergy Organ J. 2021;14(3):100530.
5. Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). Allergy.2014;69:1397–404.
6. Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. Allergy. 1993;48(14):48-82.

7. Pascal M, Grishina G, Yang AC, Sánchez-García S, Lin J, Towle D et al. Molecular Diagnosis of Shrimp Allergy: Efficiency of Several Allergens to Predict Clinical Reactivity. J Allergy Clin Immunol Pract. 2015;3(4):521-9.e10.

8. Carter MC, Akin C, Castells MC, Scott EP, Lieberman P. Idiopathic anaphylaxis yardstick: Practical recommendations for clinical practice. Ann Allergy Asthma Immunol. 2020;124(1):16-27.

9. Cifuentes L. Allergy to honeybee not only stings. Curr Opin Allergy Clin Immunol. 2015;15(4):364-8.

Table. Component resolved diagnosis results.

ELICITOR GROUP (N)	FOOD GROUPS	Causative allergens No cases	Co-sensitization	CRD USEFULNESS
FOODS (72)	FRUITS (14)	Bromeline (1) GRP (1)LTP (6) LTP + thaumatin (1) NA (5), NP (0)	Absent (11) Art v 1 (1) LTP, PR10, Taumatine (1) Parvalbumin & tropomyosin (1)	D 64.3% I 35.7% NP 0

doi: 10.18176/jiaci.0912

	NUTS/TREE NUTS (16)	**Albumine 2S (1) Albumine 2S + LTP (1) Albumine 2S + G11S (2) LTP (8) NA (3), NP (1)**	**Absent (14) Profilin (1)**	**D 75% I 18.8% NP 6.25%**
	VEGETABLES (4)	**LTP (3) NA (1), NP (0)**	**Absent (2) LTP (1) PR10 (1)**	**D 75% I 25% NP 0%**
	GRAINS (3)	**Gliadin (1) LTP (1) NA (1), NP (0)**	**Absent (2) Globuline 11 S (1)**	**D 66.7% I 33.3% NP 0%**
	ANIMAL FOODS (20)	**Galactose-α- 1,3 galactose (2) Casein (2) Ovalbumin and ovomucoid (2) Parvalbumin (1) Sarcoplasmic Calcium-binding Protein (1) Tropomyosin (2) NA (8), NP (2)**	**Absent (14) LTP and profilin (1) Ovalbumin (1) Profilin (2)**	**D: 55% I 35% NP 10%**
	LEGUMES (8)	**Albumine 2S, globuline 7S and globuline 11S (2) LTP (2) PR10 (1) UA (2), NP (1)**	**Absent (5) LTP (1) Profilin (1)**	**D 62.5% I 25.5% NP 12.5%**
	SEEDS (1)	**LTP (1)**	**Absent (1)**	**D 100%**
	DFG (6)	**Gliadine (1) LTP (5)**	**Absent (4) Ovalbumin, Tri a 14 & aA-Ti (1) PR10 (1)**	**D100%**
DEG (2)		**Galactose-α- 1,3 galactose (2)**	**Ani s 1 (1)**	**D 100%**
IDIOPHATIC (4)		**NA (2), NP (2)**	**Absent (2)**	**D 0 %**
HYMENOPTERA (9)		**Ves v 1, Ves v 5 and Pol d 5 (2) Ves v 5 and Pol d 5 (1) Api m 1, Api m 2, Api m 3, Api m 5, Api m 10 (1) UA (5)**	**Absent (2) Api m 5 (1) Ves v 5 and Pol d 5 (1)**	**D 44.4 % UA 55.6%**
OTHERS (3)		**NA (1) UA (1), NP (1)**	**Absent (1) Parvalbumin (1)**	**D 0% I 66.7% NP 33.3%**

() Number of patients. NA: Negative results for available allergens. UA: not available for suspected source. CRD Usefulness: D: Diagnostic. I: inconclusive, N: Not performed. DFG: Different simultaneous food groups´ intake; DEG: Simultaneous exposure to different elicitor groups.