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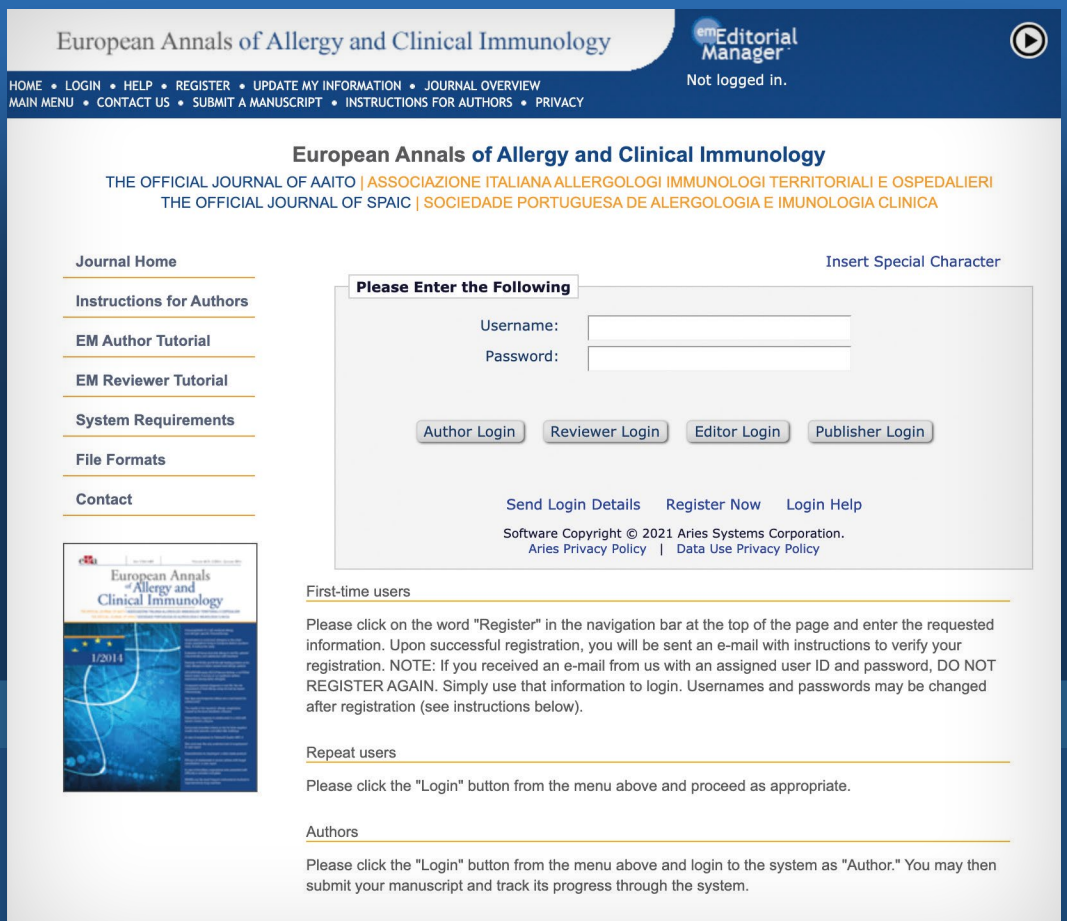
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ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 58, N.4, 147-156, 2026

Roberto Tschoepke Aires[1], Ekaterini Simões Goudouris[2], Fernanda Pinto-Mariz[2], Samyra Almeida da Silveira[3], Adriano Gomes-Silva[3,4]

Severity of papular urticaria in children is associated with specific IgG4 anti-salivary gland antigens from *Aedes aegypti*

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Key words

Salivary antigen; Aedes aegypti; papular urticaria; humoral immune response IgG4; children.

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Impact statement

Based on the symptoms and severity of the patients, we hypothesize that elevated IgG4 levels to A. aegypti salivary antigens may be associated with greater disease severity, potentially serving as a severity marker. These findings advance current knowledge of arthropod-bite hypersensitivity and provide a basis for future studies on diagnosis, prognosis, and targeted interventions. However, it is important to emphasize that further studies are required to validate this association and reach a definitive clinical conclusion.

Summary

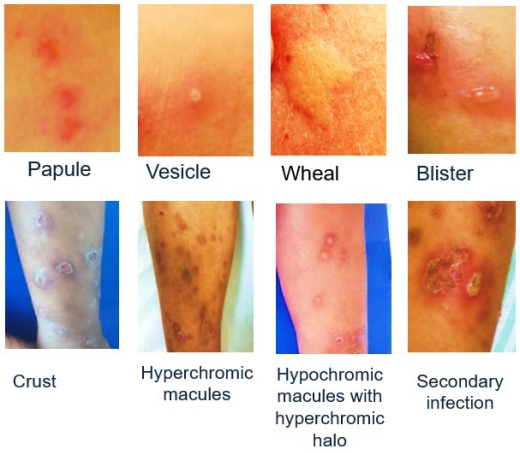
Background. *Papular Urticaria (PU) is a cutaneous hypersensitivity disorder triggered by hematophagous arthropod bites. Despite being a common condition, especially in tropical environments, many knowledge gaps are observed for this disease. The main objective of this study was to investigate the patterns of humoral immune response to mosquito antigens in children with PU and establish a correlation between this response and the severity of clinical symptoms.* ***Methods.*** *An analytical cross-sectional observational study was carried out. Clinical and sociodemographic data and children's blood samples were collected to measure the specific antibodies from: 1) A. aegypti salivary gland antigens; 2) A. aegypti whole body antigens (both produced in the laboratory of the Center for Health Sciences at the Federal University of Rio de Janeiro). A PU severity score based on clinical data is proposed to correlate disease severity with antibody reactivity signatures.* ***Results.*** *According to the clinical data, 58.9% of children received high severity scores. A significant statistical correlation was found between patients with high PU severity score and the development of symptoms before the age of two ($p = 0.0326$) and high IgG4 anti-salivary gland antigens concentration ($p < 0.05$).* ***Conclusions.*** *It is suggested that PU severity in children is associated with a high concentration of IgG4 anti-salivary gland antigens from Aedes aegypti. Further studies are recommended to deepen the understanding of the mechanisms involved.*

Introduction

Worldwide, skin diseases are observed after insect bites (1). Among these diseases, we highlight Papular Urticaria (PU). PU is defined as a chronic recurrent dermatosis. It manifests itself as diffuse papules and vesicles, with an erythematous base, in different stages of evolution. The papules are extremely pruritic (**figure 1**) (2). Skin diseases caused by insects living in domestic environments have rarely been systematically studied (2). The exact prevalence of PU is still unknown. The number of affected individuals is

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Figure 1 *- Aspects of skin lesions observable in patients with PU.*



believed to be high, especially in tropical regions (1). Epidemiological studies have revealed varying prevalence rates of PU in different regions. In Italy, in a total of 105 subjects with dermatitis induced by arthropods in a domestic environment, PU was present in 46.9% of patients (1). In Bogotá, Colombia, 62.9% of children aged 1 to 6 with dermatological conditions had PU (3). In Calcutta, India, the prevalence was 10.6% among children under five (4). In Cameroon, PU was present in 5.4% of children evaluated (5). In Brazil, a study conducted in Curitiba found a 9% rate of PU among patients aged 0 to 14, and 63% were under two years of age (6). A more recent study in Rio de Janeiro reported a PU prevalence of 7.42% among 202 children with dermatoses (7).

Although the diagnosis is generally based on clinical picture and epidemiological information, sometimes it's impossible to determine the insect responsible for the lesions (8).

The saliva of various arthropods such as ticks, bed bugs, fleas, and mosquitoes may contain common antigens that can induce an immune response in the patient (9-11). Most studies indicate that PU is a result of an immune response to proteins found in insect saliva (1, 8, 11). Although most of these proteins have unknown functions (12), studies show that they can stimulate the formation of type G, A, M, and E immunoglobulins and/or activate specific CD4+ T lymphocytes in susceptible children (2, 13). Recent studies suggest the participation of more than one immunological mechanism (Gell and Coombs classification) in the PU pathophysiology, but the exact mechanism remains unknown (13).

Among the types of Gell and Coombs hypersensitivity reaction in PU patients three types were found:

In type I Gell and Coombs hypersensitivity reaction, the mosquito saliva protein, upon binding to mast cell-specific IgE, induces the degranulation of vasoactive amines, leading to local manifestations such as the immediate formation of a pruritic wheal (14). The presence of specific IgE can be demonstrated by a positive reaction to a skin test (prick test) or by serum measurement of this antibody (1, 15).

Pustular and hemorrhagic lesions, typical of cutaneous vasculitis, have also been identified in patients with PU. Immunofluorescence examinations conducted on biopsy samples of skin tissue from PU patients revealed the presence of IgG and IgM deposits along with fractions of complement system C1q and C3 on the surface of blood vessels. These findings suggest the formation of immune complexes, with complement system activation, as in Gell and Coombs type III hypersensitivity reactions (14, 15).

Pronouncedly pruritic papules may emerge at the site of insect bite a few days after insect bites and persist for weeks. These late-onset lesions may indicate a cell-mediated reaction, characteristic of Gell and Coombs type IV hypersensitivity (16). Studies conducted by Peng *et al.* revealed that the average lymphocyte proliferation index in response to mosquito allergens was significantly higher in patients with late-onset cutaneous reactions (hardened papules) induced by insect bites (14).

An immunohistochemical study of the cellular infiltrate in the skin lesions of 45 patients with PU revealed a predominance of CD4+ T lymphocytes and eosinophils in papules that emerged after the cutaneous injection of flea antigens (17). The presence of these cells reinforces the theory that both immediate and delayed mechanisms (type I and IV hypersensitivity reactions) are involved in these responses, suggesting the participation of more than one immunological mechanism (15, 18).

The role of immunoglobulins in PU pathophysiology is still unclear. Some authors correlate the presence of specific IgE and IgG with immediate and late reactions. These same authors identified the presence of IgE, IgG1, and IgG4 at high levels in patients with extensive cutaneous manifestations (14). In contrast, others reported that heavily exposed patients produced little or no specific IgG against mosquito antigens (19).

Primary and secondary objectives

In Brazil, no studies on PU have associated clinical information with the specific immune response to insect antigens. The primary objective of this study was to investigate the patterns of humoral immune response to mosquito antigens (*Aedes aegypti*) in children with PU and establish a correlation between this response and the severity of clinical symptoms. The secondary objective was to define the clinical and demographic characteristics of these children.

Materials and methods

Study design

This cross-sectional, observational, and analytical study collected clinical, demographic, and epidemiological data from patients

affected by PU treated at the Allergy and Immunology outpatient clinic of the Hospital Federal de Bonsucesso (Rio de Janeiro, Brazil) from September 2018 to March 2020.

Inclusion and exclusion criteria

The study exclusively enrolled patients under 15 years old with a clinical diagnosis of PU. Schoolchildren and preschoolers who were using antihistamines (for at least five days before the interview), systemic immunosuppressive medication (for at least three months prior to blood sample collection), using immunotherapy, or had any primary or acquired immunodeficiency were excluded from the study.

Papular urticaria severity score

PU is a neglected disease. As such, there are no established criteria to assess its severity. Because of this, a severity scoring system was developed, adapting information from SCORAD (20) (used in atopic dermatitis) to categorize patients into mild, moderate, or severe groups. However, it is essential to highlight that this score has not been validated and has never been used in other populations. The PU severity score developed considers the following clinical data: 1) clinical manifestation of asthma, rhinitis, or atopic dermatitis (skin prick tests for aeroallergens were not conducted), 2) extension of the affected body area, 3) use of systemic antibiotics to treat skin infections, and 4) itching intensity. These four criteria were chosen because they correlate well with the severity of symptoms (**table I**).

A Likert Scale ranging from 0 to 10 was employed to assess itching in the last 48 hours, with 0 signifying the complete absence of itching and 10 indicating severe itching involving nocturnal awakenings (**table I**). The large relative weight of this clinical aspect reflects its contribution to the patient´s discomfort and resulting compromised well-being. The participant PU severity score was calculated by the sum of these values.

The score ranges from 3 to 18 points, with 3 being the least severe and 18 the most severe. We classified the severity of the patient's clinical condition using this scoring method into two groups: one with less severity and the other with greater severity. PU severity score from 3 to 10 were classified as "mild" and scores from 11 to 18 were classified as "moderate to severe".

Preparation of mosquitoes' antigenic extracts

The antigenic extract from *Aedes aegypti*'s salivary gland (AgGlan) was obtained by dissecting adult female mosquitoes (n = 50) six days old before feeding. mosquitoes were anesthetized and treated with 70% alcohol, then phosphate-buffered saline (PBS). Salivary glands were isolated, transferred to microtubes, and frozen at -80 °C. Another antigenic preparation was obtained from the whole body of *Aedes* mosquitoes without glands (AgCor). The salivary gland and abdomen mass were solubilized in PBS with 2% neutral detergent and protease inhibitors. After maceration and freeze-thaw cycles, the suspensions underwent ultrasound treatment, centrifugation, and were stored at -80 °C for later use.

Blood sample collection

The study obtained blood samples from 34 participants via digital puncture on filter paper during outpatient visits, stored in a humidity and light-controlled refrigerator. An image analysis tool was utilized to standardize blood volume. Blood spots were excised, placed in microtubes with PBS, vortexed, and incubated at room temperature for 24 hours. The eluted blood was then pre-diluted to a 1:50 ratio, homogenized, and stored at 2 to 8 °C for further analysis.

Detection of specific immunoglobulin to mosquito antigenic extracts

Initially, 96 well microplates were coated with 20 µg/mL of the antigen extracted and diluted in sodium carbonate and

Table I *- Severity score criteria for papular urticaria patients.*

Clinical aspects	Description	Attributed value
Manifestation of atopic disease (asthma, rhinitis or atopic dermatitis)	No	1
	Yes	2
Body extension	Lower limbs only	1
	Lower limbs and upper limbs	2
	Lower limbs, upper limbs and chest	3
Previous use of antibiotics to treat skin infections	Denies use	1
	Used between 1 and 4 times	2
	Used more than 4 times	3
Intensity of itching in the last 48 hours	Scale from 0 to 10 obtained from the interview with the responsible	0-10

bicarbonate solution at pH 9.6. Subsequently, the wells were blocked with PBS containing 10% Fetal Bovine Serum (FBS). Then, diluted serum (1:50) in PBS with 1% FBS was added in duplicate and incubated. Following incubation, anti-IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgE, or IgM conjugated with HRP were added to each well. A chromogen solution (Orthophenilenediamine + H_2O_2) was then added, and after color development, the reaction was stopped with 2N HCL. The microplate was read at 492 nm, and the number of specific antibodies was determined based on the absorbance value (Enzyme-Linked Immunosorbent Assay).

Data analyses considerations

The study presented categorical data as proportions and continuous data as medians and interquartile ranges (IQR). Statistical comparisons between study groups involved Fisher's exact test or Pearson's chi-square test for categorical variables and the Mann-Whitney U test or Kruskal-Wallis test for continuous variables. Significance was considered when $p < 0.05$. Analysis was conducted using Graph Pad Prism Version 10.0.2. Multidimensional analyses were employed to delineate immunological profiles among participants and their association with clinical data. Patients were categorized into three clusters based on the intensity of antibody recognition towards *Aedes aegypti* gland antigens (AgGlan) and body antigens (AgCor). Cluster 1 exhibited reduced reactivity, cluster 2 moderate, and cluster 3 high reactivity to antigenic preparations. Heatmap matrix analyses of immunoglobulin levels were conducted using Heat mapper®, employing hierarchical clustering with average linkage and Euclidean distance measurement.

Ethical approval

The study was approved by the Research Ethics Committee of Hospital Federal de Bonsucesso under approval number 2.830.938. As all participants were children under 15 years of age, written informed consent was obtained from their parents or legal guardians before inclusion in the study, in accordance with the approved study protocol.

Results

Sociodemographic and clinical results

A total of 107 children with a clinical diagnosis of PU was included, 64 of these (59.8%) were male. The mean age of the children assisted was 5.9 years ± 3.7 years, ranging from 1.1 to 14 years. Regarding the clinical data, 83 (77.6%) of the patients with PU had clinical manifestations of atopic diseases (asthma, rhinitis, or atopic dermatitis). When the person responsible was asked about the intensity of pruritus in the last two days, on a scale from zero (no pruritus) to ten (severe pruritus, with sleep impairment), 62 (57.8%) reported a value greater than or equal to 6. The mean pruritus intensity was 6.0 ± 3.0. The other sociodemographic and clinical data are described in **table II**.

Table II *- Demographic, clinical, and epidemiological characteristics for the entire PU population (n = 107) and for a group of children evaluated for ELISA-specific antibodies to Aedes aegypti (n = 34).*

Parameter	The entire PU population (n = 107)	PU subgroup evaluated for ELISA-specific antibodies (n = 34)	P-value
Gender			N/S
Male	64 (59.8%)	16 (47.1%)	
Female	43 (40.2%)	18 (52.9%)	
Age			N/S
<5 years	47 (43.9%)	15 (44.1%)	
≥5 <11 years	48 (44.9%)	15 (44.1%)	
≥11 years	12 (11.2%)	4 (11.8%)	
Illness duration			N/S
<6 years	79 (73.8%)	24 (70.6%)	
≥6 years	28 (26.2%)	10 (29.4%)	
Region			N/S
Urban/periurban	83 (77.6%)	28 (82.4%)	
Rural	24 (22.4%)	6 (17.6%)	

Parameter	The entire PU population (n = 107)	PU subgroup evaluated for ELISA-specific antibodies (n = 34)	P-value
Type of insects			N/S
Unaware	2 (1.9%)	2 (5.9%)	
Mosquito	63 (58.9%)	19 (55.9%)	
Mosquito and ant	29 (27.1%)	8 (23.5%)	
Mosquito, ant and flea	9 (8.4%)	3 (8.8%)	
Mosquito and flea	4 (3.7%)	2 (5.9%)	
First symptoms (age)			N/S
< 2 years	74 (69.1%)	23 (67.6%)	
≥2 years	33 (30.9%)	11 (32.4%)	
Body regions affected			N/S
Only superior members	0 (0%)	0 (0%)	
Lower limbs only	66 (61,7%)	19 (55.9%)	
Thorax only	0 (0%)	0 (0%)	
Upper limbs and lower limbs	36 (33.6%)	13 (38.2%)	
Upper limbs, lower limbs and thorax	5 (4.7%)	2 (5.9%)	
Season related to worsening of the condition			N/S
Spring/summer	49 (45.8%)	16 (47.1%)	
Autumn/winter	12 (11.2%)	4 (11.7%)	
No relation	46 (43.0%)	14 (41.2%)	
Intensity of pruritus in the last 2 days			N/S
0	12 (11.2%)	4 (11.8%)	
1	1 (0.9%)	0 (0%)	
2	3 (2.8%)	2 (5.9%)	
3	7 (6.5%)	3 (8.8%)	
4	4 (3.7%)	3 (8.8%)	
5	17 (15.9%)	3 (8.8%)	
6	7 (6.5%)	2 (5.9%)	
7	10 (9.3%)	1 (2.9%)	
8	23 (21.5%)	7 (20.6%)	
9	9 (8.4%)	5 (14.7%)	
10	13 (12.1%)	4 (11.8%)	
Unknown	1 (0.9%)	0 (0%)	
Aspect of injuries			N/S
Papule	19 (17.8%)	3 (8,8%)	
Vesicle	2 (1.9%)	0 (0%)	
Wheal	0 (0%)	0 (0%)	
Crusts	15 (14.0%)	6 (17.7%)	
Papule and cust	25 (23.3%)	9 (26.5%)	
Papule and wheal	2 (1.9%)	1 (2.9%)	
Papule, wheal and crust	5 (4.7%)	2 (5.9%)	

Parameter	The entire PU population (n = 107)	PU subgroup evaluated for ELISA-specific antibodies (n = 34)	P-value
Papule and vesicle	4 (3.7%)	2 (5.9%)	
Papule, vesicle and crust	2 (1.9%)	1 (2.9%)	
Papule, vesicle, wheal and crust	2 (1.9%)	1 (2.9%)	
Absent	31 (28.9%)	9 (26.5%)	
Macules pigmentation			N/S
Hyperchromic	25 (23.3%)	13 (38.2%)	
Hypochromic	11 (10.3%)	4 (11.8%)	
Both	66 (61.7%)	15 (44.1%)	
Absent	5 (4.7%)	2 (5.9%)	
Manifestation of atopic disease			N/S
Yes	83 (77.6%)	27 (79.4%)	
No	24 (22.4%)	7 (20.6%)	
Type of atopic diseases			N/S
Asthma	4 (3.7%)	1 (2.9%)	
Atopic dermatitis	5 (4.7%)	1 (2.9%)	
Rhinitis	44 (41.1%)	16 (47.1%)	
Rhinitis and asthma	20 (18.7%)	9 (26.5%)	
Rhinitis and asthma and atopic dermatitis	8 (7.5%)	0 (0%)	
Rhinitis and atopic dermatitis	2 (1.9%)	0 (0%)	
Absent	24 (22.4%)	7 (20.6%)	
Previous antibiotic use			N/S
Yes	64 (59.8%)	15 (44.1%)	
No	43 (40.2%)	19 (55.9%)	
Family members affected (father, mother and brothers)			p<0.001
Yes	47 (43.9%)	15 (44.1%)	
No	56 (52.3%)	7 (20.6%)	
Unknown	4 (3.7%)	12 (35.3%)	
Pattern of injuries at exam			N/S
In activity	15 (14.0%)	7 (20.6%)	
Scarring	48 (45.0%)	10 (29.4%)	
Both	42 (39.2%)	17 (50.0%)	
Have not been evaluated	2 (1.8)	0 (0%)	

N/S = non-significant.

Table III shows how the severity of symptoms varies with gender, age, season of the year, clinical parameters and other variables. Regarding the severity score, we observed that 63 children (58.9%) had moderate to severe PU, as evidenced by the clinical severity score developed for this study. Among these, we observed that 78% had the onset of symptoms before two years of age (p = 0.032). We did not verify statistical significance for any other association.

Clusters were defined based on the intensity of recognition of antibodies specific to the different antigenic preparations. When we evaluated the reactivity of antibodies to *Aedes aegypti* AgGlan in the heat map, we identified that the signature generated by cluster 3 was associated with a greater PU severity (median = 12.50; IQR = 11.0 and 15.0) in relation to cluster 2 (median = 9.0; IQR = 4.5 and 13.5; p < 0.05). We could highlight that augmented reactivity of IgG4 and IgG specific to AgGlan was

Table III *- Severity levels for different variables.*

Variable	Intensity level mild (score < 11) n = 44 (41.1%)	Intensity level moderate to severe (score ≥ 11) n = 63 (58.9%)	P-value
Gender	19 (43.0%)	24 (38.0%)	N/S*
Female	25 (57.0%)	39 (62.0%)	
Male			
Age			N/S*
<5 years	19 (43.0%)	28 (44.0%)	
≥ 5 <11 years	19 (43.0%)	29 (46.0%)	
≥11 years	06 (14.0%)	06 (10.0%)	
Illness duration			N/S*
< 6 years	33 (75.0%)	46 (73.0%)	
≥ 6 years	11 (25.0%)	17 (27.0%)	
Region			N/S*
Rural	9 (20.0%)	15 (24.0%)	
Urban/peri-urban	35 (80.0%)	48 (76.0%)	
First symptoms (age)			*p=0.032**
<2 years	25 (57.0%)	49 (78.0%)	
≥2 years	19 (43.0%)	14 (22.0%)	
Season of the year related to worsening of the condition			N/S*
Spring/summer	23 (52.0%)	26 (41.0%)	
Autumn/winter	2 (4.5%)	10 (16.0%)	
No relation	19 (43.5%)	27 (43.0%)	
Manifestations of atopic disease (asthma, atopic dermatitis, rhinitis)			N/S*
Yes	32 (73.0%)	51 (81.0%)	
No	12 (27.0%)	12 (19.0%)	
Family members affected			N/S **
Father, mother or sibling	22 (50.0%)	21 (33.3%)	
Other members	6 (13.6%)	18 (28.6%)	
Unknown	16 (36.4%)	24 (38.1%)	

N/S = non-significant; *Fischer's exact test; **chi-square test.

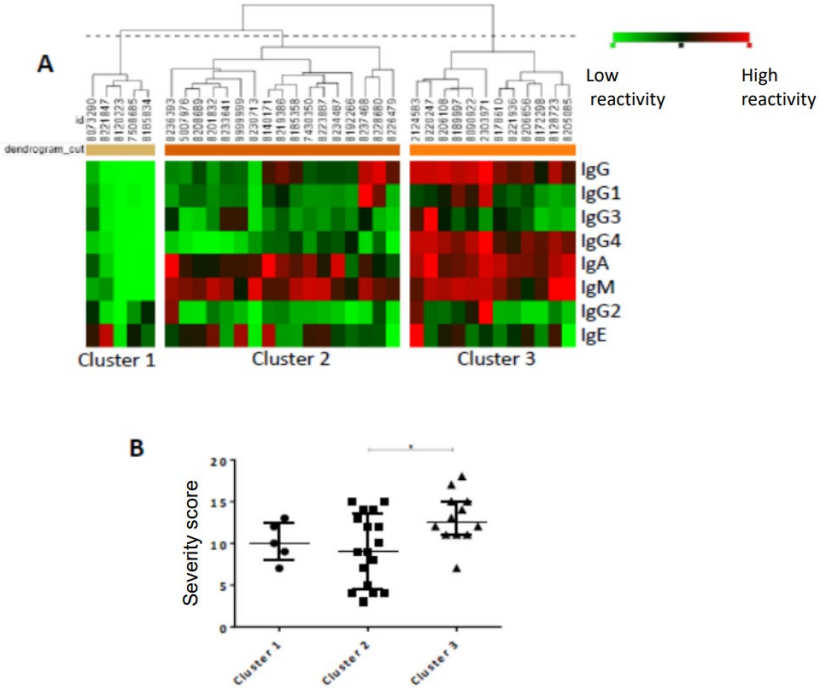
observed for the signature associated with greater severity. There was no greater reactivity of specific IgE to AgGlan that could be related to greater PU severity (**figure 2**). Cluster 1 showed a profile of low antibody reactivity to AgGlan, and although the median severity score presented by cluster 1 patients (median = 10.0; IQR = 8.0 and 12.5) was smaller than cluster 3, the difference was not significant.

The reactivity profile of specific antibodies to the *Aedes aegypti* body antigen (AgCor) didn't show a statistically significant association with PU severity score. Specific IgE reactivity was not determinant in the definition of signatures and was not associated with PU severity.

Discussion and conclusions

In our study, most patients (88.8%) were under 11 years old and had symptoms for less than 6 years (73.8%), suggesting, as in several studies, a natural desensitization over the years (21, 22). Furthermore, our study found that most patients had a personal history of allergic disease (77.6%) with rhinitis and asthma being the most prevalent.

Figure 2 *- Association between the PU patient's severity score and the immune response profile based on the reactivity index of specific antibodies to AgGlan (n = 34).*



(A) Heat map showing reactivity indices of antibody isotypes (low reactivity = green; high reactivity = red) specific to AgGlan. **(B)** Analysis of the severity score between clusters (1, 2 and 3) based on the reactivity indices of specific antibodies to AgGlan.

Unlike what is seen in the literature, where the patient is the only one affected in the family (11), our study revealed a high number of family members affected: 43.9% of the children had at least one close relative with the same symptoms. Because of this finding, one can consider the possibility of a genetic predisposition in addition to environmental exposure.

Children whose symptoms appeared before 2 years of age had a higher severity score when compared to those who started after 2 years of age ($p = 0.032$). This finding suggests that the age of onset of symptoms may be related to the severity of PU. Genetic causes that interfere with immune tolerance mechanisms, causing impaired production of regulatory cytokines (IL-10) could be present, as Cuéllar *et al.*, showed in patients with PU due to flea bites. Low levels of regulatory cytokines may favor the secretion of pro-inflammatory T2 cytokines that contribute to the generation and maintenance of cutaneous hypersensitivity reactions generated by insect bites during childhood (23). Other clinical correlations with score severity did not show statistical significance (**table III**).

In the heat map, the signature of cluster 3 antibody reactivity to AgGlan was associated with a higher PU severity score compared with cluster 2 ($p < 0.05$). Notably, higher specific IgG4 reactivities were observed in the most severe patients. This observation suggests that IgG4 could be associated with a more severe symptom. Researchers in Finland have already identified the presence of IgE and IgG4 against proteins present in *Aedes communis* saliva in the serum of adults with immediate and delayed skin cutaneous reactions to mosquito bites. These antibodies were not identified in unexposed infants, suggesting that specific IgE and IgG4 may play a critical role in the pathogenesis of hypersensitivity reactions to mosquito bites (24).

The study of Palosuo *et al.* verified an increase in the production of IgE, IgG1 and IgG4 against the proteins in the saliva of *Aedes* found in the serum of volunteers after the mosquitos' season. This finding suggests the association of IgG4 with the pathophysiology of PU (25).

On the other hand, a study by Srivastava *et al.*, in India, in sensitized patients demonstrated an improvement in cutaneous reactivity associated with reduced IgE and increased specific IgG4 against whole-body mosquito extracts of *Culex quinquefasciatus* after receiving specific immunotherapy for one year (26).

The role of IgG4 in the pathophysiology of reactions to mosquito bites is still uncertain. This association suggests two pos-

sibilities: 1) either this increase in IgG4 specific to AgGlan can be interpreted as a marker for the severity of PU, or 2) it can be considered as a confounding factor, *i.e.*, part of a compensatory mechanism of the immune system indicating that the patient is evolving to immune tolerance.

However, based on the symptoms and severity of patients in our study, with elevated IgG4 levels to *A. aegypti* AgGlan, we hypothesize that this antibody may be associated with greater disease severity, potentially serving as a severity marker. Additionally, based on the authors' experience and considering that other mosquitos have several antigens in common, it is possible to infer that these findings can be generalized to bites of different species of mosquitos. Nevertheless, further studies are required to confirm this hypothesis.

Regarding the immunoglobulin profile, the low reactivity of the immunoglobulins to *A. aegypti* AgGlan observed in cluster 1 patients can be explained by different stages of the disease for each individual or because antigens from insect species other than *A. aegypti* induce PU. In some patients, the immune response related to the pathogenesis of PU is possibly mediated by antigens of different insect species, especially in children living in households where more than one type of insect is present. What we see in our results may be one part of the complex process of the immune system's response to different antigens associated with the pathogenesis of PU.

This original article examines clinical and laboratory data from patients with PU in South America, particularly Brazil. The study highlights the need for a validated scoring system to improve patient care and support future research. Furthermore, it is worth highlighting the substantial correlation identified between IgG4 levels to *A. aegypti* AgGlan and the severity of the clinical condition.

We emphasize that we could not evaluate the reactivity index to *Culex* mosquito antigens, which, depending on the geographic location in the city of Rio de Janeiro, is much more prevalent than *Aedes* (27). Another limitation is this study is the exclusive use of patients from a single center. Future research should involve a larger multicenter sample with a control group to understand the disease-immunoglobulin isotype relationship. Moreover, the use of a non-validated clinical score developed by researchers presents a challenge when conducting comparative studies. It is critical to note that the need for validated severity scores and biomarkers poses significant challenges for future research.

In conclusion, the results show that a statistically significant correlation exists between the severity of PU in children and a high concentration of IgG4 anti-salivary gland antigens of *Aedes aegypti*. This investigation also highlights the importance of developing a globally validated severity scoring system to validate comparative studies worldwide. Finally, we aspire to encourage the search for a biological marker that helps diagnose and assess the severity of patients with PU.

Further studies on PU will deepen our understanding of the mechanisms involved in this prevalent, uncomfortable, and often neglected hypersensitivity manifestation, not only in South America, but also in other continents.

Fundings

None.

Contributions

AGS, RTA: conceptualization, data curation, formal analysis, writing – original draft. AGS, SAS, RTA: methodology. RTA: investigation. AGS: resources. AGS, RTA, FPM, SAS, ESG: visualization. AGS, ESG, FPM: supervision. RTA, ESG, FPM, SAS, AGS: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Clinical and atopic features of patients with wheat allergy dependent on augmentation factors (WALDA) presenting with urticaria: a monocentric study

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Key words

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Impact statement

Wheat allergy dependent on augmentation factor (WALDA) presenting with intermittent urticaria seems to display specific demographic features (female sex) and atopic (shrimp sensitization/allergy) and possibly comorbid nonatopic features (IBS).

Summary

Background. *Clinical and laboratory features of wheat allergy dependent on augmentation factor (WALDA) are scarcely characterized as compared to wheat anaphylaxis dependent on augmentation factor (WANDA). In this study we assessed the pattern of comorbid atopic and gastrointestinal diseases and the sensitization profile in patients with WALDA presenting with intermittent urticaria.* ***Methods.*** *We retrospectively assessed all patients with WALDA-urticaria in a tertiary referral center, with a combined gastrointestinal- allergy unit. WALDA diagnosis was based upon recognized clinical/serological criteria, atopic features, allergy tests and gastrointestinal comorbidities were compared to a cohort of O5G negative patients sensitized/allergic to wheat and one of patients allergic to shrimp.* ***Results.*** *Overall, we recruited 11 patients with WALDA presenting with intermittent urticaria (median age 44 years, IQR 29-58, F:M ratio 1.7:1). Atopy was a frequent finding among patients (8/11, 72.7%), with food allergy (6/11, 54.5%) followed by respiratory allergies (5/11, 45.5%). Shrimp sensitization was present in 8/11 patients (72.7%); half of them were also clinically reactive to shrimp. Irritable bowel syndrome (IBS) was present in 4/11 patients (36.3%). The prevalence of shrimp sensitization was 15.3%, (p = 0.01), in a group (n = 13) of O5G negative patients with wheat sensitisation/allergy (median age 31 years, IQR 27.7-52.0, F:M ratio 0.4:1), while IBS prevalence was 9% (p = 0.12). In the group of patients with shrimp allergy (n = 13) with or without allergic rhinitis, the prevalence of O5G positivity was 0% and that of IBS 7.7%.* ***Conclusions.*** *Patients with WALDA-urticaria seems to present specific demographic features (female sex) and atopic (shrimp sensitization/allergy).*

Introduction

Immunoglobulin-E (IgE)-mediated wheat allergy imposes a significant burden on patients due to potentially severe manifestations, including anaphylaxis, often characterized by cardiovascular involvement, as well as challenges related to management, such as strict wheat avoidance and its associated nutritional impact (1-3). Omega-5 gliadin (O5G) is the most common allergen involved in wheat anaphylaxis dependent on augmentation factors (WANDA) (1-4). In this form of IgE-mediated food allergy, allergic reactions usually occur when wheat ingestion is combined with a cofactor, such as physical exercise, nonsteroidal anti-inflammatory drugs, or alcohol. These reactions are usually severe, with frequent cardiovascular involvement, including cases of refractory anaphylaxis (1, 5-7).

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However, more recently, cases with isolated urticaria/angioedema have been described (8-9). Consequently, the broader term wheat allergy dependent on augmentation factor (WALDA) has been coined, to encompass the wider spectrum of clinical manifestations beyond anaphylaxis and, including skin-limited presentations (4). O5G is also the most frequent allergen in WALDA (11). Factors responsible for different symptom severity in wheat allergy are still elusive. Indeed, most clinical studies have focused on WANDA, identifying its main features, such as male sex and nonatopic background (1, 12, 14). In contrast, WALDA remains less characterized, with limited understanding of its etiopathogenesis, and no widely accepted diagnostic criteria. More importantly, male sex, the defining features of WANDA, may not to be a distinguishing feature of WALDA, as suggested by the findings of an Italian study (9).
In the current study, we investigated the clinical background and sensitization profile of O5G positive patients with WALDA-urticaria to look for demographic aspects, comorbidities, clinical presentation patterns and laboratory markers, which may serve as salient clinical features or potential biomarkers of this subset of wheat allergic patients. More specifically, we hypothesized that this skin-limited form of wheat allergy may involve specific demographic and clinical-immunological features.

Materials and methods

Patient population and study design

This was a monocentric, observational, retrospective study conducted in a tertiary referral center specialized in the diagnosis and management of wheat-related disorders, including celiac disease and wheat allergy, with a combined gastroenterology and allergy outpatient clinic (Fondazione IRCCS San Matteo, Pavia).
We herein retrospectively enrolled all consecutive adult (≥ 18 years) patients who were diagnosed with O5G allergy over the last five years (2021-2025), since the start of the allergy outpatient clinic. The diagnosis of WALDA related to O5G was made through adaptation of the criteria proposed by Jiang *et al.* (12) for wheat-dependent, exercise-induced anaphylaxis. More precisely, the diagnosis was based on the fulfilment of criteria 1, 2, 3 and 4 or 5. Criterion 1, which originally required the involvement of two or more systems, was adapted for the classification of patients with WALDA-urticaria, allowing skin-only manifestations to be sufficient. Recurrent urticaria was defined if > 1 episode of acute urticaria occurred over 6 months, and it was not present daily and continuously for > 6 weeks and it was not induced by physical factors. Patients with a concomitant history of episodes of physically induced urticaria or dermographism were also excluded.
With reference to criterium 3, skin prick tests were performed with a commercial extract for wheat (Lofarma, Italy) or with gluten flour (Spain) dissolved in saline solution 0.9%, specific IgE were determined for wheat (f4) omega-5 gliadin (f416), gluten (f79), gliadin mix (f98) by FEIA, (Immunocap, Thermofischer, Sweden).
Some patients of the present cohort were included in one previous work of Rossi *et al.* (9). Demographic (sex, age) and clinical data of patients were extracted and pseudo-anonymized from the electronic hospital records onto a pre-defined spreadsheet. Clinical data included clinical manifestations, atopic comorbidities, sensitization profile, general and allergy laboratory data, pharmacologic therapies and diets. In all cases, a diagnosis of celiac disease was ruled out by means of serology (*i.e.*, anti-tissue transglutaminase antibodies IgA). *A posteriori*, clinical and atopic features of O5G positive patients were compared to control groups from the same center, including all wheat-allergic/sensitized patients, who were O5G-negative, and a group of consecutive shrimp-allergic patients. All data that were not present in the electronic records or in the physicians' assessment forms were retrieved through a phone call with the patient. Informed consent was obtained from all patients. The study was performed as a clinical audit using routine collected clinical and laboratory data. All participants provided written informed consent for the use of their data in an aggregated and anonymous format. The study was approved by the local ethics committee (0023744/22). All results are reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations for quality assurance. Due to privacy compliance, the raw data cannot be made public but can be shared by the corresponding author upon reasonable request.

Statistical analysis

Continuous data were described with the median and interquartile range (IQR; *i.e.*, 25^{th}-75^{th} percentiles), and categorical data as counts and percent. Comparisons between two groups were performed using the Student t test for continuous variables and the Chi-Square test for categorical variables. Missing data were excluded from percentage calculation, when specified. Given the limited sample size and the exploratory purpose, no corrections for multiple testing were applied.
The software GraphPad Prism (Boston, USA) was used for all computations. A 2-sided P-value<0.05 was considered statistically significant.

Results

Demographic, clinical, and laboratory data of patients with WALDA

Overall, we recruited 11 patients (median age 44 years, IQR 29-58, F:M ratio 1.7:1). Demographic and clinical features are summarized in **table I**. All patients presented with a history of intermittent urticaria, with a median number of 7 episodes (IQR 4-11). In seven patients (63.6%) the diagnosis was confirmed with the remission of clinical manifestations after wheat avoidance, while in four patients (36.3%) the diagnosis was based on a positive oral food challenge, all of whom developed urticaria during the procedure. More precisely, an open food challenge with wheat (100 g of boiled gluten-containing pasta) followed by physical exercise

(10-15 minutes running, adjusted to individual fitness levels) (13) was offered to 10 patients, excluding patients presenting with anaphylaxis. Of these, only four accepted and underwent the challenge. Most patients deemed it unnecessary, due to the disappearance of urticaria with wheat avoidance and hence refused the food challenge. At least a three-month period of wheat avoidance was used to confirm the diagnosis. Additionally, anaphylactic reactions were documented in three patients, further supporting the diagnosis. More precisely, in one patient who received the indication of avoidance of cofactors anaphylaxis occurred after gluten and in two patients who were not adherent to a gluten-free diet (**table I**). Given the predominantly skin-limited manifestations, several competing differential diagnoses had to be considered and excluded, including chronic spontaneous urticaria, physical urticaria, *Helicobacter pylori* infection, celiac disease, and nonsteroidal anti-inflammatory drug hypersensitivity, among others.

The median diagnostic delay, as calculated from the onset of symptoms (mostly urticaria) and diagnosis was 3 years, IQR 1-6. Results of specific IgE and skin prick tests of the patients are reported in **table II** and **III**. As per protocol, all patients displayed IgE positivity to the allergen O5G (**table II**). The most frequently positive wheat allergenic fraction was gluten (n = 6, out of nine tested patients), followed by gliadin (n = 3 out of seven tested patients), as detected by specific IgE and prick tests with gluten flour and specific IgE, respectively.

Overall, most patients displayed higher levels of O5G IgE compared to IgE other wheat allergenic fractions, accounting for missing data **table I(Suppl)**, **table III(Suppl)**.

Commercial skin prick tests were positive for wheat in only three patients (not performed in one patient), while skin prick tests with gluten flour were positive in four patients (not performed in three patients). IgE for wheat were positive in four patients (not performed in three patients), IgE for gluten were positive in six patients (not performed in two patients), while IgE for gliadin in three (not performed in four patients). Generally, gluten sensitization detected by either prick test or IgE testing was more frequently positive than that to wheat.

To explore possible diagnostic or clinical markers of WALDA or its clinical features, correlation analyses were performed. No statistically significant correlation was found between diagnostic delay and O5G specific IgE (p = 0.2), total IgE levels (p = 0.7) and age (p = 0.5) and between O5G specific IgE and age (p = 0.4), total IgE (p = 0.1) and number of urticaria episodes (p = 0.3).

Atopic and gastrointestinal diseases of patients with WALDA

Atopy was a frequent finding among patients (8/11, 72.7%), with food allergy (6/11, 54.5%) being more frequent than the respiratory allergies (5/11, 45.5%). No patient had eczema, drug or Hymenoptera venom allergy, among atopic comorbidities.

With regards to gastrointestinal comorbidities, irritable bowel syndrome (IBS) was a frequent finding in these patients being present in (4/11, 36.3%), according to the Rome IV criteria, while no cases of celiac disease, inflammatory bowel disease, atrophic autoimmune gastritis, lactose intolerance were detected.

Table I *- Demographic, clinical, and therapeutical features of O5G allergic patients.*

Patient number	Sex	Age	Atopy	Eczema	Rhinitis	Asthma	Food allergy¥	Food	1st food allergy	Diagnostic Delay (years)	Type Cofactor	OFC	Therapy at last follow-up	Anaphylaxis in the follow-up
1	M	58	Yes	No	Yes	No	No		Wheat	3	E	No	GFD	No
2	F	44	No	No	No	No	No		Wheat	5	E	No	GFD	Yes
3	M	29	No	No	No	No	No		Wheat	1	NSAID	Yes	GFD	No
4	M	52	No	No	No	No	No		Wheat	1	No	Yes	GFD	No
5	F	23	Yes	No	Yes	No	Yes	Peach	Wheat	6	E+A	No	GFD	Yes
6	F	58	Yes	No	Yes	Yes	No		Wheat	13	E	No	C	No
7	F	46	Yes	No	No	No	Yes	Shrimp	Shrimp	2	E	Yes	C	No
8	F	22	Yes	No	No	No	Yes	Peach, shrimp	Wheat	1	E	No	GFD	Yes
9	F	32	Yes	No	No	No	Yes	Peach	Wheat	5	No	No	GFD	No
10	M	55	Yes	No	Yes	No	Yes	Shrimp	Shrimp	1	E	No	C	No
11	F	38	Yes	No	Yes	No	Yes	Shrimp	Shrimp	10	E+A	Yes	C	No

A: alcohol; C: avoidance of gluten-containing foods in association with cofactors (physical exercise, anti-inflammatory drugs, alcohol, menstrual cycle, fever, *etc.*); E: physical exercise; GFD: gluten-free diet; NSAID: non-steroidal anti-inflammatory drug; OFC: oral food challenge, LTP: lipid transfer protein. ¥Any food allergy in addition to wheat allergy.

Table II - *Specific serum IgE levels of O5G allergic patients.*

Patient number	Total IgE	O5G	Wheat	Gluten	Gliadin	Shrimp	D. ptero	*Der p 1*	*Der p2*	*Der p 10*	*rPen a 1*	*Pru p 3*	*Tri a 14*	*Bet v 1*	*Phl p 12/ Bet v 2*
1	144	18.40	0.90	3.99	2.74	0.67	0.81	Neg	Neg	1.98	0.87	Neg	N/A	13.5	Neg
2	375	4.49	0.25	1.75	0.61	0.14	Neg	N/A	N/A	N/A	N/A	Neg	N/A	Neg	Neg
3	389	2.76	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	N/A	Neg	0.32
4	147	1.72	Neg	0.47	0.21	1.46	Neg	Neg	Neg	Neg	Neg	Neg	N/A	Neg	Neg
5	1147	7.04	3.59	1.69	N/A	1.69	85.6	N/A	N/A	N/A	N/A	18.5	N/A	9.51	Neg
6	1170	0.53	0.13	Neg	Neg	Neg	Neg	N/A	N/A	N/A	N/A	Neg	Neg	Neg	Neg
7	133	0.15	N/A	N/A	N/A	0.15	0.11	N/A	N/A	Neg	Neg	Neg	Neg	Neg	Neg
8	115	0.23	N/A	4.89	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.36	Neg	Neg	Neg
9	534	0.93	N/A	N/A	N/A	Neg	0.18	N/A	N/A	N/A	N/A	10.1	1.25	Neg	Neg
10	212	0.12	Neg	Neg	Neg	0.70	0.60	N/A	N/A	1.45	0.68	Neg	N/A	Neg	Neg
11	18	0.52	Neg	0.15	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Bet v: *Betula verrucosa;* D. ptero: Dermatophagoides pteronyssinus; Der p: *Dermatophagoides pteronyssinus*; N/A: not assessed; neg.: negative if <0.10 kU/L; 05G: omega 5 gliadin; rPen a: recombinant *Penaeus aztecus*; Phl p: *Phleum pretense;* Pru p: *Prunus persica;* Tri a: *Triticum aestivum.*

Table III - *Skin prick tests of O5G allergic patients.*

Patient number	Wheat	Gluten*	HDM	Shrimp	Peach	Grass	Beach	Weed	Cat	Dog	Aspergilllus	Alternaria
1	+	N/A	-	+	-	+	+	-	-	-	-	-
2	+	N/A	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-
4	-	+	-	+	-	-	-	-	-	-	-	-
5	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A	-	-	-	-
6	-	-	+	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-
8	-	+	-	+	+	+	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-
10	+	N/A	+	+	-	-	-	-	-	-	-	-
11	-	+	-	+^	-	-	-	-	-	-	-	-

HDM: house dust mite; N/A: not available. In patient #5 skin prick tests were not performed due to histamine inhibition. +Denotes positive results; -denotes negative results; *denotes gluten flour; ^denotes prick by prick test.

Sensitization profile of patients with WALDA

Six patients (54.5%) were sensitized to house dust mite, three (37.3%) to grass and two (18.1%) to beach among respiratory allergens, as assessed by specific IgE and/or skin prick tests (**table II** and **III**). No patient was sensitized to weeds, animal dander, or molds (**table III**). An extensive panel of commercial prick test for food allergens was negative except for shrimp (**table III**). Considering molecular allergens, three patients displayed positivity to the peach LTP, *Pru p 3*, two patients to PR-10, Bet v1, and one to *Phl p12* (**table II**). Among the patients sensitized to *Pru p 3*, only one was also positive for *Tri a 14,* but was unreactive to wheat when ingested at rest, hence reducing the likelihood that this allergen had a role in the clinical reactivity to wheat in addition to O5G.

Shrimp sensitization, related clinical symptoms and gastrointestinal comorbidities in patients with WALDA compared to control groups

Shrimp sensitization was a frequent finding, since eight out of the eleven patients (72.7%) were sensitized to shrimp, as assessed by either positive specific IgE (n = 6) or skin prick tests (n = 5). Three patients tested positive on both diagnostic modalities. Specific IgE to shrimp tropomyosin, *rPen a 1,* was detected in only two patients (**table II**). These patients were also sensitized to the house dust mite tropomyosin, *Der p 10*. In these patients, the higher levels of *Der p 10* compared to *Pen a 1,* with a 2:1 ratio, suggest a primary respiratory route of sensitization to this allergen. Indeed, one of these patients also reported perennial rhinitis related to dust mite exposure.

Among shrimp-sensitized patients (n = 8), four (36.3% of the whole cohort), exhibited clinically reactive to shrimp. More precisely, three cases presented urticaria and one anaphylaxis. Notably, these reactions occurred after consuming shrimp without wheat co-ingestion. Moreover, in three of these four patients, allergic reactions to shrimp temporally preceded those to wheat (**table IV**), suggesting that shrimp allergy occurred before wheat allergy in this patient subset.

Correlation analysis revealed no statistically significant association between O5G IgE and shrimp and *D. pteronyssinus* specific IgE (Spearman's rho 0.23, p = 0.2 and Spearman's rho 0.21, p = 0.2, respectively).

We then compared the prevalence of shrimp sensitization in patients with omega-5 allergy with that of a control group from our center, consisting of patients sensitized/allergic to wheat (n = 13, median age 31 years, IQR 27.7-52.0, F:M ratio 0.4:1). These patients, whose characteristics are reported in **table I(Suppl)**, were, by definition, O5G-negative and were more frequently male as compared to O5G positive ones (p = 0.80). Sensitization to gluten (n = 9) or to wheat LTP, *Tri a 14* (n = 5, one patient was co-sensitized to both glutenin and *Tri a 14*) was observed in this group. In this control group, the prevalence of shrimp sensitization, as assessed by either positive specific IgE (n = 2) or skin prick tests (n = 1), with one patient being positive for both skin prick test and specific IgE, was observed in only 2 of 13 patients (15.3%). This prevalence was approximately four times lower compared to that of patients with O5G allergy (p = 0.01).

The prevalence of IBS was also assessed in this cohort and estimated at 9% (one in 11 patients, p = 0.12 for comparison with patients with O5G allergy).

Finally, we assessed the prevalence of O5G sensitization in a separate and unselected cohort (of patients with shrimp allergy n = 13) with or without allergic rhinitis (**table II(Suppl)**). None of these patients displayed IgE to O5G, nor positivity to wheat, gluten or gliadin. Eleven out of 13 (84%) patients were sensitized to house dust mite. The prevalence of IBS in this group was 7.7% (1/13) (p = 0.08 for comparison with the prevalence in patients with O5G allergy).

Discussion and conclusions

In this retrospective real-life study, we assessed the prevalence of atopic and gastrointestinal comorbidities, as well as the sensitization profile of patients with WALDA presenting with urticaria. The diagnosis was based on the adaptation of the criteria by Jiang *et al.* (12) and already used in a preliminary communication by our group (9).

Table IV - *Clinical symptoms of patients with O5G allergy and shrimp sensitization.*

Patient number	Shrimp sensitization*	Shrimp allergy	Shrimp allergy symptoms	First Symptomatic food	Perennial rhinitis	HDM sensitization*
1	Yes	No		Wheat	Yes	Yes
2	Yes	No		Wheat	No	No
3	No	No		Wheat	No	No
4	Yes	No		Wheat	No	No
5	Yes	No		Wheat	Yes	Yes
6	No	No		Wheat	Yes	Yes
7	Yes	Yes	Urticaria	Shrimp	No	Yes
8	Yes	Yes	Urticaria	Wheat	No	No
9	No	No		Wheat	No	Yes
10	Yes	Yes	Urticaria	Shrimp	Yes	Yes
11	Yes	Yes	Urticaria+rhinitis	Shrimp	Yes	No

HDM: house dust mite. *Shrimp and HDM sensitization was considered positive when either prick tests including prick by prick with fresh shrimp or serum IgE for shrimp were positive (> 0.10 kU/L). Shrimp allergy diagnosis was made upon the combination of evidence of sensitization and consistent clinical manifestations.

The first result of our study is the substantial prevalence of female sex and that of allergic comorbidities (atopy overall in 72.7% of patients) in those with WALDA presenting with urticaria. These features are in stark contrast with data from the European Anaphylaxis Registry from central Europe, since according to this study male sex was more frequent, the prevalence of atopic comorbidities was collectively low and estimated at 36.9%, and cardiovascular symptoms were a very common finding (86.7%) in patients with wheat allergy (1). However, it is likely that, due to selection bias, mostly severe forms were enrolled in this registry, so that its results are probably not representative of a general outpatient population of wheat allergic patients. Of note, in a series from China, including patients with anaphylaxis, but also isolated urticaria, male sex was only slightly more common overall than female sex (12). It cannot be ruled out that the incorporation of patients with skin manifestations could have altered the male to female sex in this study, although information about sex in the subgroup of patients presenting with urticaria was not reported. Moreover, another interesting finding of this study is that in 64% of patients with anaphylaxis a history of previous recurrent urticaria was present. Hence urticaria may be a prodromal manifestation of more severe forms, at least in some patients. Alternatively, the presence of less severe skin manifestation may be related to the general lower level of physical exercise as a cofactor in female patients who are more represented in our studies of patients with WALDA presenting with isolated urticaria, as compared to WANDA (usually men) (2). An in-depth analysis of cofactors in our study was not performed. Yet, it also possible that the higher prevalence of female sex in patients with WALDA-urticaria underlies a biological phenomenon. Another result of our study is that the diagnostic delay of this form of allergy is significant (median 3 years, IQR 1-6), as compared to those series where anaphylaxis was reported among clinical manifestations (2, 5). Some not exclusive explanations can be put forward. It is likely that these patients due to the intermittent nature of urticaria do not recognize wheat as the implied allergen, together with cofactors, and/or that, due the presence of isolated skin manifestations, they are not promptly referred to the allergist, while other specialists could be prioritized, such as the dermatologists. Another result of the study is that IBS appears frequently in patients with WALDA, being present in 36.6% of patients. Interestingly, we did not find an association with other gastrointestinal diseases, including inflammatory bowel disease and celiac disease, which are characterized by allergic comorbidities (14). While it is possible that this association could simply mirror the higher prevalence of IBS compared to the other gastrointestinal diseases, it is noteworthy that this finding was not replicated in patients with wheat allergy who were negative for O5G and that prevalence of IBS in omega-5 allergic patients was disproportionally high as compared to the general population (up to 11%) (15). Moreover, this finding lends itself to a mechanistic interpretation. Patients with IBS may self-impose wheat free diets to alleviate gastrointestinal symptoms. Therefore, oral tolerance to wheat would be impaired, hence leading to the occurrence of wheat allergy. Unfortunately, we could not estimate the precise temporal sequence of development of IBS and wheat allergy in every patient to corroborate this hypothesis.

Another finding is the frequent rate of sensitization of patients with WALDA to shrimp, in up to 72.7% of patients, with 36.3% of the whole cohort being also clinically reactive. This data seems to be specific of patients with WALDA, since in the control group of wheat allergic patients not sensitized to O5G, the prevalence of shrimp sensitization was four times lower (15%). On the contrary, no cases of omega-5 positivity were detected in patients sensitized to shrimp.

A considerable proportion of patients in our cohort with omega-5 had perennial rhinitis (5/11, 45.5%) and house dust mite sensitization (6/11, 54.5%). Yet, given higher rate of sensitization to shrimp (72.7%) compared to that of house dust mite, cross-reactivity between these allergenic sources cannot explain the sensitization pattern in all patients. However, in the small subset of patients (n = 2) with positive mice and shrimp tropomyosin, higher levels of IgE to *Der p 10*, the mite tropomyosin, than that of *rPen a 1*, the shrimp tropomyosin were detected. Hence, even though in only few patients both determinations were available, a primary respiratory route of sensitization to this allergen is plausible. Moreover, half of the patients sensitized to shrimp were also clinically reactive and in these patients the reactivity to shrimp preceded that to wheat. Conversely, it has been hypothesized that shrimp sensitization in patients with omega-5 allergy could be related to the high gluten diet used for crustacean farming (16). Since it is not known whether gluten is fully digested in this species, it is possible that undigested fragments may interact with shrimp proteins and hence lead to new allergens and/or promote shrimp sensitization (12, 17). Yet this hypothesis needs formal validation. The mechanistic interpretation of the association between omega-5 sensitization and that to shrimp is still elusive. The absence of a significant correlation between specific IgE levels for O5G and that of shrimp makes cross-reactivity between these two allergens a less likely explanation. ImmunoCap inhibition experiments could not be performed in the present study, however they are envisaged as a future aspect of research to help clarify the eventual presence of a primary sensitizer. Nonetheless, screening patients with omega-5 allergy for shrimp allergy appears worthwhile, given the significant rate of clinical reactivity. Moreover, the evidence of shrimp sensitization may suggest the diagnosis of WALDA in patients presenting with recurrent urticaria and hence serve as a possible diagnostic biomarker. Indeed, in the correlation analysis no other demographic or laboratory marker, among those analyzed, had an influence on the diagnostic delay. The study has some limitations including the small sample of patients, the low rate of open food challenges, the possible selec-

tion bias of patients from a gastrointestinal unit and the main skin manifestation of WALDA in our cohort. Moreover, the enrolment of patients from a previous series may have introduced a bias. Larger, multicenter and prospective studies enrolling patients from other geographical regions and including non-cutaneous manifestations are needed in order to confirm these findings. While our focus was on O5G positivity, it is important to note that other wheat allergens also play a role in WALDA. For example, wheat lipid transfer protein (LTP), *Tri a 14*, is particularly relevant in the Mediterranean region (13). Sensitization to O5G and *Tri a 14* appears to occur independently. Therefore, our findings may not be extendable to other WALDA populations defined by different serological profiles.

Collectively, the results of the present study suggest that patients with WALDA-urticaria may constitute a specific subset of wheat allergic patients and possibly a different phenotype, characterized by specific demographic features (female sex) and a high prevalence of atopic comorbidities, as opposed to patients with WANDA. Moreover, IBS is one of most frequent clinical nonatopic comorbidities of patients with WALDA-urticaria, implying that gastroenterological evaluation/referral in these patients is required. Finally, shrimp and house dust mite sensitization/reactivity appears to be one relevant aspect, among others, in the management of allergic comorbidities in these patients.

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None.

Contributions

CMR: conceptualization. CMR, SM, MDA: project administration; CMR, SM, MVL: data curation, writing – original draft. SM: formal analysis. ADS: writing – review & editing, supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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Assessment of concentrations of multidirectional omega-3 fatty acids in inborn errors of immunity with predominantly antibody defects: a pilot study

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Key words

Inborn errors of immunity; primary immunodeficiency; primary antibody deficiency; common variable immunodeficiency; omega-3 fatty acids.

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Impact statement

The identification of immunodeficiencies associated with altered levels of omega-3 fatty acids will facilitate the introduction of improved diagnostic techniques and therapies for these disorders in the future.

Summary

Background. *Omega-3 fatty acids are involved in many processes in the human body. Their beneficial effects were documented mainly in relation to cardiovascular and immune systems. Patients with immunodeficiencies with predominantly antibody defects, due to their reduced immunoglobulin levels, should have factors adversely affecting the course of the disease eliminated.* ***Methods.*** *Nineteen primary immunodeficient patients with predominantly antibody defects (out of which fourteen with CVID) and eighteen immunocompetent participants had their blood tested in order to determine concentration of EPA, DHA and omega-3 index values. The Mann-Whitney U tests were used to determine statistical significance.* ***Results.*** *Immunodeficient participants, especially with CVID, in overall tend to have slightly lower mean concentration of omega-3 fatty acids such as DHA and in particular EPA (CVID: 0.86% ± 0.28% vs 1.06% ± 0.31%, p = 0.095) as compared with the control group and the differences were most evident among patients aged 30-39 (0.67 ± 0.16% vs 1.12 ± 0.12%, p = 0.025). 63% of patients with immunodeficiency had an omega-3 index value between 4-8 compared to 39% of people in the control group. 37% of participants with predominantly antibody defects had an omega-3 index value > 8% (29% of all CVID group) compared with 61% of the control group. None of the participants achieved a result of 4% or lower. People without immunodeficiency consumed products rich in omega-3 acids more often.* ***Conclusions.*** *These findings suggest that primary immunodeficient patients with predominantly antibody defects tend to have lower omega-3 index values, albeit not significantly and seem to have higher cardiovascular risk than the control group. Research has also shown that education is needed regarding the effects and necessity of consuming products rich in omega-3 fatty acids, especially in patients with immunodeficiency.*

Introduction

Over the past several years in published clinical and epidemiological studies from around the world, an increased interest of the scientific community on the subject of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is observed, as representatives of omega-3 fatty acids, in the context of their beneficial effects on human health. Both of these acids are involved in

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various processes in the human body, including regulation of the immune system, reduction in risk of cardiovascular events and an anti-inflammatory effect (1-3). Due to the fact that omega-3 acids are found in large concentrations in the brain tissue and in the human retina, it is believed that their insufficient supply within the diet may contribute to impaired fetal development and even be a risk factor for the development of Alzheimer's disease (1, 4). It has also been proven that these acids can prevent the development of atherosclerosis by inhibiting inflammation and rupture of atherosclerotic plaque, hence by increasing the consumption of products containing DHA, it is possible to reduce the risk of mortality due to coronary artery disease by as much as 7% (5-7).

Structure and occurrence of DHA and EPA

Eicosapentaenoic and docosahexaenoic acids are considered, in terms of the human diet, to be the main representatives of long-chain n-3 polyunsaturated fatty acids (LC-PUFA), which means that in their molecular structure, the first double bond is located at the third carbon atom counting from the end of the methyl group, the so-called carbon Ω-3. In its 19-membered hydrocarbon chain, EPA contains 5 double bonds connected by methylene bridges, and DHA, consisting of a 21-membered chain, has as many as 6 of these bonds. Due to the lack of appropriate enzyme mechanisms that introduce multiple bonds at the appropriate carbon atom, these acids are not synthesized *de novo* in the human body and therefore they must be supplied with food (1, 8). The main source of omega-3 fatty acids is primarily the fatty tissue of marine animals and fish such as tuna, mackerel and salmon, as well as marine algae, which these fish feed on.

In addition, these acids can also be found in products such as meat (beef, lamb, pork, and poultry), milk and dairy products, chicken egg yolk and seafood. In the case of products of plant origin, sources of omega-3 fatty acids include oils obtained from basil, chia, flax, soybean and rapeseed seeds (1).

Effect of omega-3 fatty acids on the immune system

Despite such a wide spectrum of action of omega-3 acids and the existence of many studies and scientific papers indicating the beneficial effect of these acids on the human body, still little is known about the exact mechanisms in which they affect the human immune system *in vivo*. The literature contains extensive studies (9, 10) summarizing the knowledge gathered so far on the impact of omega-3 fatty acids on individual components of innate and acquired immunity mechanisms. However, many of the articles quoted there refer to conclusions based on *in vitro* studies on animals or in people with immunocompetence. Therefore, there is significant evidence that EPA and DHA may affect a number of processes taking place during inflammation through various mechanisms, including inhibition of leukocyte chemotaxis and adhesion molecule expression, signal transmission regulation by affecting both surface and intracellular receptors, the reactivity of B and T lymphocytes modulation, and modification of the composition of fatty acids in cell membranes (9, 10). Due to the small number of studies conducted and the absence of unequivocal conclusions, it would therefore be interesting to check whether omega-3 acids play an important role in people with impaired function of the immune system, *i.e.*, in people with immunodeficiencies, and if such a relationship exists, to see whether supplementation with these acids could bring any benefits for them.

Primary antibody deficiencies

Primary antibody deficiencies (PADs) are the most common inborn errors of immunity (IEIs) and account for more than 50% of all cases. In symptomatic patients, there is an increased risk of not only infections but also of selected cancers, autoimmune diseases, and allergies (11).

The recognition of IEI is systematically improving, which is associated not only with extending the life of patients but also with the occurrence of new complications and accompanying diseases. Therefore, prevention should become a priority, also in the field of non-communicable diseases. IEI patients develop immune dysregulation, which not only causes immunodeficiency, but may also affect the course of co-occurring chronic diseases. In order to provide patients with IEI with the best possible care, it is necessary to know whether it is possible to interfere with modifiable factors affecting health. Determination of the concentration of multidirectional omega-3 acids seems to be an important parameter, which, in case of deficiency, can be supplemented.

Common variable immunodeficiency (CVID) is one of the most common symptomatic primary humoral immunodeficiencies, characterized by decreased serum levels of IgG, IgA and in some patients IgM, among others. It is estimated that the disease affects, on average, 1:25,000 of the population. Its incidence in men and women is equal, although boys predominate among children. The age of onset of the disease is variable. Some authors speculate that there might be two peaks of incidence: in early childhood and around the third decade of life (12, 13). Patients require immunoglobulin substitution for the rest of their lives. The etiology of CVID is unknown, although it is believed that certain environmental and genetic factors may predispose to the development of this disease. Due to the heterogeneous clinical picture, the diagnosis of this disease is a substantial diagnostic problem and, in many cases, results in a delay of many years between the diagnosis and the onset of the first symptoms. This translates not only into long-term, incorrectly used treatment, but also into an increased risk of complications, which mainly consists of pulmonary complications, autoimmunity and an increased, from 4 to 20%, risk of developing cancer (including non-Hodgkin's lymphoma and gastric cancer) (14, 15). It seems that patients with CVID are a group of patients in whom unfavorable factors influencing the course of immunodeficiency and the occurrence of

chronic diseases should be eliminated. However, this requires additional research and comparison of this group with a control group of unaffected individuals. The aim of this study is to evaluate whether there is a difference in omega-3 fatty acid concentration in blood between people with primary immunodeficiency with predominantly antibody defects and immunocompetent.

Materials and methods

This pilot study was approved by the Bioethics Committee of the Nicolaus Copernicus University in Toruń (KB 215/2022). All participants have given informed consent to participate in the study.

Study population

Participants (n = 50) were divided between two groups based on the presence of humoral immunodeficiency. Patients with humoral immunodeficiency (n = 25) were recruited from a group under the supervision of Allergology, Clinical Immunology and Internal Diseases Clinic in Jan Biziel University Hospital No. 2 in Bydgoszcz, Poland. Inborn errors of immunity were diagnosed according to the European Society for Immunodeficiency (ESID) criteria (16). Immunocompetent participants (n = 25) were selected from a population inhabiting an area of north-central Poland. During the study, four immunodeficient and two immunocompetent patients failed to attend blood testing. Additionally, two participants with immunological disorders and five without such disorders, were rejected during data analysis as a consequence of not meeting inclusion criteria. Ultimately 18 immunocompetent and 19 immunodeficient patients were included in the study (**figure 1**), out of which 14 (74%) were previously diagnosed with common variable immunodeficiency (CVID), 3 (16%) with selective deficiency of immunoglobulin G (IgG) subclasses, 1 (5%) with hereditary agammaglobulinemia and 1 (5%) with non familial agammaglobulinemia. Additional information regarding comorbidities in immunodeficient participants is included in **table I(Suppl)**. Considering participants with humoral immunodeficiency, the mean age (± SD) was 37.6 ± 10.6 years and BMI 22.63 ± 2.97 kg/m². In the immunocompetent group, the mean age was 34.9 ± 10.6 years and BMI 24.09 ± 2.99 kg/m², which resulted in P-values of 0.447 and 0.146, respectively. In the subgroup of immunodeficient patients, a large subset of participants suffering from common variable immunodeficiency may be distinguished. The mean age of the CVID group was 36.0 ± 8.0 years and BMI 23.10 ± 3.08 kg/m², which, compared to the control group, gave P-values of 0.747 for age and 0.367 for body mass index (**table I**).

Inclusion criteria

Participants were eligible for the study if they met the following criteria:

- Aged ≥ 18 years and < 60 years
- Body mass index ≥ 18.5 kg/m² and <30 kg/m²
- Have given informed consent

Additionally, in order to be included into the immunodeficiency group, participants must have been diagnosed as primary immunodeficiency with predominantly antibody defects according to the European Society for Immunodeficiency (ESID) criteria (16).

Figure 1 *- Initial and final number of participants.*

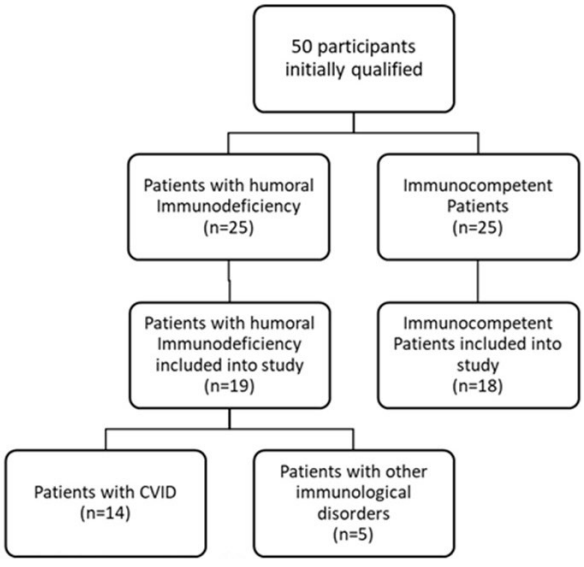


Table I - *Comparison of demographic parameters between patients with humoral immunodeficiency, a subgroup of common variable immunodeficiency (CVID) patients and immunocompetent participants.*

Parameter	Immunocompetent	Patients			
		Immunodeficient			
		Overall		CVID	
n	18	19	-	14	-
Sex (F/M)	8 / 10	11 / 8	-	8 / 6	-
Age	34.9 σ = 10.6	37.6 σ = 10.6	p = 0.447	36.0 σ = 8.0	p = 0.747
BMI	24.09 σ = 2.99	22.63 σ = 2.97	p = 0.146	23.10 σ = 3.08	p =0.367

Age and BMI are expressed as mean values with standard deviation. A P-value < 0.05 was considered statistically significant. The letter sigma (σ) denotes the standard deviation calculated for each result.

Questionnaire

Participants were asked to complete the questionnaire regarding their health status, age, weight, height, sex and dietary habits, including variable sources of omega-3 fatty acids. Closed questions with five possible answers were used to measure the frequency of most commonly consumed food ingredients containing omega-3 fatty acids, such as fish, olive oil, canola oil, linseed oil, walnuts, chia seeds and chicken eggs. The options from which participants could have chosen an answer were as follows: everyday, few times a week, once a week, 1-3 times a month, I do not consume. In order to estimate the mean monthly frequency of goods consumption containing omega-3 fatty acids, for each answer a corresponding average monthly value was assigned: for the everyday answer the value was set as 30, few times a week as 16, once a week as 4, 1-3 times a month as 2 and I do not consume as 0. The questionnaire template is attached in **table III(Suppl)**.

Blood sample collection

In order to determine the concentration of EPA and DHA, venous blood samples from median cubital veins were collected using 6ml vacuum tubes with EDTA. Samples were obtained in the morning, on an empty stomach, after the patients had rested overnight. Prior to the collection of blood samples, patients were instructed to rest for approximately 15 minutes. Furthermore, it was imperative that no food or drink had been consumed for a minimum of eight to twelve hours. Until laboratory testing, the material was stored at a temperature of 2-8 degrees Celsius. Samples were analyzed using gas chromatography in cooperation with certified external commercial laboratories. The results were available to investigators and participants individually. The omega-3 fatty acid testing involved assessing the concentration of polyunsaturated fatty acids EPA and DHA in venous blood and summarizing their percentage values (omega-3 index). Omega-3 Index was defined as the sum of EPA % and DHA % as measured in whole blood and derived by validated calculations to yield the equivalent sum of EPA % and DHA % in red blood cell membranes. Omega-3 index < 4 indicated low cardioprotective effect (supplementation and dietary changes recommended). An index of 4-8 indicated a moderate cardioprotective effect (changes in diet recommended, supplementation to be considered). An index > 8 indicated a high cardioprotective effect (continuation of current activities recommended).

Statistical analysis

Data analysis included demographic characteristics of immunocompetent and immunodeficient participants with CVID subpopulation, such as age or BMI and data obtained from blood testing: EPA, DHA and omega-3 index. Determination of P-values in demographic analysis was conducted using independent t-tests, which were preceded by Kolmogorov-Smirnov tests for normal distribution and two sample F-tests for variances. Parameters determined from blood were compared using the Mann-Whitney U test. Statistical analysis was performed in Microsoft Excel 2019 with the addition of the Analysis ToolPak.

Results

Omega-3 fatty acids concentration

In general, there were no statistically significant differences in EPA and DHA concentration or omega-3 index values between the immunodeficient group and immunocompetent group, as well as between the CVID group and immunocompetent group, except the 30-39 age group, which indicated a greater level of EPA in immunodeficient participants as compared to immunocompetent (p = 0.025). However, groups with immunological disorders, especially with CVID, tend to have slightly lower mean concentrations of omega-3 fatty acids such as DHA and, in par-

ticular, EPA when compared with the group without immunological disorders (**tables II** and **III**).

Interestingly, males were found to have higher EPA values, both among those with and without immune deficiencies, than females. On the other hand, such a trend did not occur in the context of DHA. In immunocompetent individuals, males had a higher percentage of DHA and, consequently, of the entire omega-3 index, whereas in immunodeficient individuals, including those with CVID, females had greater levels of those indices.

A similar tendency may be observed in terms of BMI, where overweight participants had higher mean EPA concentrations compared to normal weight subjects. Immunocompetent individuals of normal weight had lower average DHA and omega-3 index values than overweight participants, while immunocompetent individuals showed higher values than those with increased BMI. A comparison of EPA, DHA and omega-3 index values by sex, BMI and age in individuals with different levels of immune function are presented in **figures 2** and **3**.

Omega-3 as a cardioprotective marker

Sixty-three percent of patients with immunodeficiency (n = 12) had an omega-3 index value between 4-8 compared to 39% of people in the control group (n = 7). 37% of participants with prevalent antibody defects (n = 7) had an omega-3 index value > 8% (29% of the whole CVID group, n = 4) compared with 61% of the control group (n = 11). None of the participants achieved a result of 4% or less. Omega-3 index results and patient characteristics are detailed in **table II(Suppl)**.

Sources of omega-3 fatty acids amongst participants

The most common source of omega-3 fatty acids among immunodeficient patients, as well as participants without immunological disorders, were eggs, which were consumed on average 9.5

Table II *- Summary of arithmetic mean concentrations of EPA and DHA, as well as omega-3 index, stratified by age, BMI and sex, for immunocompetent (c) and immunodeficient (def) patients.*

Parameter	n (c)	n (def)	EPA [%] (c)	EPA [%] (def)	EPA P-value	DHA [%] (c)	DHA [%] (def)	DHA P-value	Omega-3 index [%] (c)	Omega-3 index [%] (def)	Omega-3 index P-value
Age											
18-29	8	6	0.95 σ = 0.36	0.79 σ = 0.18	0.439	7.48 σ = 1.43	7.4 σ = 2.63	0.439	8.43 σ = 1.61	8.19 σ = 2.75	0.333
30-39	3	5	1.12 σ = 0.12	0.67 σ = 0.16	**0.025**	6.65 σ = 1.54	6.45 σ = 1.13	0.881	7.77 σ = 1.59	7.12 σ = 1.19	0.881
40-49	5	6	1.02 σ = 0.13	1.17 σ = 0.10	0.100	7.73 σ = 1.25	7.79 σ = 1.96	1.000	8.74 σ = 1.31	8.96 σ = 1.99	0.855
50-59	2	2	1.52 σ = 0.36	1.23 σ = 0.58	0.439	10.75 σ = 2.38	8.25 σ = 1.48	0.439	12.26 σ = 2.74	9.48 σ = 2.06	0.439
BMI											
18.5-24.99	12	15	0.97 σ = 0.23	0.91 σ = 0.30	0.272	7.37 σ = 1.41	7.48 σ = 2.01	0.661	8.34 σ = 1.46	8.38 σ = 2.16	0.626
25-29.99	6	4	1.23 σ = 0.40	0.99 σ = 0.35	0.667	8.59 σ = 2.25	6.93 σ = 1.86	0.394	9.82 σ = 2.59	7.92 σ = 2.14	0.394
Sex											
Female	8	11	1.02 σ = 0.22	0.91 σ = 0.27	0.265	7.4 σ = 1.41	7.74 σ = 2.37	0.901	8.42 σ = 1.48	8.65 σ = 2.50	0.934
Male	10	8	1.09 σ = 0.38	0.95 σ = 0.36	0.399	8.08 σ = 2.03	6.85 σ = 1.10	0.155	9.17 σ = 2.31	7.79 σ = 1.41	0.143
Overall											
	18	19	1.06 σ = 0.31	0.92 σ = 0.30	0.171	7.77 σ = 1.77	7.36 σ = 1.94	0.354	8.83 σ = 1.97	8.29 σ = 2.11	0.302

A P-value < 0.05 was considered statistically significant. The letter sigma (σ) denotes the standard deviation calculated for each result.

Table III *- Summary of arithmetic mean concentrations of EPA and DHA, as well as omega-3 index, stratified by age, BMI and sex, for immunocompetent participants (c) and patients with common variable immunodeficiency (CVID).*

Parameter	n (c)	n (CVID)	EPA [%] (c)	EPA [%] (CVID)	EPA P-value	DHA [%] (c)	DHA [%] (CVID)	DHA P-value	Omega-3 index [%] (c)	Omega-3 index [%] (CVID)	Omega-3 index P-value
Age											
18-29	8	4	0.95 σ = 0.36	0.72 σ = 0.18	0.234	7.48 σ = 1.43	7.55 σ = 3.337	0.610	8.43 σ = 1.61	8.27 σ = 3.52	0.445
30-39	3	5	1.12 σ = 0.12	0.67 σ = 0.16	**0.025**	6.65 σ = 1.54	6.45 σ = 1.13	0.881	7.77 σ = 1.59	7.12 σ = 1.19	0.881
40-49	5	5	1.02 σ = 0.13	1.17 σ = 0.11	0.117	7.73 σ = 1.25	8.05 σ = 2.08	0.754	8.74 σ = 1.31	9.22 σ = 2.11	0.602
50-59	2	0	1.52 σ = 0.36	-	-	10.75 σ = 2.38	-	-	12.26 σ = 2.74	-	-
BMI											
18.5-24.99	12	11	0.97 σ = 0.23	0.83 σ = 0.24	0.132	7.37 σ = 1.41	7.50 σ = 2.28	0.538	8.34 σ = 1.46	8.33 σ = 2.40	0.498
25-29.99	6	3	1.23 σ = 0.40	0.98 σ = 0.43	0.606	8.59 σ = 2.25	6.75 σ = 2.24	0.439	9.82 σ = 2.59	7.73 σ = 2.58	0.439
Sex											
Female	8	8	1.02 σ = 0.22	0.87 σ = 0.30	0.189	7.4 σ = 1.41	7.99 σ = 2.77	0.793	8.42 σ = 1.48	8.87 σ = 2.95	0.834
Male	10	6	1.09 σ = 0.38	0.85 σ = 0.27	0.303	8.08 σ = 2.03	6.46 σ = 0.56	0.065	9.17 σ = 2.31	7.31 σ = 0.73	0.058
Overall											
	18	14	1.06 σ = 0.31	0.86 σ = 0.28	0.095	7.77 σ = 1.77	7.34 σ = 2.20	0.314	8.83 σ = 1.97	8.20 σ = 2.36	0.254

A P-value < 0.05 was considered statistically significant. The letter sigma (σ) denotes the standard deviation calculated for each result.

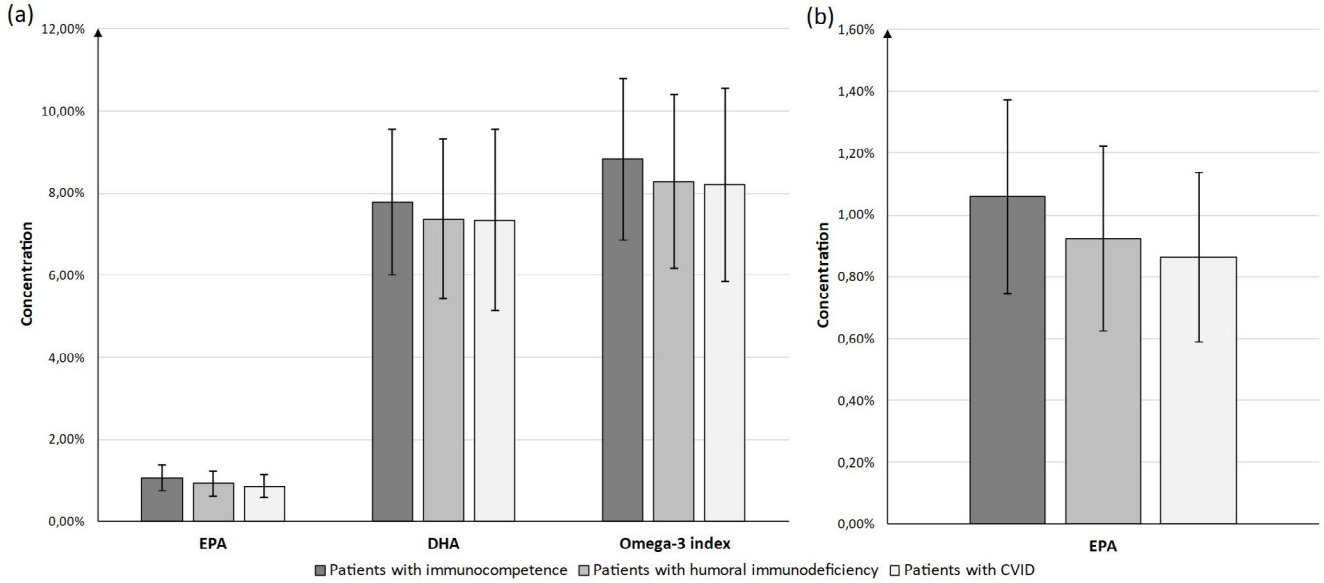
and 13.3 times per month, respectively. The second most common omega-3 source was canola oil, which was used for food preparation 7.5 times per month in the immunodeficiency group and 10.1 times per month in the immunocompetent group. Other significant sources of omega-3 fatty acids included fish, which were consumed by participants with immunological disorders 2.7 times per month and 4.8 times per month by immunocompetent participants and additionally olive oil, which was added 2.3 and 6.2 times per month, respectively. Gathered data suggests that, in general, people without immunodeficiency were more likely to consume products rich in omega-3 acids.

Discussion and conclusions

The findings from this study suggest that people with humoral immunodeficiencies and with common variable immunodeficiency (CVID) in particular, might have decreased levels of omega-3 fatty acids: EPA and DHA compared to immunocompetent people. There was no evidence of a statistically significant difference in concentration of EPA and DHA between compared groups, except from one age group in terms of EPA. Nevertheless, there was a trend for the immunodeficient patients to have reduced EPA concentration in comparison with the control group (**figure 2**), especially pronounced within the CVID group.

Those findings are similar to the results of the study performed by Skarpengland *et al.* (17). In the study, 39 CVID patients and 30 healthy controls had plasma fatty acids measured and gut microbial profile defined. The researchers observed potentially unfavorable fatty acid profiles in CVID patients with decreased levels of EPA, DHA and anti-inflammatory index in blood plasma. Those changes were linked with gut microbial composition and were alternated by a 2-week course of treatment with rifaximin, suggesting a potential correlation between gut microbiota and

***Figure 2** - Overall results of EPA, DHA and omega-3 index measurements with standard deviation error bars.*



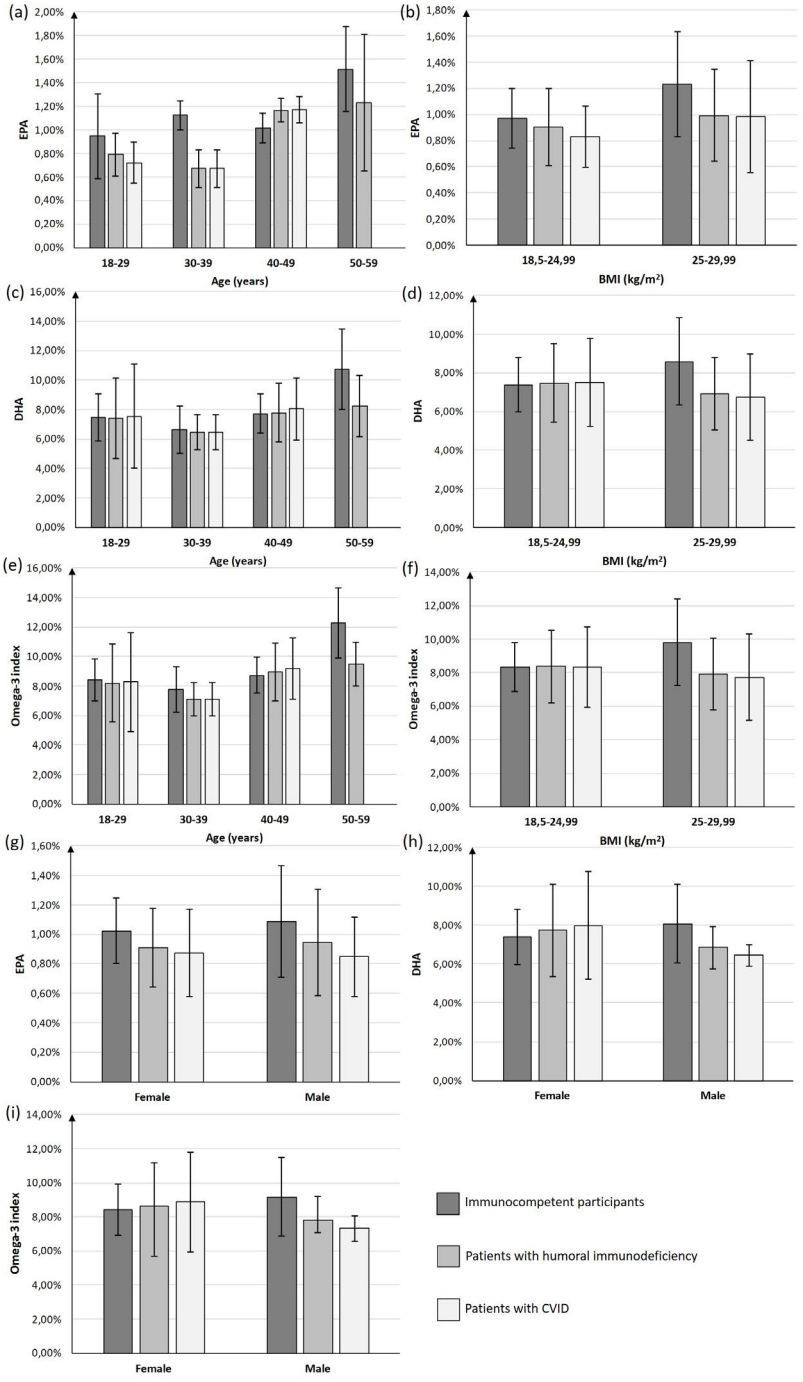
(a) Comparison of overall EPA, DHA concentrations and omega-3 index between immunocompetent participants, patients with humoral immunodeficiencies and patients with CVID. Scale adjusted to show the difference between EPA and DHA levels and their effect on omega-3 index values. **(b)** Zoomed-in comparison of EPA results of immunocompetent participants, patients with humoral immunodeficiencies and patients with CVID.

polyunsaturated fatty acid levels in blood plasma. Analyzing currently available literature, no other research focused on the topic of omega-3 fatty acids in patients with primary immunodeficiencies with predominantly antibody defects was found. Considering the promising results of research on omega-3 fatty acids concentration in CVID, it might be worth conducting further research concentrating on the mentioned disorders. Considering the omega-3 index, a value > 8% is commonly associated with the greatest cardioprotection, whereas an index of < 4% is associated with the mean cardioprotective effect (18). In our study, only seven immunodeficient participants (37%) had a good level of omega-3 index cardioprotection (>8%), including 4 participants with CVID (29% of all CVID patients). Out of immunocompetent participants, 11 (61%) achieved an omega-3 index of > 8%. This difference suggests an increased risk of cardiovascular disease development in primary immunodeficient participants with predominantly antibody defects, however such conclusions on this topic require further research.

It is important to note that this study has some limitations. Most importantly, 50 participants initially recruited resulted ultimately in only 37 of them being included in data analysis. A relatively small number of participants might have resulted in the P-value being statistically insignificant, although visible trends (**figure 3**) may suggest otherwise. Moreover, rigorous inclusion criteria reduced the number of participants, however the criteria were supposed to eliminate nutritive disorders, children and elders. Unlike Skarpenglad *et al.* research (17), inclusion criteria included BMI values, which only allowed people to fall within the normal or overweight category (≥ 18.5 kg/m² and < 30 kg/m²) to participate and age (≥ 18 years and < 60 years). Another factor affecting the number of participants was the lack of widespread access to the omega-3 index value determination and its high cost. Furthermore, the questionnaire, despite the fact that it was primarily intended to gather demographic data and allow estimation of mean monthly consumption of omega-3 fatty acids, eventually only enabled the evaluation of the consumption frequency focused on products included within the questionnaire. Estimation of monthly omega-3 consumption was not possible due to discrepancies between products available on the market belonging to one category and the lack of average portion size consumed by each participant.

In conclusion, this pilot study suggests that the concentration of omega-3 fatty acids in people with primary immunodeficiencies with predominantly antibody defects and CVID, in particular, are slightly decreased, albeit not significantly, and mostly expressed in EPA concentration. However, further research on a larger scale is needed to determine potential discrepancies and implications of omega-3 concentration in humoral immunodeficiency before generalized conclusions may be drawn. This research has also shown that education is needed regarding the

Figure 3 *- Differences in blood omega-3 fatty acid concentrations, namely EPA, DHA and omega-3 index between immunocompetent individuals, patients with humoral immunodeficiencies and those with CVID depending on age, sex and BMI with marked standard deviation error bars.*



(a) EPA concentrations in different age groups of patients. **(b)** EPA concentrations in patients of normal weight and overweight. (**c**) DHA concentrations in different age groups of patients. **(d)** DHA concentrations in patients of normal weight and overweight. **(e)** Omega-3 index values in different age groups of patients. (**f**) Omega-3 index values in patients of normal weight and overweight. **(g)** Sex differences in EPA concentration. **(h)** Sex differences in DHA concentration. **(i)** Sex differences in omega-3 values.

effects and necessity of consuming products rich in omega-3 fatty acids, especially in patients with immunodeficiency.

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Contributions

KNB: conceptualization, data curation, investigation, funding acquisition, supervision, writing – original draft, writing – review & editing. BS: conceptualization, data curation, investigation, formal analysis, funding acquisition, visualization, writing – original draft, writing – review & editing. JL: conceptualization, investigation, funding acquisition, writing – original draft. ZB: supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Demographic and clinical characteristics of chronic histaminergic angioedema and chronic urticaria with angioedema: a multicenter Italian experience

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Key words

Chronic spontaneous urticaria; chronic histaminergic angioedema; angioedema; wheals.

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Impact statement

CHA may be distinguished from AE-CSU by considering comorbidities, frequency and site of angioedema attacks. As CSU is a heterogeneous disorder, differentiating its forms might improve prognosis and individualized treatment.

Summary

Background. *Chronic spontaneous urticaria (CSU) is a common disorder characterized by the recurrence of wheals and/or angioedema for more than 6 weeks. About 35% of patients experience wheals and angioedema (AE-CSU) and around 6% of patients only presents angioedema, also known as chronic histaminergic angioedema (CHA). As few data comparing CHA and AE-CSU are published, we analyzed the differences between demographic and clinical characteristics of these populations.* ***Methods.*** *A multicenter, observational, retrospective study, involving eight Allergology Centers in Lombardy, Italy, including 44 CHA and 34 AE-CSU pediatric and adult patients was performed. Data about sex, age, comorbidities, inflammatory markers, complement fractions, blood count, use of ACE inhibitors or angiotensin receptor blockers, site of angioedema attacks, therapy used to treat attacks, frequency of attacks at diagnosis, after 6 months of therapy and after 12 months of therapy were collected and analyzed.* ***Results.*** *A higher rate of atopy was found in AE-CSU than in CHA (58.8% vs 29.5%, $p = 0.01$). Hypothyroidism and antithyroid antibodies were more frequently detected in AE-CSU ($p < 0.05$). Face was the site majorly involved in both populations. Tongue angioedema was more reported in CHA than AE-CSU (22.7% vs 2.9%, $p = 0.019$). In CHA patients, upper airway involvement was reported mainly in male patients ($p = 0.02$). Monthly frequency of angioedema attacks at diagnosis was higher in AE-CSU than in CHA (2.1 vs 1.45, $p = 0.045$).* ***Conclusions.*** *Some characteristics may differentiate CHA from AE-CSU, as the latter experience higher rates of atopy, hypothyroidism and anti-thyroid antibodies positivity, as well as higher frequency of attacks and less tongue involvement.*

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Introduction

Angioedema is a self-limited swelling of subcutaneous and submucosal tissues due to increased vasopermeability (1). A recent classification divided angioedema syndromes into five types: mast cell-mediated, bradykinin mediated, vascular endothelium dysfunction, drug induced and unknown etiology (2). It is widely known that mast cell-mediated angioedema (AE-MC) might present in chronic spontaneous urticaria (CSU) (3), that is recurrent wheals and/or angioedema for more than 6 weeks (4). About 35% of patients with CSU feature angioedema with wheals (AE-CSU), whereas 6-10% of patients with CSU are characterized by angioedema without wheals (5, 6). The latter is also often termed as chronic histaminergic angioedema (CHA) (7-9). CHA is self-limiting and can be controlled by the administration of antihistamines, corticosteroids, adrenaline and/or omalizumab (10, 11). Several studies about CHA have been published in recent years (12-16) and some have looked at the clinical differences between patients with CHA and patients with AE-CSU (17-21). We performed a multicenter, observational, retrospective study in Northern Italy in order to assess the clinical and epidemiological features of patients affected by CHA and AE-CSU.

Materials and methods

The present study involved eight Allergology Centers in Lombardy, Italy, and included both pediatric and adult patients affected by CHA and AE-CSU. Pediatric patients were two in each group. Data were anonymized and every patient signed informed consent to participate in the study. Ethical approval was not required for this study involving anonymized clinical records collected retrospectively and analyzed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Patients presenting recurrent angioedema with or without wheals for more than 6 weeks, and whose angioedema attacks responded to antihistamines, corticosteroids and/or omalizumab were included. Low C1-inhibitor levels were considered an exclusion criterion.

Forty-four patients with CHA and thirty-four patients with AE-CSU were included. Recorded data included: a) comorbidities (allergies, cancer, infections, cardiovascular diseases, respiratory diseases, endocrinological diseases), b) use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), c) blood count, d) complement fractions, e) autoantibodies, f) inflammatory markers, g) location of attacks and frequency of attacks at the moment of diagnosis, after 6 months and after 12 months.

Every patient underwent a complete physical examination.

Statistical analysis was performed using SPSS Statistics version 29. Quantitative variables are reported as means with standard deviation in brackets. Comparisons were carried out using the Student t-test. Qualitative variables are reported as total number or percentage, and comparisons were carried out using the Fisher exact test or the Chi-squared test when appropriate. Values were interpreted as significant with $p < 0.05$.

Results

Study population demographics and characteristics

The mean age was slightly but not significantly higher in CHA than AE-CSU patients (53.3 *vs* 47.2 years). Median age was respectively 61 *vs* 49. The male/female ratio did not differ between the two populations (0.76 *vs* 0.7 in CHA and AE-CSU, respectively).

Atopy (allergic rhinitis, asthma or atopic dermatitis) prevailed in AE-CSU patients (58.8% *vs* 29.5%, $p = 0.01$), as did the prevalence of hypothyroidism (29.4% *vs* 11.4%, $p = 0.045$). As for other comorbidities, including Helicobacter pylori (HP) infection, no significant difference was detected. HP infections in both populations were treated with no angioedema and/or urticaria improvement. Population demographics and comorbidities are reported in **table I**.

In both populations most patients on ACEi and ARB were shifted to another drug (four CHA patients and four AE-CSU patients), except for one patient who was kept on ARB and another who was shifted from ACEi to ARB (both in the AE-CSU population). Nonetheless, no angioedema improvement was recorded after 6 months. No use of gliptins was reported.

In the CHA group one patient reported the occurrence of angioedema attacks with non-steroidal anti-inflammatory drugs (NSAIDs) and one patient reported physical activity (cholinergic angioedema) and emotional stress as triggers for the onset of angioedema attacks. In the AE-CSU group a case of exacerbation with NSAIDs and two cases of delayed pressure angioedema were noted.

Blood tests

Blood eosinophilia and blood markers are reported in **table I**. A significantly higher proportion of patients tested positive for anti-thyroid antibodies (anti-thyroperoxidase and anti-thyroglobulin) in the AE-CSU group compared to the CHA group (26.5% *vs* 6.8%, $p = 0.026$). The remaining parameters did not differ between the populations. In both groups thyroid autoantibodies were detected in female patients only (20.4% of patients in CHA and 35.3% of patients in AE-CSU); $p < 0.01$ *vs* male patients. Moreover, in both groups inflammatory markers were more elevated in the female population. In the CHA group, elevated ESR values, considering age and sex, were present only in the female population ($p < 0.05$). In the AE-CSU population, females showed more frequently elevated CRP and/or ESR than male patients (50% *vs* 7.1%; $p < 0.05$).

Table I *- Demographic characteristics, clinical features and blood markers of study populations.*

	CHA (n = 44)	CSU-AE (n = 34)	P-value
Sex n (%)			
Male	19 (43.2%)	14 (41.2%)	
Female	25 (56.8%)	20 (58.8%)	
M/F ratio	0.76	0.7	0.859
Age (years) mean (std)	53.3 (23.1)	47.2 (18.6)	0.217
Range	3-88	8-88	
Comorbidities n (%)			
Atopy (allergic rhinitis, asthma, atopic dermatitis)	13 (29.5%)	20 (58.8%)	**0.01**
Cardiovascular disease	11 (25%)	12 (35.3%)	0.323
Hypertension	10 (22.7%)	9 (26.5%)	0.703
Respiratory disease	1 (2.3%)	0	1.000
Endocrinological disease	10 (22.7%)	13 (38.2%)	0.136
Hypothyroidism	5 (11.4%)	10 (29.4%)	**0.045**
Helicobacter pylori infection	3 (6.8%)	5 (14.7%)	0.285
Recurrent urinary tract infections	4 (9.1%)	2 (5.9%)	0.691
Cancer	1 (2.3%)	1 (2.9%)	1.000
Eosinophilia n (%)	2 (4.5%)	1 (2.9%)	1.000
Autoantibodies n (%)*	9 (20.4%)	12 (35.3%)	0.143
ANA positivity	3 (6.8%)	4 (11.8%)	0.693
Anti-thyroid antibodies	3 (6.8%)	9 (26.5%)	**0.026**
Anti-phospholipid antibodies	1 (2.3%)	0	1.000
Anti-mitochondrial antibodies	2 (4.5%)	0	0.502
Anti-centromere antibodies	0	1 (2.9%)	0.436
CRP n (%)**			
Elevated values	8 (18.2%)	8 (23.5%)	0.562
ESR n (%)	10 (22.7%)	7 (20.6%)	0.821
Elevated values			
Location of attacks n (%)***			
Face	42 (95%)	32 (94%)	1.000
Tongue	10 (22.7%)	1 (2.9%)	**0.019**
Pharyngolaryngeal	10 (22.7%)	5 (14.7%)	0.373
Upper limbs	6 (13.6%)	5 (14.7%)	0.893
Lower limbs	6 (13.6%)	5 (14.7%)	0.893
Genitalia	2 (4.5%)	4 (11.8%)	0.395
Frequency of attacks per month (std)			
At diagnosis	1.45 (0.93)	2.1 (1.82)	**0.045**
At 6 months (n=35 for CHA, n=30 for CSU-AE)	0.58 (0.39)	0.44 (0.63)	0.291
At 12 months (n=33 for CHA, n=26 for CSU-AE)	0.27 (0.45)	0.39 (0.72)	0.078
Therapy n (%)			
Antihistamines	44 (100%)	34 (100%)	1.000
Corticosteroids	15 (34.1%)	12 (35.3%)	0.912
Omalizumab	6 (13.6%)	6 (17.6%)	0.626
Tranexamic acid	4 (9.1%)	2 (5.9%)	0.691
Hydroxychloroquine	0	1 (2.9%)	0.436

*Autoantibodies positivity only in female patients (*vs* male patients, $p < 0.01$); **elevated values mostly in female patients ($p < 0.05$); ***upper airway involvement mostly in male patients in CHA ($p < 0.05$). Std: standard deviation; n: number of patients. Bold: statistically significant.

D-dimer was not measured systematically in this study; one female patient in the CHA group reported an elevated D-dimer value (597 µg/L) during an angioedema attack-free period.

Characteristics of angioedema attacks and therapy

The most frequent location of angioedema attacks was face (95% in CHA patients and 94% in AE-CSU patients). Tongue angioedema was significantly more frequent in the CHA group than in the AE-CSU group (22.7% *vs* 2.9%, p = 0.019). No significant differences between the two groups were recorded for other locations. One abdominal attack was reported by a patient in the AE-CSU group. In the CHA population, the upper airway involvement affected more men than women (50% *vs* 16%, p = 0.02). No deaths were recorded.

Regarding the frequency of angioedema attacks at the time of diagnosis, the AE-CSU group reported a higher mean frequency of attacks than the CHA group [2.1 (± 1.82) *vs* 1.46 (± 0.93) attacks/month (p = 0.045), respectively]. We also considered the frequency of attacks after 6 months and after 12 months of therapy. We could not collect data from all patients, as, at the time of data collection, some were newly diagnosed and others were lost to follow-up. At both 6 months and 12 months, no statistically significant difference was detected between the two groups, who reported similar mean monthly attack frequencies. Data about attack locations and frequency of attacks are reported in **table I**.

As shown in **table II**, in the AE-CSU group the mean monthly frequencies of attacks in patients with or without cardiovascular comorbidity were significantly more frequent in the former [3.19 (± 2.46) *vs* 1.51 (± 0.99), respectively; p = 0.008]. No difference regarding angioedema locations was detected.

No differences in attacks frequency were recorded by sex, age, atopy, autoimmunity, other comorbidities, or inflammatory markers.

100% of patients in both populations were prescribed antihistamines, on demand (11.9% in CHA and 8.8% in AE-CSU) for less symptomatic patients or continuously up to fourfold the standard dose. Exactly 35.3% of patients in the AE-CSU group and 34.1% of patients in the CHA group used short oral corticosteroid courses on demand in addition to preventive therapy.

As some patients did not achieve disease control (similar attack frequency and impactful symptoms on daily life) with antihistamines, therapy was implemented with omalizumab, tranexamic acid or hydroxychloroquine in 26.5% of AE-CSU patients and in 22.7% of CHA patients.

The frequency of angioedema attacks in patients treated with antihistamines alone or in association with corticosteroids and patients who implemented their therapy with omalizumab, tranexamic acid or hydroxychloroquine was compared. As displayed in **table III**, a significant difference was found within the CHA population, as the former group experienced less attacks at diagnosis (1.27 *vs* 2.1, p = 0.011) and at 12 months (0.18 *vs* 0.57, p = 0.028). One patient on omalizumab did not optimally respond to such prophylactic therapy, however, no attempt at increasing the dose was tried. No significant difference was found in the AE-CSU population. No significant difference in response between omalizumab, tranexamic acid and hydroxychloroquine evaluated singularly was recorded.

Table II *- Frequency of attacks per month between CSU-AE patients with cardiovascular comorbidity and CSU-AE patients without cardiovascular comorbidity.*

	Patients with cardiovascular comorbidity	Patients without cardiovascular comorbidity	P-value
Frequency of attacks per month (std)			
At diagnosis	3.19 (2.46)	1.51 (0.99)	**0.008**
After 6 months	0.68 (0.81)	0.29 (0.42)	0.092
After 12 months	0.39 (0.89)	0.37 (0.60)	0.925

Std: standard deviation. Bold: statistically significant.

Table III *- Frequency of attacks per month between CHA patients treated with antihistamines with/without corticosteroids and CHA patients treated with omalizumab or tranexamic acid.*

	Antihistamines with/without corticosteroids	Omalizumab or tranexamic acid	P-value
Frequency of attacks per month (std)			
At diagnosis	1.27 (0.84)	2.1 (0.94)	**0.011**
After 6 months	0.56 (0.39)	0.64 (0.43)	0.664
After 12 months	0.18 (0.28)	0.57 (0.72)	**0.028**

Std: standard deviation. Bold: statistically significant.

Discussion and conclusions

Chronic histaminergic angioedema is a common form of recurrent angioedema without wheals (3, 10). The treatment is the same recommended for CSU, with response to antihistamines and/or omalizumab (though not specifically licensed for CHA) as a means to diagnosis (4, 11). Some data providing new insights into clinical features and highlighting the differences between CHA and AE-CSU have been recently published (17-19, 21).

In our series, the male/female ratio did not differ between the two populations, with a higher female prevalence, as previously observed (12, 13, 20) but that was lower than the one reported for CHA by Faisant *et al*. (14) and Zajac *et al*. (15). Other authors found a significantly higher male/female ratio in CHA than in AE-CSU (18, 19, 21). As a matter of fact, considering all types of CSU, female patients are almost two times more frequent than male patients (22-24). Mean age was slightly older in CHA than in AE-CSU, unlike previous reports (18, 21).

Atopy was significantly more prevalent in AE-CSU patients. Some previous studies (15, 16), but not others (18-21), reported a higher prevalence of atopic disorders in CHA.

Most patients on treatment with either ACEi or ARB did not show any improvement after withdrawal of these drugs. Along with the good response to antihistamines and corticosteroids recorded, we concluded these patients were not affected by drug-induced angioedema. This highlights the difficulty of the differential diagnosis between drug-induced and histaminergic angioedema (25).

In our study, autoantibodies were detected in females patients only ($p < 0.01$), which is not surprising, as females are more at risk of autoimmune diseases (26). However, no systemic autoimmune diseases were reported. AE-CSU patients reported a significantly higher prevalence of hypothyroidism and antibody positivity than CHA patients. Although this was not recorded in other studies (18-21), CSU as a whole is frequently associated with thyroiditis and anti-thyroid antibodies (5, 6). ANA showed the same prevalence as the general population (27) and that found by other authors (19, 20), but lower than that found by others (18). CRP and/or ESR were elevated in 22.7% of CHA patients *vs* 32.4% of AE-CSU patients, mostly in females ($p < 0.05$). Previous studies suggested that in CSU, ESR levels correlate with disease severity (28), but we were unable to confirm this observation. This result might imply an elevated level of immune activity and inflammation (18).

The face was the most involved site of angioedema in almost all patients in both groups (14-16, 18-21, 29) but we recorded a significantly more frequent involvement of tongue in CHA than in AE-CSU ($p = 0.019$) (18, 21). In the CHA population a male prevalent involvement of upper airways was observed ($p = 0.02$), which supports the finding of a French group (14). An unusual case of abdominal attack was recorded in AE-CSU. Although abdominal angioedema is predominantly reported in hereditary angioedema syndromes, rare cases of abdominal involvement are also described in histaminergic angioedema (30, 31).

We found a higher mean monthly frequency of attacks at diagnosis in AE-CSU than in CHA, confirming a more severe phenotype of disease in AE-CSU than in CHA patients (17, 20, 21). Such difference was lost at 6 months and 12 months suggesting the effectiveness of the therapeutic intervention.

In AE-CSU patients, those affected by cardiovascular diseases (mainly hypertension) showed a higher prevalence of attacks at diagnosis. Buttgereit *et al*. reported a higher occurrence of metabolic diseases in patients affected by angioedema (21), and hypertension and metabolic disorders are frequent comorbidities in CSU (32, 33) that can be associated with a more severe disease (34). Since evidence suggests that CSU is characterized by systemic inflammation (35), it could be hypothesized that the additional inflammation caused by cardiovascular diseases may contribute to a more severe disease phenotype.

In both groups some patients did not respond optimally to antihistamine prophylactic treatment. Although short cycles of corticosteroids may be beneficial to the control of the disease (36), prolonged treatments with corticosteroids should be avoided, particularly in relatively young populations. Thus, the use of other preventative treatments should be considered. In CHA, attacks were significantly more frequent in those requiring an additional treatment at diagnosis ($p = 0.011$) and after 12 months ($p = 0.028$). No associations with biomarkers or comorbidities were detected.

It should be stated that, as omalizumab is recommended for CSU (4), the use of tranexamic acid and hydroxychloroquine may lie on single centers' experience. Overall, satisfactory responses were observed across all therapeutic groups: antihistamine prophylaxis, tranexamic acid, hydroxychloroquine and omalizumab. Only one patient reported almost no response to omalizumab, recording after one year a similar attack frequency to that of diagnosis. As recently stated by Zuberbier *et al*., the need for personalized treatment and disease-modifying drugs in CSU is still relevant (37). As a matter of fact, the current use of the term AE-MC highlights the contribution of mast cells' mediators (2). A recent review clarified the effect that mast cell degranulation exerts on the contact system, since degranulated heparin and polyanions may contribute to the activation of factor XII (38). In addition, the latest description of higher activation of the contact system in idiopathic angioedema (39) suggests a possible much larger role of the contact system in different types of angioedema. Importantly, the activation of the intrinsic coagulation pathway may contribute to CSU pathogenesis (40), remarking the inhibitory effect of tranexamic acid.

The limitations of this study are its retrospective nature, as some clinical information may be inaccurate and some patients were lost to follow-up, as well as the limited number of patients. No activity scores were employed, and total IgE values were not available for every patient.

Diagnosing CHA requires a clinical approach based mainly on response to treatment to antihistamines, corticosteroids and/or omalizumab. Understanding demographic and clinical features may be of help to diagnose such condition and to provide the right therapy, since CHA is considered part of CSU.

When differentiating CHA from AE-CSU, some characteristics are more typically found in the former group as distinguishable features: higher male prevalence, older age, lower prevalence of hypothyroidism and anti-thyroid antibodies, tongue involvement, upper airways involvement in male patients, lower frequency of attacks, reduced signs and symptoms of atopy. Overall, prognosis is reassuring.

As diseases often have various presentations, it could be stated that CSU is a protean disorder with heterogeneous forms, ranging from only wheals to isolated angioedema (41). Thus, efforts pointing to characterize phenotypes and to a better understanding of the whole spectrum of CSU remain relevant.

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Contributions

SS: data curation, investigation, formal analysis, writing – original draft. FR: conceptualization, methodology, writing – original draft, supervision. AT: investigation, writing – review & editing. GM, MP, AMM, FC, MRY, SN, LM, VL, AS, VP: investigation. RA: validation, visualization, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Challenges in egg allergy: a retrospective look at the utility of cut-off values

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Key words

Egg allergy; IgE cut-offs; oral food challenges; pediatric allergy.

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To the Editor,

egg allergy is a prevalent and clinically significant condition in pediatric populations, demanding precise diagnostic procedures like oral food challenges (OFCs) (1, 2). The European Academy of Allergy and Clinical Immunology (EAACI) has formulated distinct IgE cut-off values to refine patient selection regarding OFCs with both baked (BE) and cooked egg (CE) forms (3). Considering the EAACI guideline cut-offs, as well as the systematic review presented at FAAM 2022, a retrospective analysis was conducted to evaluate the results of pediatric OFCs performed from 2015 to 2022 within our Allergy Department. Specific IgE cut-off values for ovomucoid (OVM) (0.8kU/L) and egg white protein (EWP) (3.8 kU/L for CE and 8.0 kU/L for BE) were compared to the OFCs outcomes. Demographics, clinical data and IgE levels to different egg proteins were also collected. A total of 70 children were included, predominantly males (57.1%), with a median age of the index reaction at 1.67 years (IQR 1-3).

Table I *- Demographic and clinical data.*

Variables	Total (n = 70) (n %)
Male gender	40 (57.1)
Age (years), median	1.67 (IQR 1-3)
Patients with onset reaction to cooked egg	55 (78.6)
Reported symptoms	52 (74.3)
Mucocutaneous	36 (51.4)
Exanthema/urticaria/angioedema	16 (22.9)
Eczema exacerbation	27 (38.6)
Gastrointestinal	8 (11.4)
Respiratory	15 (21.4)
Anaphylaxis	
Rhinitis/rhinoconjunctivitis	53 (75.7)
Atopic dermatitis	45 (64.3)
Asthma/ recurrent wheezing	37 (52.3)
Concomitant Cow milk allergy	22 (31.4)

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Table II *- Results of egg oral food challenges.*

Categorical variables (n; %) / Numerical variables (median - IQR)	Egg OFCs (n = 87)							
	Cooked (n = 49; 56.3%)				Baked (n = 38; 43.7%)			
	Total (n = 49;100)	Positive (n = 6;12.2)	Negative (n = 43;87.8)	P-value	Total (n = 38;100)	Positive (n = 6;15.8)	Negative (n = 32;84.2)	P-value
Age at Egg OFC (years)	6.67 (4-10)	10.5 (4.17-11.53)	6.33 (4-9.33)	0.547	7.63 (5-9)	5.08 (4.25-7.00)	8.16 (5.92-11.5)	0.060
Age of IgE measurement (years)	5.5 (3-10)	10 (4-11)	5 (3-9)	0.182	7 (4-9)	4.5 (3-7)	7.62 (0.069)	0.069
Time from IgE measurement to OFC (years)	0.5 (0.2-0.8)	0.25 (0.17-0.5)	0.5 (0.25-0.92)	0.182	0.75 (0.2-1)	0.25 (0.17-1.17)	0.92 (0.12-1.00)	0.669
Time from index reaction to OFC (years)	4.25 (0.92-8)	7.50 (3-8.33)	4.25 (0.67-7)	0.349	4.12 (3-7.33)	3.46 (1.33-4)	5.12 (3.12-8.08)	0.095
IgE to egg white (EWP) (k/UI)	0.91 (0.32-2.37)	1.95 (0.65-2.57)	0.83 (0.32-2.28)	0.248	1.26 (0.57-5.56)	4.82 (0.51-12.1)	1.23 (0.57-4.70)	0.385
IgE to ovomucoid (OVM) (k/UI)	0.30 (0.04-1.26)	1.88 (0.76-3.46)	0.19 (0.04-1.09)	**0.005**	0.82 (0.24-1.85)	4.46 (0.45-11.7)	0.74 (0.18-1.68)	0.074
Total IgE (k/UI)	141 (37-885)	1070 (508-1770)	134 (29-565)	**0.041**	413 (106-1675)	340 (72-556)	418 (108-1834)	0.464
Children with IgE to EWP above the cut-off * n (%)	7 (14.3)	1 (16.7)	6 (14.0)		4 (10.5)	3 (50.0)	1 (3.1)	
Children with IgE to EWP below the cut-off *n (%)	42 (85.7)	5 (83.3)	37 (86.0)		34 (89.5)	3 (50.0)	31 (96.7)	
Children with IgE to OVM above the cut-off (0.8 kU/L) n (%)	17 (34.7)	4 (66.7)	13 (30.2)					
Children with IgE to OVM below the cut-off (0.8 kU/L) n (%)	32 (65.3)	2 (33.3)	30 (69.8)					
Children with IgE to EWP and OVM both IgEs above the cut-off n (%)	6 (34.7)	2 (33.3)	4 (9.3)					
Children with IgE to EWP and OVM both below the cut-off n (%)	30 (34.7)	2 (33.3)	28 (65.1)					

*Egg white cut-offs: cooked – 3.8 kU/L; baked – 8.0 kU/L; statistically significant in bold ($p < 0.050$); EWP: egg white protein; IQR: interquartile range; OFCs: oral food challenges; OVM: ovomucoid.

Concerning the spectrum of egg forms, the majority of reported reactions occurred with CE (n = 55; 78.6%).
The most frequently reported manifestations were mucocutaneous symptoms (74.3%), mostly exanthema, urticaria and angioedema, with 22.9% experiencing eczema exacerbation after food intake. Gastrointestinal symptoms were observed in 38.6% of cases, whereas respiratory manifestations were reported in 11.4%. Fifteen children (21.4%) presented with anaphylaxis.
Among our cohort, 75.7% had rhinitis/rhinoconjunctivitis; 64.3% atopic dermatitis and 52.3% asthma/recurrent wheezing. Additionally, 31.4% had a history of coexisting confirmed or suspected cow's milk allergy. Demographic and clinical data are represented in **table I**.
Overall, 87 OFCs were conducted (1.2/children), of which 56.3% were with CE and 43.7% with BE, with a total of 12 (13.8%) positive OFCs. Among positive OFC cases, mucocutaneous symptoms were prevalent (n = 9, 75.0%), with gastrointestinal symptoms reported in 3 cases (25.0%), and respiratory symptoms in 2 (16.7%). Only one child (8.3%) reacted after reaching cumulative dosage (~20 g) in the OFC protocol, with 91.7% reacting mid-OFC.
Symptoms in 10 out of the 12 positive OFC cases (83.3%) aligned with the index-reaction, though none progressed to an anaphylactic reaction.
Regarding CE OFCs, 12.2% of children had a positive OFC; 83.3% of children with positive OFCs exhibited sIgE levels to egg white below the cut-off, while 33.3% had OVM sIgE below the threshold. Conversely, 14.0% of negative OFCs exceeded the EWP sIgE cut-off, and 30.2% exceeded the OVM cut-off. In OFC with both sIgE levels below the cut-offs, 33.3% were positive and 65.1% were negative.
In the BE OFCs there were 15.8% of positive challenges, 50.0% of which had EWP sIgE levels above 3.8 kU/L, while only 3.1% of negative OFC exceeded this cut-off. Results are shown in **table II**.
Among all CE OFCs, elevated OVM sIgE and total IgE levels were indicative of a positive OFC. Notably, these associations remained statistically significant in the sub-group of the 42 CE OFCs with EWP sIgE below the cut-off. No correlation was found between OFCs outcomes, in both BE and CE forms, regarding gender, median age of allergy onset, clinical presentation or personal history of atopy.
Predictors of OFC outcomes play a pivotal role in refining diagnostic accuracy in pediatric allergy (3, 4). This analysis underscores the importance of a comprehensive approach to egg OFC, highlighting the value of complementary testing, including diverse egg protein-specific IgE measurements in enhancing decision-making (5, 6).
The use of a single EAACI cut-off to predict OFC results lead to large proportions of patients yielding contradicting results. Conversely, the integration of dual IgE cut-offs in CE OFCs showed significant value.
Notably, higher OVM sIgE levels associated with positive OFC with CE among children with EWP IgE levels below the cut-off, further reinforcing the value of this complementary approach.
Additionally, integrating skin tests (which also have EAACI cut-offs) in future studies could further enhance the accuracy of predicting egg OFC outcomes (3, 7).
Nevertheless, the varying cut-off values among populations underscore the necessity for customized thresholds, taking into account comorbidities, IgE trends, and national considerations, while never undermining the role of OFCs as the definitive diagnostic test in determining food allergy status.
Systematic longitudinal analysis of the application of the EAACI cut-offs would be instrumental for refining diagnostic approaches and advancing the management of this prevalent pediatric condition.

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Contributions

PBA, HPP: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. IC: conceptualization, formal analysis, resources, supervision. GL: formal analysis, resources, supervision. IF, ML, TF: data curation, investigation. ATB: resources, supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Gabriele Di Lorenzo

Clinical terminology and biological mediators in allergology: why biomarkers do not define a syndrome

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Key words

Defensins; pollen-food syndrome; clinical terminology; biomarkers; precision medicine.

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To the Editor,

the present letter is prompted by the recent introduction in the scientific literature of molecular designations, such as "defensin syndrome" or "defensin-related allergy syndrome", to describe clinical presentations that are already well-characterized under established nosological categories. The term "defensin-related allergy syndrome" was first introduced by Cosi and colleagues to denote a novel type of cross-reactive IgE-mediated allergy involving plant defensin-like proteins (1). The terminological and methodological appropriateness of such designations warrants critical scrutiny.

Clinical medicine rests on a methodological principle that has accompanied the development of modern medicine since its origins: the precision of scientific language. Medical terminology is not merely a descriptive tool; it constitutes one of the fundamental elements through which medicine organizes knowledge, defines pathological entities, and ensures the coherence of clinical reasoning. In an era characterized by a remarkable expansion of biological and molecular knowledge, the relationship between clinical language and scientific understanding assumes even greater relevance.

Over recent decades, clinical allergology has benefited substantially from advances in molecular immunology. The structural characterization of allergens, the identification of novel allergenic protein families, and the development of molecular diagnostics have considerably deepened our understanding of the pathogenetic mechanisms underlying allergic diseases – achievements that represent a cornerstone of modern precision medicine.

At the same time, however, the growing availability of molecular information raises a methodological question of considerable importance: how biological knowledge can be correctly integrated into the language and conceptual categories of clinical medicine. In particular, it is essential to avoid the inappropriate transformation of biological mediators or biomarkers into clinical definitions.

Among the foundational terms in the tradition of internal medicine is the concept of syndrome, which denotes a recognizable cluster of signs and symptoms that tend to present with a degree of consistency, thereby constituting a defined clinical picture.

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Although a syndrome may be associated with specific pathogenetic mechanisms or with particular laboratory findings, its definition remains intrinsically clinical, deriving from the systematic observation of the patient and from the integration of historical, clinical, and diagnostic data (2).

This distinction between clinical observation and biological description is particularly relevant in the era of molecular medicine. Biomarkers serve as indicators of biological or pathogenetic processes and may have diagnostic, prognostic, or therapeutic utility. Nevertheless, they do not automatically coincide with clinical entities. As emphasized in the translational medicine literature, biomarkers must be interpreted within the clinical context and cannot substitute for the clinical definition of disease (3).

An instructive example concerns defensins, a family of small cationic antimicrobial peptides that are principal effectors of innate immunity, produced by neutrophils and epithelial cells, with both direct antimicrobial and immunomodulatory properties (4-6). Defensin-like proteins are also present in the plant kingdom, where they serve defense functions and may act as allergens, participating in IgE-mediated sensitization in humans (7).

The clinically best-characterized syndrome involving plant allergenic proteins is the pollen-food syndrome, in which individuals sensitized to pollens develop allergic reactions upon ingestion of specific plant-derived foods through cross-reactive IgE epitopes (8); celery allergy associated with pollen sensitization, involving lipid transfer proteins and other plant defense proteins, is a well-documented example (9).

The fact that certain plant proteins belong to the defensin family constitutes an interesting and scientifically valid biological observation. It does not, however, justify the introduction of a clinical definition based solely on the presence of a specific biological molecule. The use of the expression defensin syndrome to describe clinical presentations of food allergy associated with pollen sensitization is therefore methodologically inappropriate. Such conditions are already clearly classified in the scientific literature under the well-established category of pollen-food syndrome – a clinically defined syndrome characterized by the relationship between pollen sensitization and allergic reactions to specific plant-derived foods.

This is not a matter of mere terminological detail. The clarity of scientific language is an essential component of the quality of scientific communication and of the methodological coherence of clinical medicine. Clinical allergology, having developed historically within the tradition of internal medicine, has always grounded its strength in the integration of clinical observation, laboratory data, and biological knowledge. In the era of precision medicine, preserving terminological precision and conceptual rigor becomes even more imperative: biological mediators are indispensable for understanding pathophysiological processes, but the definition of clinical entities continues to rest on the systematic observation of the signs and symptoms that characterize disease in the patient. We therefore propose that the naming of clinical syndromes in allergology should continue to be grounded in phenotypic and clinical criteria, reserving molecular nomenclature for the characterization of specific sensitization profiles within established diagnostic frameworks.

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Contributions

GDL contributed entirely to this work.

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LETTER TO THE EDITOR

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Luiza Salvador Schmid, Carolina Sanchez Aranda, Lara Novaes Teixeira, Rafaela Rola Leite Guimarães, Dirceu Solé, Gustavo F. Wandalsen

Stress in Brazilian patients with Inborn Errors of Immunity during the SARS-CoV-2 pandemic

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Key words

COVID-19; SARS-CoV-2; inborn errors of immunity; pandemic; stress.

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To the Editor,

the COVID-19 pandemic severely impacted vulnerable IEI patients (1). To assess the impact is this specific population, an online stress questionnaire was administered to individuals with IEI at two time points during the pandemic: May-June 2020 and May-June 2021. All patients with IEI met the diagnostic criteria of the European Society for Immunodeficiencies, received ongoing care at a specialized immunology center, and were aged 12-80 years. A control group (CG) participated by completing the PSS-4 during the second assessment period (May-June 2021). The CG consisted of healthy individuals aged 18-45 years. Informed consent was obtained from all study participants.

Stress levels were assessed using the abbreviated four-item version of the Perceived Stress Scale (PSS-4; Portuguese version) (2). The maximum score is 16; higher scores indicate higher stress levels. One hundred and one IEI patients completed both questionnaires. The mean age was 30.5 years, 64% being women. Predominantly antibody defects were present in 80 patients (80.8%). Most participants were adolescents (39.6%), and adults aged 20 to 44 years (33.7%). **Table I** displays the clinical diagnoses and general characteristics of the IEI patients and their perceptions of the COVID-19 pandemic at the initial assessment period.

The mean IEI PSS-4 score was high during both assessments (8.85 ± 2.23 at the first assessment and 8.93 ± 2.14 at the second), showing no significant difference between them. No difference between them. No significant differences related to sex and age were observed, however adolescents showed non-significantly higher PSS-4 means. Additional findings are presented, and the mean PSS-4 score for each IEI group are presented in **table II**.

One hundred and one healthy individuals completed the PSS-4 in 2021, with a mean age of 24.3 years, and the majority were women (64%). The CG reported a mean PSS-4 score of 7.30 ± 1.23. The CG reported a mean PSS-4 score of 7.30±1.23, values significantly lower than the EII group (p = 0.00). Comparisons between the mean PSS-4 CG and each EIE group are shown in **table II**.

Data on COVID-19 in patients with IEI started to surface by the end of 2020. Goudouris *et al.* reported a mortality rate in patients with IEI reaching 5% (3): twice as high as the average mortality rate observed in the Brazilian population (4). Never-

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Table I *- General features of the patients with IEI studied and their perceptions about the Coronavirus pandemic at the beginning time.*

Knowledge about the existence of the Coronavirus	100.0%
Clinical diagnosis	
CVID	46.4%
Agammaglobulinemia	4.0%
Other humoral deficiencies*	30.3%
Combined immunodeficiency	12.1%
Immune dysregulation	9.0%
IVIG monthly	94.0%
Antibiotic prophylaxis	40.6%
Maintain regular treatment	37.6%
Had been hospitalized in a ward >3 times	53.5%
Had been in an ICU at least once in their lifetime	33.6%
Recognize the symptoms of SARS-CoV-2 infection	71.3%
Recognized protective measures	93.1%
Washing your hands with soap and water works just like using 70% alcohol gel	88.1%
Fear of getting sick	90.1%
Fear of a family member becoming ill	98.0%
Do you know someone who fell ill with COVID	64.4%
Became more scared after learning that an acquaintance had become ill	51.5%
Patients with IEI are at higher risk of becoming infected	96.0%
Believe you can become infected without regular treatment	92.1%
Anxiety	
Normal, how I always felt before	13.9%
Anxious/distressed, but not afraid	32.7%
Anxious/distressed and afraid	41.6%
Very afraid	11.9%
Fear to die	
Never had	17.8%
I was afraid before, but without compromising my QoL	20.8%
I was afraid before, to the detriment of QoL	11.9%
I started to be afraid due to the coronavirus	30.7%
Always had	18.0%

First questionnaire assessment; n = 101. IVIG: Intravenous Human Immunoglobulin; ICU: Intensive Care Unit; CVID: common variable immunodeficiency. *Polysaccharide antibody deficiency (SAD), hypogammaglobulinemia, IgA deficiency and IgG subclass deficiency.

theless, no data were found that evaluated stress perception in this patient cohort using the PSS-4.

Pandemic-era studies using the PSS-4 revealed diverse stress levels across populations. Zhao *et al*. reported a mean PSS-4 score of 8.39 ± 2.33 in physicians presenting with symptoms consistent with irritable bowel syndrome (5). Steel *et al*. identified cancer patients with significantly elevated PSS-4 scores compared to normative data (6). Pham *et al.* suggested that stress adversely affected patients with rheumatoid arthritis (7). In contrast, stud-

Table II *- Perceived Stress Scale (PSS-4) items in the two assessments in patients with inborn errors of immunity and the PSS-4 average by diagnosis and comparison with control group (n = 101).*

	1a. Assessment (%)	**2a. Assessment (%)**	**P-value**
In the last month, how often have you felt that you were unable to control the important things in your life?			**0.030**
Never	4.0%	5.9%	
Almost never	20.8%	6.9%	
Sometimes	24.8%	38.6%	
Fairly often	22.8%	12.9%	
Very often	27.7%	35.6%	
In the last month, how often have you felt confident about your ability to handle your personal problems?			0.418
Never	5.9%	14.9%	
Almost never	15.8%	8.9%	
Sometimes	23.8%	22.8%	
Fairly often	19.8%	14.9%	
Very often	34.7%	38.6%	
In the last month, how often have you felt that things were going your way?			0.653
Never	6.9%	5.9%	
Almost never	3.6%	29.7%	
Sometimes	24.8%	31.7%	
Fairly often	24.8%	20.8%	
Very often	6.9%	11.9%	
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?			0.405
Never	3.0%	6.9%	
Almost never	11.9%	6.9%	
Sometimes	21.8%	24.8%	
Fairly often	24.8%	17.8%	
Very often	38.6%	43.6%	

→

n (%)	PSS-4		
	1a. Assessment#	2a. Assessment#	P-value
PSS-4 score			
Total IEI; 101 (100)	8.85 ± 2.23	8.93 ± 2.14	0.769
PSS-4 by diagnosis			
CVID; 46 (46.4)	8.87 ± 2.28	8.80 ± 2.26	0.891
Humoral deficiencies$^{\gamma}$; 34 (33.6)	8.73 ± 1.83	9.18 ± 2.02	0.421
Combined immunodeficiencies; 2 (12.1)	10.18 ± 2.04	9.00 ± 2.04	0.253
Comparison of controls and IEI at 2a. Assessment	**Controls# (n = 101)**	**IEI# (n = 101)**	
Mean PSS-4 score	7.30 ± 1.23	8.93 ± 2.14	**0.000**
Comparison of controls to each specific IEI group			
CVID (n = 46)		8.80 ± 2.26	**0.009**
Humoral deficiencies$^{\gamma}$ (n = 34)		9.18 ± 2.02	**0.001**
Combined immunodeficiencies (n = 12)		9.00 ± 2.04	**0.015**
Immune dysregulation (n = 9)		8.00 ± 2.00	0.328

Descriptive level of the McNemar test was used for P-values; γ: polysaccharide antibody deficiency (SAD), hypogammaglobulinemia, agammaglobulinemia, IgA deficiency and IgG subclass deficiency; IEI: Inborn errors of immunity; CVID: common variable immunodeficiency. #Mean (± SD).

ies of individuals without reported comorbidities revealed mean PSS-4 scores of 6.31 in Australians (8) and 7.00 in young Americans (9).

Our data clearly show that EII patients had higher levels of stress than controls. Interestingly, when individual IEI subgroups were compared to the CG, statistically significant differences were observed in all but the immune dysregulation subgroup (**table II**). Despite extensive efforts to mitigate the COVID-19 pandemic, our findings demonstrate elevated stress levels among individuals with IEI during that period. This study highlights the critical need to identify patients experiencing heightened perceived stress during crises. Future research is warranted to elucidate this association and optimize management strategies to enhance overall patient care.

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Contributions

All authors: conceptualization, formal analysis, methodology, writing – review & editing. LSS, DS, GWF: data curation. LSS, CSA, DS, GWF: funding acquisition. LSS: investigation, writing – original draft. LSS, CSA: project administration, validation, visualization. LSS, CSA, LNT, DS, RRLG, GWF: supervision. RRLG, GWF: validation. DS: project administration. GFW, DS, LSS, CSA: resources.

Conflict of interests

The authors declare that they have no conflict of interests.

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COMMENTARY | Eur Ann Allergy Clin Immunol | Vol 58, N.4, 189-190, 2026

Allen Kaplan[1], Marta Ferrer[2,3]

CSU, CHA and CSU-AE

Comment on: Demographic and clinical characteristics of chronic histaminergic angioedema and chronic urticaria with angioedema: a multicenter Italian experience - doi: 10.23822/EurAnnACI.1764-1489.411

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Doi
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We read with great interest the article by Sartorio *et al.* (1). Despite finding clear clinical and demographic differences between mast cell-mediated angioedema (CHA) and chronic spontaneous urticaria with angioedema (CSU-AE), CHA is considered to be a subtype of CSU, mostly based on shared treatment options, rather than true clinical equivalence. This classification persists even as evidence accumulates supporting their separation as distinct conditions.

Very few studies compare mast cell mediated angioedema with CSU-AE; the present paper confirms the differences found except for a similar male/female distribution. One possible reason is the sample size of 78 patients since previous studies include larger samples with a M/F ratio from 0.56 (2), 0.65 (3) and 0.78 (4) with patient samples of 131, 254 and 3,698, respectively.

All other features also highlighted in this study confirm that CHA and CSU-AE differ in several aspects: CHA typically presents at an older age and shows a higher frequency of tongue angioedema and limb involvement, while eyelid and perioral involvement is less frequent compared to CSU-AE. There is a lower frequency of attacks with a longer duration of episodes and less impairment in quality of life when CHA is compared to CSU-AE (4, 5). Regarding treatment, CHA responds especially well to high-dose H1-antihistamines and omalizumab (a fact sometimes used to justify grouping with CSU), even though the pathophysiological profiles differ. Cold urticaria, for example, is also mediated by mast cell activation and is responsive to antihistamines and omalizumab; however, it is clearly a separate condition.

There is also pathophysiological evidence of differences, CHA and CSU-AE are also distinguished by one key difference which is the absence of IgG anti FceRI receptor in CHA with a 34% incidence in CSU-AE. Basopenia is common in CSU-AE but there is no basopenia in CHA (3). There is a large difference between CHA and CSU-AE in autoimmunity comorbidities (4) also found in the present study.

Classifying CHA as an urticaria subtype risks confusing patients and non-specialist providers – especially when it presents without hives. This confusion can delay the critical recognition and proper management of bradykinin-mediated *versus* mast cell-mediated angioedema. Calling a condition "urticaria" without hives is problematic, as it means defining a disease by a key symptom that is missing.

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The conclusion that CSU-AE and CHA are part of a "protean" urticaria spectrum does not address their fundamental differences. Robust evidence now supports considering these as separate entities given their clinical, immunologic and physiologic differences. More focused research, revised guidelines, and refined diagnostic criteria are urgently required to improve clarity for clinicians, and – most importantly – to ensure optimal patient care. In summary, while CHA and CSU-AE share similar treatments, their clinical behavior, comorbidity profiles, and pathophysiology are distinct enough that continuing to consider CHA merely as a urticaria subtype is neither clinically nor scientifically justified.

Fundings

None.

Contributions

Both authors contributed equally to the work.

Conflict of interests

The authors declare that they have no conflict of interests.

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COMMENTARY | Eur Ann Allergy Clin Immunol | Vol 58, N.4, 191-191, 2026

Maria Beatrice Bilò[1], Danilo Villalta[2]

Clinical syndromes and molecular allergens: a clarification on the proposed "defensin-related allergy syndrome"

Comment on "Clinical terminology and biological mediators in allergology: why biomarkers do not define a syndrome" – doi: 10.23822/EurAnnACI.1764-1489.438

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Doi
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We read with great interest the Letter to the Editor by Prof. Di Lorenzo addressing the methodological relationship between clinical terminology and molecular mediators in allergology (1). We fully concur with the central argument that biomarkers and biological mediators should not, per se, define clinical syndromes, and that terminological precision remains essential for maintaining coherence in clinical reasoning.

Within this conceptual framework, we would like to offer a complementary clarification regarding the proposed notion of "defensin-related allergy syndrome". While we agree that the designation of a syndrome should be grounded in a consistent constellation of clinical signs and symptoms, it is also important to recognize that, in contemporary allergology, certain clinical entities are increasingly defined by the identification of specific allergenic molecules that drive distinct patterns of sensitization and clinical reactivity.

In this context, the so-called "defensin-related allergy syndrome" should not be interpreted as an independent clinical syndrome in the classical nosological sense, but rather as a form of food allergy characterized by sensitization to a specific family of allergenic proteins, namely defensin-like molecules. From this perspective, it may be more appropriately framed as a molecularly defined subtype within the broader spectrum of food allergy, rather than as a novel clinical syndrome.

This conceptual approach is consistent with other well-recognized entities in molecular allergology. For example, the lipid transfer protein (LTP) syndrome and the alpha-Gal syndrome are not merely defined by clinical phenotype, but by sensitization to specific allergenic molecules (plant LTPs and galactose-α-1,3-galactose, respectively), which confer distinctive clinical and immunological characteristics. These entities illustrate how molecular specificity can meaningfully contribute to the definition of clinically relevant subgroups within broader disease categories, without necessarily replacing the primacy of clinical observation. Analogously, sensitization to defensin-like proteins may identify a subgroup of patients within the spectrum of plant-derived food allergy, potentially associated with particular patterns of cross-reactivity and clinical expression. However, this molecular characterization should be understood as complementary to, rather than substitutive of, established clinical classifications such as pollen-food syndrome.

In conclusion, while we agree that biomarkers alone do not define a syndrome, we would emphasize that allergen-specific sensitization can, in certain contexts, delineate clinically meaningful entities within broader diagnostic frameworks. A balanced integration of clinical phenotyping and molecular characterization, rather than a strict dichotomy between the two, may best reflect the current evolution of precision medicine in allergology.

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CORRESPONDENCE | Eur Ann Allergy Clin Immunol | Vol 58, N.4, 192-192, 2026

Silvio Sartorio (on behalf of other authors)

Reply to "CSU, CHA and CSU-AE"

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Doi
N/A

I appreciate the interest expressed by our colleagues in their letter, which highlights the scientific discussion that this topic continues to generate among physicians and researchers in the field of Allergy and Clinical Immunology. We would like to clarify the following points:

1. Mast cell-mediated angioedema (CHA) and chronic spontaneous urticaria with angioedema (CSU-AE) show certain differences that are not consistently confirmed in the limited number of published studies. A major limiting factor is the low prevalence of CHA and the resulting small patient samples in most investigations, including our own, which restricts the generalisability of these findings.
2. Although some evidence suggests that immunological differences may exist between CHA and CSU-AE, such as the absence of IgG autoantibodies against the FcεRI receptor, this aspect was not investigated in our study. In reference to the pathogenic classification of chronic spontaneous urticaria (CSU) into type I and type IIb, the latter characterised by the presence of IgG autoantibodies, our patients were not stratified according to these features. Consequently, assessing clinical severity and treatment response in relation to specific disease subgroups remains challenging, potentially influencing the interpretation of results for both CHA and CSU-AE in the absence of these immunological markers.
3. Even though CHA and CSU-AE share the same therapeutic approach, it is undeniable that relevant differences exist. Research is still ongoing and larger, well-designed studies are needed to better define CHA and to further clarify its distinction from CSU-AE.

In conclusion, more detailed characterisation of CHA and CSU-AE may ultimately lead to updates in guidelines, improving disease awareness and diagnostic accuracy, fostering a more uniform consensus and contributing to a clearer definition of CSU.

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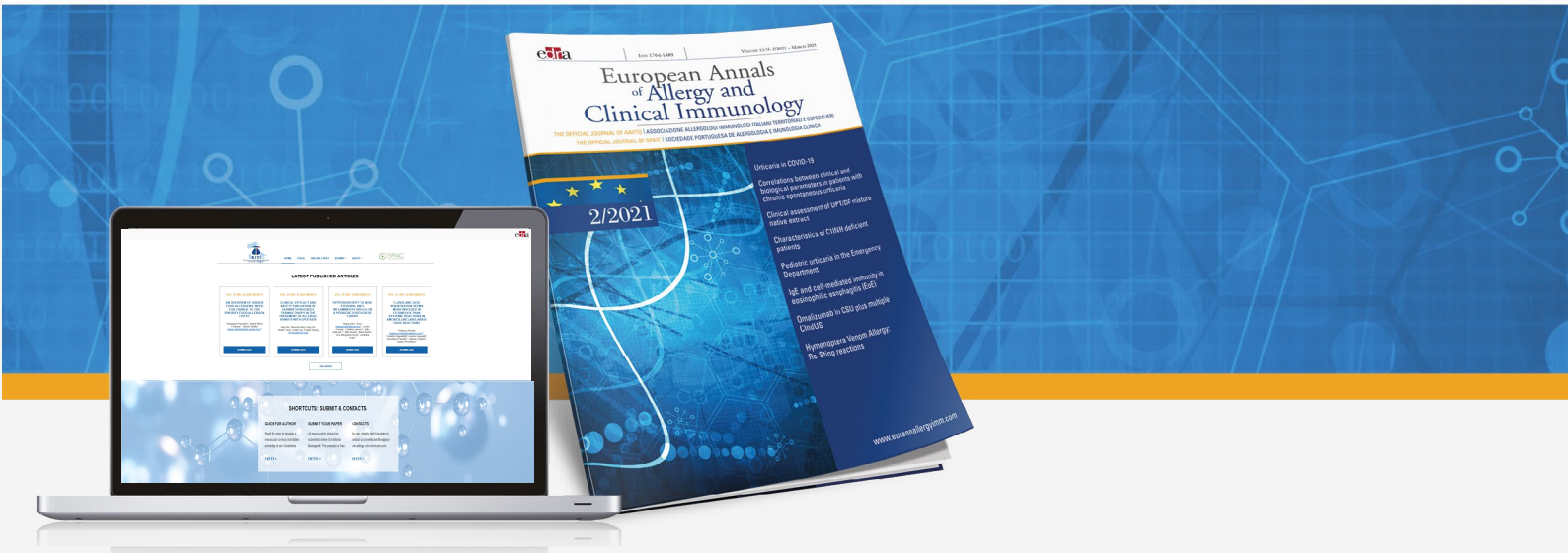
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