ORIGINAL REPORT

Characterization of Contact Urticaria Syndrome Phenotypes: A Retrospective Study of 95 Cases

David PESQUÉ[1,2], Paloma TORRES-BOSÓ[1,3], Evelyn ANDRADES[1,3], Ramon M. PUJOL[1,3], Fernando GALLARDO[1,3] and Ana M. GIMÉNEZ-ARNAU[1,3]

[1]Department of Dermatology, Hospital del Mar Research Institute, Barcelona, [2]Department of Medicine, Autonomous University of Barcelona (UAB), Barcelona, and [3]Pompeu Fabra University (UPF), Barcelona, Spain

Contact urticaria syndrome, encompassing immunological contact urticaria and protein contact dermatitis, comprises immediate cutaneous reactions with potential systemic manifestations, including anaphylaxis. These conditions are frequently underdiagnosed despite their significant occupational impact. This study aimed to evaluate the clinical and laboratory features associated with distinct phenotypes of contact urticaria syndrome. A retrospective, observational analysis was performed at Hospital del Mar (Barcelona) from January 2010 to January 2024, including adult patients diagnosed with immunological contact urticaria and/or protein contact dermatitis and a positive prick test. Demographic data, clinical data, and complementary test results, including culprit agents, were compared between patients with isolated contact urticaria and those with protein contact dermatitis. A total of 95 patients were included. Results indicated that isolated contact urticaria was more frequently associated with facial involvement ($n = 19$, 28.8%) and a higher rate of systemic reactions ($n = 18$, 27.3%), including anaphylaxis, whereas protein contact dermatitis was frequently occupational-related ($n = 19$, 65.5%), and with a trend toward higher atopic dermatitis comorbidity ($n = 12$, 41.4%). These findings emphasize the heterogeneity of contact urticaria syndrome and underscore the importance of comprehensive clinical evaluation for effective diagnosis and management.

Key words: contact urticaria; protein contact dermatitis; immediate skin reaction; immediate allergy; prick test; occupational.

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Corr: David Pesqué, Department of Dermatology, Hospital del Mar Research Institute and Department of Medicine, Autonomous University of Barcelona (UAB), Barcelona, Spain. E-mail: pesquedavid@gmail.com

SIGNIFICANCE

Contact urticaria syndrome can appear as contact urticaria or protein contact dermatitis. This study shows that isolated contact urticaria may be associated more frequently with systemic symptoms, including anaphylaxis, while protein contact dermatitis is often linked to occupational involvement and these patients may experience longer follow-up periods in specialized units. By exploring these differences, the results provide insights into recognizing and managing these underrecognized conditions.

Contact urticaria syndrome includes several forms of immediate skin reactions, including immunological and non-immunological contact urticaria as well as protein contact dermatitis (1, 2). Contact urticaria is an immediate-type cutaneous reaction characterized by transient wheal-and-flare after direct skin contact with a triggering substance. Protein contact dermatitis is a chronic eczematous dermatitis of the hands or exposed areas induced by contact with high-molecular-weight protein allergens, typically in occupational settings. Clinically, protein contact dermatitis often shows eczematous plaques with intermittent or concomitant immediate-type stinging or whealing on exposure (1, 3). These conditions are less frequent than delayed hypersensitivity, but are relevant in daily practice due to their association with systemic manifestations, including anaphylaxis (3). Both contact urticaria and protein contact dermatitis are suspected to be underdiagnosed (4) and are associated with a significant occupational impact (5, 6). Their diagnosis is based on clinical suspicion and complementary tests, including prick testing (7).

The natural history of these conditions may be linked, with an initial clinical picture of contact urticaria that evolves into protein contact dermatitis (1). However, some patients present exclusively with isolated contact urticaria without further evolving to protein contact dermatitis (8, 9). Furthermore, the association of previous contact urticaria is not always apparent for patients experiencing protein contact dermatitis and/or their physicians (5). Therefore, this may lead to the observation of different phenotypes within the contact urticaria syndrome depending on whether patients present isolated or combined conditions (contact urticaria plus protein contact dermatitis). Despite contact urticaria and protein contact dermatitis sharing common pathogenic mechanisms (e.g., type I hypersensitivity reaction) and clinical features (e.g., immediate pruritus) (2), it is unclear whether different phenotypes in clinical practice may show distinct disease profiles in respect of clinical manifestations, comorbidities, triggering agents, and/or complementary tests results.

The aim of this study is to evaluate the clinical (disease features, comorbidities, systemic involvement) and

laboratory (total IgE, allergen-specific IgE) features associated with different phenotypes (contact urticaria and/or protein contact dermatitis) of the contact urticaria syndrome.

MATERIALS AND METHODS

Patients

An observational, unicentric, retrospective study of adult patients, with the diagnosis of immunological contact urticaria and/or protein contact dermatitis plus a positive prick test in the hospital prick registry, from January 2010 to January 2024 of Hospital del Mar (Barcelona) was performed. Positive prick tests were considered in relation to clinically relevant suspected allergens identified from the exposure history. Clinical and laboratory variables were collected and transferred to an anonymized database and are specified in the following sub-section. The study was approved by the local institutional review board with the identification number "CEIm 2024/11625".

Clinical parameters

Demographic data (age, sex), contact urticaria syndrome condition (contact urticaria, protein contact dermatitis, or both), clinical characteristics (clinical presentation, involved areas, atopic dermatitis and associated atopic conditions such as allergic rhinitis and asthma, occupation, occurrence of systemic reactions, disease duration, time of follow-up) and complementary test features (total IgE, specific IgE, prick test and triggering agent, patch test, and allergens, if any) were collected retrospectively. All patients after diagnosis had a minimum follow-up of 6 months. Prick testing was performed depending on the suspected triggering agent. If there was a commercially available allergen extract (e.g., latex), prick test with standardized extracts was performed. If commercial preparations were not available, prick-by-prick tests were performed. Wheals larger than 3 mm and at least half the size of the wheal produced by the positive control were regarded as positive (10). Patch testing with the Spanish baseline series was performed routinely to rule out any other associated delayed hypersensitivity according to the European Society of Contact Dermatitis guidelines (11).

Laboratory parameters

Baseline total IgE in serum was analysed by a chemiluminescence immunoassay with IMMULITE 2000 XPi System (Siemens Healthineers AG, Forchheim, Germany) (12). When specific IgE for the suspected culprit(s) were available, those were performed. Specific IgEs were performed with the radioallergosorbent test.

Statistical analysis

Demographic characteristics of patients with contact urticaria syndrome were reported using descriptive statistics. Results are expressed as median and interquartile range for quantitative variables or number and percentage for qualitative variables.

In order to compare between phenotypes, groups were pre-defined according to the presence or absence of protein contact dermatitis. In this regard, one group was created only of patients with isolated immunological contact urticaria and the other comprised patients with either both contact urticaria and protein contact urticaria or isolated protein contact urticaria. The rationale for this is that patients with protein contact dermatitis may not experience contact urticaria, but also it may be mild and not evident to the patient (5). Groups were compared using a C2 test of homogeneity (categorical variables) or the Mann–Whitney *U* test (continuous variables) was performed. If the conditions to apply the C2 test were not fulfilled, Fisher's exact test was used.

A p-value <0.05 was considered statistically significant. Statistical analyses were performed with Stata-17 (StataCorp LLP, College Station, TX, USA).

RESULTS

Total demographic and clinical data

A total of 95 patients met the inclusion criteria. Isolated contact urticaria was diagnosed in 66 patients (69.5%), isolated protein contact dermatitis in 16 patients (16.8%), and 13 patients (13.7%) were diagnosed with both conditions (protein contact dermatitis and contact urticaria). In terms of demographic features, the sample was primarily made up of middle-aged (median age: 49 years) women (72 patients, 75.8%). Median follow-up in the cohort was 9.0 (IQR: 15.5–6.0) months. A total of 44 patients had the regular 6 months' follow-up and were discharged and the rest had a longer follow-up at our unit.

The main clinical features of the sample included frequent hand involvement ($n=87$, 91.6%) and a high occurrence of atopic comorbidities, including allergic rhinitis ($n=53$, 55.8%) and atopic dermatitis ($n=28$, 29.5%). The occurrence of systemic reactions included oral allergy syndrome ($n=15$, 15.8%) and even anaphylaxis ($n=5$, 5.3%). In terms of atypical symptomatology, 2 women with latex contact urticaria presented with gynaecological symptomatology (pruritus, discomfort, and/or dysuria) that was linked to the use of latex-containing prophylactic contraceptive barriers. Nearly half of the patients ($n=44$, 46.3%) were considered to have an occupational-related condition, with food-handling workers (e.g., cooks) being the most frequently involved occupation ($n=20$, 21.1%). The median disease duration at consultation was 12.0 (IQR: 23.5–12.0) months.

Complementary tests results and culprit agents

In terms of complementary tests, all patients had at least 1 positive prick reaction, but a significant proportion had 2 or more positive patch tests ($n=21$, 22.8%).

In terms of culprit agents, a myriad of agents was identified. In order to ease the presentation of these agents, culprit agents have been categorized into 6 subgroups. Natural rubber latex was the most frequently found culprit agent ($n=39$). The remaining subgroups comprised edible fruits/vegetables ($n=50$), fish and seafood ($n=24$), garden plants ($n=4$), animal meat or hair ($n=4$), and other health-related products ($n=5$). Latex-fruit syndrome was identified in 6 patients and included different culprit agents, including latex and kiwi ($n=3$); latex, kiwi, and peach ($n=1$); latex, melon, and strawberries ($n=1$), as well as latex and potato ($n=1$). **Table I** presents the main culprit agents in each subgroup and the number of patients detected for each culprit agent.

Patch testing with the baseline series was routinely performed and revealed positive patch test reactions in 28 individuals (29.5%), with nickel sulphate ($n=15$) and formaldehyde ($n=6$) being the 2 main haptens found. Despite the relatively high occurrence of positive patch tests, the relevance of the test in relation to their clinical picture was low. Only in 4 (14.3%) patients was the positive patch test relevant to their current problem.

In terms of median laboratory features, median total IgE was elevated (178.5 IU/mL; IQR 391.0–63.5). Specific IgEs were performed in 43 patients and were positive in 17 (39.5%).

Analysis of clinical features according to phenotypes

The demographic comparison between patients with isolated contact urticaria vs those with protein contact dermatitis revealed no differences in terms of age and gender.

With regard to clinical features, several differential features were found. Facial involvement was more frequent in patients with isolated contact urticaria ($n=19$, 28.8% vs $n=2$, 6.9%), while no differences for other locations were found (hands, legs). No differences in atopic comorbidities were detected between the 2 groups. However, atopic dermatitis was higher in the protein contact dermatitis group ($n=12$, 41.4% vs $n=16$, 24.2%, p-value 0.09). In terms of systemic reactions, oral allergy syndrome was more frequent in patients with isolated contact urticaria ($n=13$, 19.7% vs $n=2$, 6.9%) and the occurrence of anaphylaxis was seen only in patients with isolated contact urticaria ($n=5$, 7.6%). All patients with anaphylaxis episodes were treated with on-demand adrenaline. Median follow-up in patients with protein contact dermatitis (12.0 [IQR: 18.0–7.0] months) was higher than in patients with isolated contact urticaria (6.5 [14.25–6.0] months, p-value 0.04).

In terms of occupation, a higher frequency of occupation-related clinical pictures in the protein contact dermatitis group was detected ($n=19$, 65.5% vs $n=25$, 37.8%). The analysis of the specific occupations related to each group revealed a differential profile between the 2 groups. Contact urticaria was related to a myriad of occupations, including healthcare workers ($n=12$, 48.0%), food-handling workers ($n=7$, 28%), cleaning workers ($n=3$, 12.0%), industry workers ($n=2$, 8.0%), and a teacher. In contrast, protein contact dermatitis was mostly associated with food-handling workers ($n=12$, 63.2%), and occasionally with healthcare workers ($n=5$, 26.3%) and industry workers ($n=2$, 10.5%). The only statistical difference in terms of specific occupations was found for food-handling workers (p-value 0.02). **Table II** presents the total demographic and clinical data according to phenotype.

Analysis of complementary test features according to phenotypes

In relation to the design of the study, all patients presented with at least 1 positive prick-test reaction. The main culprit agents in patients with isolated contact urticaria were natural rubber latex ($n=29$), kiwi ($n=5$), peach ($n=4$), corn ($n=4$), pineapple ($n=3$), prawn ($n=3$), *Aloe vera* ($n=2$), and melon ($n=2$). The culprit allergens that lead to anaphylaxis in this group were latex ($n=3$), *Lilium Stargazer* (flower parts and pollen) ($n=1$), and tetracaine in topical application ($n=1$). All other culprit agents were only found in unique individuals and can be found in Table SI. The main culprit agents in patients associated with protein contact dermatitis were natural rubber latex ($n=10$), squid ($n=7$), prawn ($n=4$), cod

Table I. Culprit agents according to categories in the cohort

Category	Total	Triggering agents and number of patients
NRL	39	This category includes only NRL
Edible fruits/vegetables and their derivatives	51	Kiwi ($n=7$), peach ($n=5$), corn ($n=4$), eggplant/aubergine ($n=3$), mango ($n=3$), melon ($n=3$), pineapple ($n=3$), tomato ($n=3$), pear ($n=2$), celery ($n=2$), potato ($n=2$), zucchini ($n=1$), onion ($n=1$), cherry ($n=1$), chipotle ($n=1$), strawberries ($n=1$), fig ($n=1$), green beans ($n=1$), lettuce ($n=1$), orange ($n=1$), paprika ($n=1$), banana ($n=1$), arugula ($n=1$), avocado ($n=1$), artichoke ($n=1$)
Fish and seafood	23	Squid ($n=8$), prawn ($n=7$), salmon ($n=2$), cod ($n=2$), octopus ($n=1$), crayfish ($n=1$), tuna ($n=1$), lobster ($n=1$)
Other health-related products	5	Chlorhexidine ($n=1$), erythromycin ($n=1$), synthetic gloves ($n=1$), tetracaine ($n=1$), modelling material ($n=1$)
Garden plants and their derivatives	4	*Aloe vera* ($n=2$),* *Lilium Stargazer* ($n=1$), *Hedera helix* ($n=1$)
Animal meat/hair	4	Chicken meat ($n=2$), pork meat ($n=1$), rabbit hair ($n=1$)

NRL: natural rubber latex. *Contact urticaria in this case was due to direct application of the *Aloe* flesh on the face plus an *Aloe*-based cosmetic product. Note that the total number of triggering agents exceeds the 95 included patients due to the occurrence of patients with multiple positive prick tests.

Table II. Comparison of demographic and clinical features by phenotype

Variables	Total	Phenotypes analysis		
		Isolated-CoU	PCD	*p*-value
Total	–	66	29	–
Demographic variables				
Women, *n* (%)	72	52 (78.8%)	20 (67.0%)	0.30
Age, median(IQR)	49.0 (59.5–42.0)	49.0 (62.0–42.5)	49.0 (58.3–41–0)	0.55
Anatomic involvement and disease course at diagnosis				
Hands, *n* (%)	87 (91.6)	59 (89.4)	28 (96.7)	0.25
Face, *n* (%)	21 (22.1)	19 (28.8)	2 (6.9)	0.01
Legs, *n* (%)	3 (3.2)	3 (4.5)	0	0.24
Other, *n* (%)	33 (34.7)	26 (39.4)	7 (24.1)	0.15
Time at diagnosis, months, median (IQR)	12.0 (23.5–6.5)	10.0 (18.5–6.5)	18.0 (36.0–9.0)	<0.01
Atopic comorbidities				
Allergic rhinitis, *n* (%)	53 (55.8)	35 (53.0)	18 (62.1)	0.41
Asthma, *n* (%)	16 (16.8)	10 (15.2)	6 (20.7)	0.51
Atopic dermatitis, *n* (%)	28 (29.5)	16 (24.2)	12 (41.4)	0.09
Systemic manifestations				
Total systemic manifestations, *n* (%)	20 (21.1)	18 (27.3)	2 (6.9)	0.03
Oral allergy syndrome, *n* (%)	15 (15.8)	13 (19.7)	2 (6.9)	0.13
Anaphylaxis, *n* (%)	5 (5.3)	5 (7.6)	0	0.15
Occupational features and follow-up				
Occupational (total), *n* (%)	44 (46.3)	25 (37.8)	19 (65.5)	0.01
Food-handling workers, *n* (%)*	19 (43.2)	7 (28.0)	12 (63.2)	0.02
Time of follow-up, months, median (IQR)	9.0 (15.5–6.0)	6.5 (14.3–6.0)	12.0 (18.0–7.0)	0.04

CoU: contact urticaria; PCD: protein contact dermatitis; IQR: interquartile range. *Percentage calculated across the total number of occupational patients.

(*n*=2), kiwi (*n*=2), mango (*n*=2), tomato (*n*=2), and eggplant (*n*=2). All other culprit agents were found only in unique individuals (Table SII). In regard to latex-fruit syndrome, 5 patients experienced isolated contact urticaria, while 1 patient had combined contact urticaria and protein contact dermatitis. The comparison between the most frequent triggering agents yielded no significant differences between the 2 phenotypes.

In terms of positive patch-test results, contact urticaria patients had a higher occurrence of positive patch test results (*n*=22, 33.3% vs *n*=6, 20.7%, *p*-value 0.2) without reaching significance.

In terms of laboratory findings, specific IgEs were positive in 13/33 patients with isolated contact urticaria and in 4/10 patients associated with protein contact dermatitis (*p*-value 0.97). No differences were found in terms of total baseline IgE levels between isolated contact urticaria patients (187 [IQR: 391.0–58.0] IU/mL) and those presenting protein contact dermatitis (178 [IQR: 516.0–104.0] IU/mL, *p*-value: 0.59). **Table III** presents the complementary test features according to phenotype.

Table III. Comparison of complementary test results by phenotype

Variables	Total	Phenotypes analysis		
		Isolated-CoU	PCD	*p*-value
Positive latex prick test, *n* (%)	39 (41.0)	29 (43.9)	10 (34.5)	0.39
Latex-fruit syndrome, *n* (%)	6 (6.3)	5 (7.6)	1 (3.4)	0.67
Positive patch test results, *n* (%)	28 (29.5)	22 (33.3)	6 (20.7)	0.2
Positive specific IgE, *n* (%)	17/43 (39.5)	13/33 (39.4)	4/10 (40.0)	0.99
Baseline IgE, IU/mL, median (IQR)	178.5 (388.3–64.8)	187 (391.0–58.0)	178 (516.0–104.0)	0.59

CoU: contact urticaria; PCD: protein contact dermatitis; IQR: interquartile range.

DISCUSSION

This study has focused on the phenotypes of contact urticaria syndrome by comparing the associated clinical and laboratory findings of a retrospective cohort in a tertiary-level hospital.

The first aspect to emphasize is that the frequency of isolated contact urticaria without progression or association with protein contact dermatitis was higher in the cohort than protein contact dermatitis (isolated or combined). One limitation to compare these results with previous studies is that the registration of conditions belonging to the contact urticaria syndrome has occurred under the same category and has not differentiated between contact urticaria and protein contact dermatitis (6). In terms of demographic features, previous studies have also highlighted a clear-cut predominance of women (13).

In terms of general clinical features, this study supports the high frequency of atopic comorbidities (14) and the occupational relevance of both contact urticaria and protein contact dermatitis (6). In contrast, associated systemic reactions were rarer but not negligible, with several patients presenting life-threating reactions and requiring on-demand adrenaline. In fact, despite both oral allergy syndrome and anaphylaxis having been associated with conditions of contact urticaria syndrome in the literature (3, 15, 16), the features of these systemic reactions in this subgroup of patients have not been widely studied.

In terms of phenotypical clinical features, this study has detected 3 main differential areas, including anatomic involvement, association of systemic reactions, and occupational profile. Isolated contact urticaria had more frequent facial involvement, which is probably a reflection of the increased number of cases of oral allergy

syndrome in this group as well as the direct application of some triggering agents such as facial cosmetics (e.g., *Aloe vera*). In contrast, protein contact dermatitis may rarely occur on the face (17), but is normally characterized by hand eczema, with potential additional nail and forearm involvement (18). In both phenotypes hand involvement was the most frequent location, indicating the high interaction of this anatomic region with the environment. Systemic reactions, including oral allergy syndrome and anaphylaxis, were diagnosed principally (or exclusively, for anaphylaxis) in patients with isolated contact urticaria. Although the differences were not significant due to sample size, patients with isolated contact urticaria seem more frequently to develop systemic involvement, with a significant proportion having experienced life-threatening reactions and requiring on-demand adrenaline. These differences could be explained by a combination of factors, such as immunological differences between the phenotypes, varying proneness of triggering agents to induce systemic reactions, and/or distinct host susceptibility.

In terms of immune features, contact urticaria syndrome remains widely understudied, although protein contact dermatitis is thought to have a more complex immune background with a combination of type I and type IV mechanisms (1). It is not known whether type I responses may differ between the phenotypes. In terms of allergens, latex was the most frequent triggering allergen and is a well-known cause of immediate systemic symptoms (19). The occurrence of anaphylaxis due to latex and topical tetracaine has been described (19, 20), whereas contact urticaria due to *Lilium* has also been described but not with progression to anaphylaxis (21). The occupational features between phenotypes were also differential, with the protein contact dermatitis phenotype being mostly occupational-related. Food-handling workers, mostly cooks but also food industry workers, seemed to present more frequently the protein contact dermatitis phenotype. Despite no differences between triggering agents being found between groups, the protein contact dermatitis group had a higher number of cases of triggering agents related to animal protein products, including fish and meat.

In terms of complementary tests, prick testing was the main diagnostic tool to characterize these patients. The myriad of triggering agents indicates the diversity and complexity in relation to the suspicion of these conditions, which can be caused by both low and high molecular weight agents (normally proteins, but also non-protein chemicals) (3, 22). The finding of the triggering agent seemed to impact a higher number of patients with isolated contact urticaria, who were discharged after the minimum 6-month follow-up. In contrast, protein contact dermatitis patients were followed up for longer periods, possibly indicating a higher difficulty in avoiding the triggering agents. However, the most severe clinical manifestations and the use of on-demand adrenaline were seen also in isolated contact urticaria patients, indicating a wide spectrum of manifestations. Patch testing these patients with the baseline series was only relevant for the presenting clinical picture in a small subset of patients, which included patients with mixed hand eczema due to protein contact dermatitis and allergic contact dermatitis. Baseline IgE does not seem to be a useful biomarker to differentiate these phenotypes, but the median elevated values in both groups indicates the atopic background that can be found across these conditions (23). Antigen-specific IgEs, when available, were only moderately useful, and this is in accordance with previous literature findings (24). It is known that negative specific IgEs do not rule out an immediate allergy and that skin testing (in this case, a prick test) is a highly sensitive complementary test (25).

Limitations

The main limitations of this study are related to its retrospective nature as well as the reduced number of patients. However, these data are still valuable in the context of infrequent and underdiagnosed conditions. Future multicentric studies will be needed to confirm these data.

Conclusion

This study suggests that isolated contact urticaria may present with a spectrum of clinical presentations, including severe systemic manifestations (oral allergy syndrome and anaphylaxis). In contrast, patients with protein contact dermatitis do not have such a high burden of systemic symptoms but have higher occupational involvement, longer follow-up at our unit, and seem to have more comorbid atopic dermatitis. Clinical history, and physical exam plus prick testing have been shown to be useful in clinical practice to diagnose these patients. The usefulness of other complementary tests (patch testing, specific IgE and baseline total IgE) has been limited.

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