

Omega 5-gliadin allergy in patients with recurrent acute urticaria

Running head: recurrent urticaria & omega-5 gliadin

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To the Editor,

omega-5 gliadin (O5G), *Tri a 19*, allergy is usually responsible for wheat-dependent exercised-induced anaphylaxis (WDEIA) (1-4) but not all episodes are characterised by a systemic anaphylactic reaction (5) and factors modulating the reaction severity are elusive (6).

We evaluated the prevalence and clinical/laboratory features of O5G in patients presenting with recurrent acute urticaria in a retrospective study in an Italian tertiary referral centre. We enrolled all consecutive adult patients referred in 2021-2023 for recurrent acute urticaria (3), *i.e.*, >1 episode of acute urticaria over 6 months, not induced by physical factors and not present daily and continuously for >6 weeks (7).

Patients underwent skin prick tests for aero- and food-allergens (Lofarma, Italy) according to clinical history and specific IgE (FEIA, ImmunoCAP®, Thermo fischer, Sweden), to wheat, O5G, gluten/gliadin were systematically performed. Patients underwent screening for *H.*

pylori, anti-thyroglobulin/thyroid peroxidase antibodies. Wheat challenge (100g of boiled pasta) followed by 15-minute running was offered to confirm the diagnosis.

Data from 31 patients, median age 33 years, IQR 23-47, F:M ratio: 1.4:1.1 (Table 1), were retrieved. Patients were classified according to O5G IgE (cut-off 0.1 kU/L) into O5G positive (n=7, 22.6%) and negative (n=24, 77.4%).

Among O5G negative patients, the identified cause of urticaria were *H. pylori* infection (n=5, 16.1%), non-steroidal anti-inflammatory drug allergy (n=4, 12.9%), food allergy (n=3, 9.6%), cholinergic urticaria (n=1, 3.2%). Most cases were defined as idiopathic (n=11, 35.4%). All patients with *H. pylori* were urticaria-free after eradication.

Six out of seven patients with positive specific IgE for O5G were offered a challenge with wheat and exercise (since one patient displayed anaphylaxis after wheat ingestion); eventually only two accepted (four deemed it unnecessary). Challenged patients presented urticaria. The patients who declined the challenge didn't experience any episodes after avoiding gluten within 4 hours of exercise, or by completely avoiding gluten. Collectively, the diagnosis of O5G-allergy was confirmed in all seven patients sensitized to O5G (7).

Comparing O5G positive patients to negative ones, no statistically significant demographical difference was observed (Table I), though female sex was highly represented in this sample. Notably, patients with O5G-allergy displayed more frequently allergic rhinitis among atopic comorbidities (p=0.01).

Among patients with O5G, four displayed more than 20 urticaria episodes. The mean age of those with more frequent episodes, as opposed to those with fewer ones, was lower (24.7±4 years and 49.3±12.2 years respectively, p<0.05), while no difference was found with regard to total IgE (p=0.6), specific IgE for wheat (p=0.8), gliadin mix (p=0.2), gluten (p=0.7), O5G (p=0.4), *Bet v1* (p=0.5), *Phl p12* (p=0.9), and *Pru p 3* (p=0.7).

No difference was found between having at least one episode with systemic manifestations and level of total IgE, and specific IgE for wheat (p=0.7), gliadin mix (p=0.8), gluten (p=0.8),

O5G (p=0.9). Two patients displayed extracutaneous features during follow-up (median 17 months, IQR 12.5-19.5), Table II.

In this study we observed a prevalence of O5G-allergy, reaching 22.5% in patients with acute intermittent urticaria. These patients seemed to present peculiar features, *i.e.*, female sex and comorbid atopic diseases, compared to those presenting with exercise-induced anaphylaxis, who are usually male with a low atopic background (9). A study based on the presence of O5G-specific IgE describes recurrent acute urticaria in five of 67 patients with O5G-allergy(6). Another study describes four cases of O5G-allergy presenting with urticaria (6.8%), among 104 patients with WDEIA. Notably, 70.4% of patients presented urticaria episodes before their first anaphylaxis (5). Consistently, in our series two patients displayed an anaphylaxis during the follow-up, highlighting the importance of prescribing adrenaline autoinjectors, given the general low adherence to gluten-free diets and cofactor avoiding recommendations, as reported in literature (10).

To conclude, in patients presenting with recurrent acute urticaria, a screening for O5G-allergy is warranted.

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Abbreviations: O5G, omega-5 gliadin, WDEIA, wheat-dependent exercise-induced allergy.

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Table I. Demographical, clinical and etiological features and sensitisation profile of the urticaria patients at the time of diagnosis.

Parameter*	Overall population (n=31)	O5G negative (n=24)	O5G positive (n=7)	P value O5G positive v/s negative
Demographics and clinical characteristics				
Sex, male, n,(%)	13 (41.9)	11 (45.8)	2 (28.5)	0.41
Age, years, median, (IQR)	33 (23-47)	33 (22.7-46.5)	33 (26.5-43.5)	0.89
Ethnicity, white, n,(%)	29 (93.5)	24 (100)	5 (71.4)	0.21
Smoking, n,(%)	9 (29.0)	7 (29.1)	2 (28.5)	0.65
Heavy work n,(%)	4 (12.9)	4 (16.6)	0 (0)	0.87
Onset age of sy, years, median (IQR)	28 (21.5-44.7)	28.5 (21.7-45.5)	28 (24-40)	0.91
Episode range number, n(%) [§]	0, 5(16.1) 1, 0(0) 2, 3(9.6) 3, 1(3.2) 4, 0(0) 5, 0(0) 6, 3(9.6) 7, 6(19.3) 8, 13(41.9)	0, 4 (16.6) 1, 0 (0) 2, 3 (12.5) 3, 1 (4.16) 4, 0 (0) 5, 0 (0) 6, 2 (8.3) 7, 4 (16.6) 8, 10 (41.6)	0, 1 (14.2) 1, 0 (0) 2, 0 (0) 3, 0 (0) 4, 0 (0) 5, 0 (0) 6, 1 (14.2) 7, 2 (28.5) 8, 3 (42.8)	0.48
Anaphylaxis, n (%)	3 (9.7)	1 (4.2)	2 (28.5)	0.05
Autoimmunity, n (%)	5 (16)	4 (16.6)	1 (14.2)	0.66
IBS, n (%)	1 (3.2)	0 (0)	1 (14.2)	0.06
Etiology of urticaria				
Helicobacter pylori, n (%)	5 (16.1)	5 (20.8)	/	
Idiopathic n (%)	11 (35.4)	11 (45.8)	/	
NSAID, n (%)	4 (12.9)	4 (16.6)	/	
Food allergy, n (%)	10 (32.2)	3 (8.3)	7 (100)	0.01
Cholinergic , n (%)	1 (3.2)	1 (4.1)	/	
Atopy				
Eczema, n (%)	1 (3)	1 (4.1)	0 (0)	0.58
Allergic rhinitis, n (%)	10 (32.3)	4 (16.6)	5 (71.4)	0.01
Asthma, n (%)	4 (12.9)	3 (12.5)	1 (14.2)	0.90
Drug allergy, n (%)	2 (6.4)	0	2 (28.5)	0.05

*Data are shown as a proportion or median and IQR;

[§]A score of 0 is assigned if the number of episodes is 2, 1 if 3 episodes, 2 if 4 episodes, 3 if 5 episodes, 4 if the number of episodes is 6-10 episodes, 5 if the number of episodes is 11-15 episodes, 7 if 16-20 or more 8 if more than 20 episodes are present.

Heavy work included job as carpenter, electrician, mason, etc.

Abbreviations. O5G, omega-5 gliadin, IBS, irritable bowel syndrome, IQR, interquartile range; NSAID, non-steroidal, anti-inflammatory drug; PR-10, pathogenesis related-10; LTP, lipid transfer protein, sy, symptoms.

Table II. Clinical and serological features of the seven patients with omega-5 gliadin allergy.

#	Age	Sex	Symptoms at diagnosis	Type of cofactor	Total IgE	Wheat IgE (kU/L)	Gluten IgE (kU/L)	Gliadin IgE (kU/L)	Tria 19 IgE (kU/L)	Bet v 1 IgE (kU/L)	Phl 12 IgE (kU/L)	Therapy	Adherence*	Follow-up (months)	Clinical manifestations at last follow-up
1)	57	M	A (U+C)	E	144	0.90	3.99	2.74	18.40	13.50	<0.10	D	T	22	No sy
2)	28	M	U	NSAID	389	<0.10	<0.10	<0.10	2.74	<0.10	0.32	D	T	6	No Sy
3)	18	F	A (U, D, Dy)	E E+ AL E+ M NSAID	1147	3.59	1.69	<0.10	7.04	9.51	<0.10	D	P	19	1 episode of anaphylaxis (U+V/N)
4)	44	F	U	-	1170	0.13	<0.10	<0.10	0.53	<0.10	<0.10	C	T	14	No sy
5)	45	F	U	-	133	<0.10	<0.10	<0.10	0.15	<0.10	<0.10	C	P	17	No sy
6)	20	F	U	E	115	<0.10	4.89	<0.10	0.23	<0.10	<0.10	D	P	11	1 episode of anaphylaxis (U+Co)
7)	28	F	U	-	534	<0.10	<0.10	<0.10	0.93	<0.10	<0.10	C	P	20	No sy

Abbreviations. A, anaphylaxis; AL, alcohol; C, cofactor avoidance; Co, conjunctivitis; D, gluten-free diet; Dy, dyspnoea; E, exercise; M, menses; N, nausea; NSAID, non-steroidal anti-inflammatory drug; R, rhinitis; Sy, symptoms; U, urticaria; V, vomiting.

*Adherence was rated as total or partial, if in more than 20% of meals gluten was theoretically present or if cofactor was not avoided within 5 hours of gluten-containing food ingestion.