Multiple comorbidities in patients with long-lasting chronic spontaneous urticaria☆

Dear Editor,

Chronic Spontaneous Urticaria (CSU) is a mast cell-driven skin disease, and mast cell degranulation is triggered by the activation of several receptors on its surface. IgE-FcεRI complex appears to be involved in the autoimmune etiology of CSU, through the presence of IgG anti-FcεRI, anti-IgE or IgE against autoallergens, but many other receptors can induce mast cell degranulation, as such as Mas-Related G-Protein-Coupled Receptor X2 (MRGPRX2).[1–3]

Several types of comorbidities are associated with CSU and often lead it to a worse prognosis. One of the most common comorbidities is an autoimmune disease. CSU, itself considered an autoimmune disease, is mainly associated with autoimmune thyroid disease, and the high prevalence of these autoimmune diseases in patients with CSU supports that hypothesis. Other comorbidities often associated with CSU are psychological disorders; infectious diseases, including viruses, bacteria, and parasites; as well as with metabolic syndrome (MetS).[3–7]

In this retrospective and observational study, we evaluated the association between long-lasting CSU and the occurrence of multimorbidities in patients followed up (one year or more) in a tertiary Center – UCARE, between January 2019 and December 2020.

Patients were classified according to the duration of the CSU: 1 to 2 years; 3 to 5 years; 6 to 10 years; and 11 or more years. Groups were evaluated for demographic data, angioedema, and refractoriness to antihistamines. Comorbidities assessed were gastrointestinal disorders, obesity, systemic arterial hypertension, diabetes mellitus, dyslipidemia, autoimmune thyroid diseases, respiratory diseases, and psychological disorders.

MetS comprehends a constellation of cardiovascular disease risk factors, which includes glucose intolerance, dyslipidemia, hypertension, and central abdominal obesity.[8] At least three of those four components have to being fulfilled for MetS diagnosis in CSU patients.

We included 173 patients with CSU, 86.1% were women with a mean age of 49.8 years. Angioedema was reported by 112 (64.7%) patients, *nonsteroidal anti-Inflammatory drugs* exacerbated CSU was observed in 71 (41.0%), and 45 (26.0%) patients were refractory to antihistamines (four times daily). When patients with CSU were classified according to the duration of the disease, 28 (16.2%) had 1 or 2 years ; 51 (29.5%), 3 to 5 years ; 37 (21.4%) between 6 and 10 years, and 57 (32.7%) had 11 years or more of disease. General characteristics can be observed in Table 1.

There was no statistical difference in relation to the current age of the patients in those different groups (according to the duration of the CSU), although, the age at onset of CSU was lower for patients with long-lasting CSU, and these patients had more often multimorbidities, including the components of MetS ($p < 0.05$).

Eight comorbidities were assessed in this study, the frequency of them in the same patient ranged from 0 to 6 comorbidities (Fig. 1). The most frequent comorbidities were respiratory disorder (rhinitis and/or asthma) in 82 (47.4%), followed by high blood pressure, in 54 (31.2%), and dyslipidemia, in 38 (22%) patients. There was a correlation between the duration of CSU and the frequency of comorbidities, $r^2 = 0.043$, $p = 0.007$ (Fig. 2).

Patients with CSU refractory to antihistamine had a higher frequency of angioedema, gastrointestinal disorders, and obesity, compared to those patients responsive to antihistamine (77.8% versus 60.2%, $p = 0.045$; 28.9% versus 13.3%, $p = 0.017$; and 26.7% versus 16.4%, $p = 0.039$, respectively).

In the present study, 16 (9.2%) patients had CSU-associated autoimmune diseases, a frequency higher than that observed in the general population (around 5%).[6] Of the 16 patients, autoimmune thyroid disease represented 87.5% of them. However, we did not find an increase in its frequency as CSU lasted longer or with disease severity. One explanation would be that the mean age in the studied groups, according to the duration of CSU, was similar (mean of 49.8 years), reinforcing that the frequency of autoimmune diseases increases with age.[4]

Multimorbidity is associated with a poor quality of life; patients are at higher risk of severe clinical outcomes. CSU is nowadays considered a low-grade inflammatory systemic disease. The proposed pathomechanism would be the constant or continuous activation of mast cells observed in patients with uncontrolled CSU. In addition to the autoimmune mechanism described for mast cell activation in patients with CSU, several other factors maintain or worsen the mast cell activation.[9,10] In the present study, three components or more of MetS were observed more frequently in patients with six years or more of CSU, compared with those patients with one to five years of disease (15.9% versus 1.3%, $p < 0.001$). The most common component of MetS was high blood pressure (31.2% of 173 patients), and around 10% of 173 patients had at least three of them.

In conclusion, this study showed that patients with early-onset and long-lasting CSU had more often comorbidities including three or more components of MetS. The present study has shown that almost half of the participants had at least one component of MetS. Three or more components of MetS had a statistically significant higher frequency in patients with CSU lasting six or more years. Long-lasting CSU, and probably, uncontrolled disease, could evolve with multimorbidities, suggesting that early complete control of CSU would be essential to prevent this outcome. These results need further prospective research to highlight the importance of CSU as a low-grade inflammatory disease. The present results suggest an association between long-lasting CSU and MetS, but case-control trial studies should be essential to confirm the our conclusions, further including a larger number of participants.

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Table 1 Demographic and clinical data of patients with CSU according to the duration of disease.

General characteristics	Duration of CSU				p
	1 and 2 years	3 and 5 years	6 and 10 years	11 or more years	
Gender: female	75.0	86.3	89.2	89.5	NS
Current age (year; mean, SD)	47.9	46.9	50.3	52.8	NS
Age at onset of CSU (y; mean, SD)	46.2	43.1	42.5	33.2	<0.001
Duration of CSU	1.8	4.1	7.8	19.5	NA
CIndU (%)	32.1	33.3	43.2	31.6	NS
Angioedema (%)	46.4	70.6	62.6	70.2	NS
NSAID exacerbated CSU (%)	10.7	43.1	43.2	52.6	0.002
Refractoriness to antistamines (%)	14.3	23.5	24.3	35.1	NS

CSU, Chronic Spontaneous Urticaria; SD, Standard Deviation; NA, not applicable; CIndU, Chronic Inducible Urticaria; NSAID, Nonsteroidal Anti-Inflammatory Drugs, NS, Non-significant
The Kruskal-Wallis test for current age and age at onset of CSU.
χ^2 analysis for gender, CIndU, angioedema, NSAID exacerbated CU, and refractoriness to antihistamine.

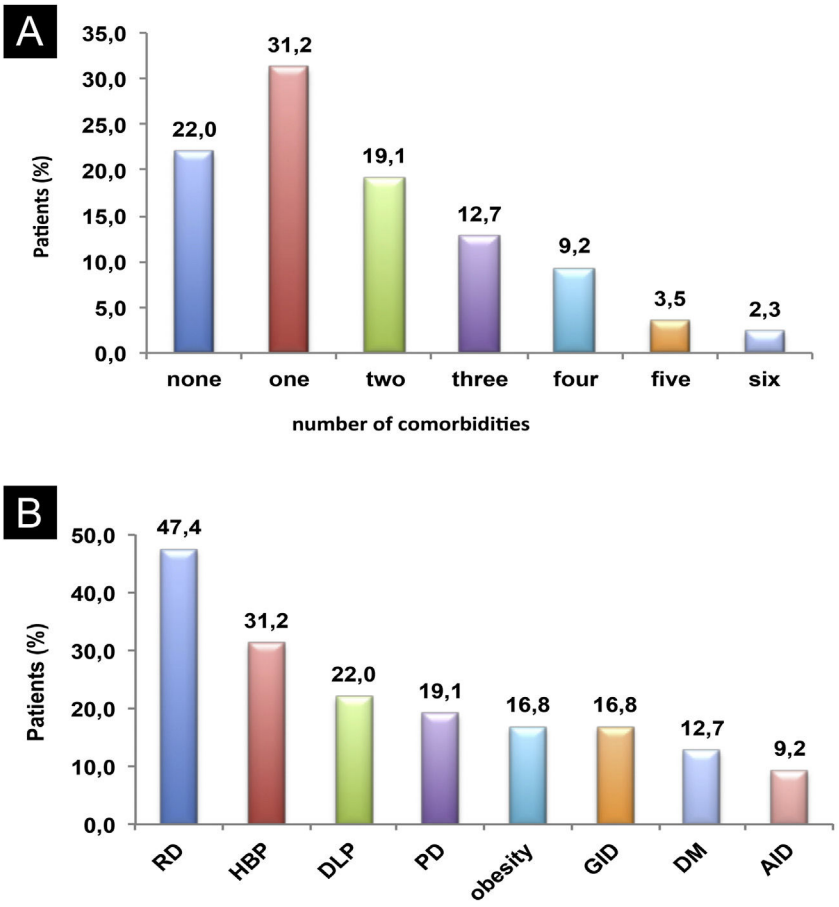

Figure 1 Comorbidities: (A) Co-prevalence of comorbidities (0 to 6) in the same patient; (B) Frequency of each comorbidity in patients with CSU. RD, Respiratory Disorders; HBP, High Blood Pressure; DLP, Dyslipidemia; PD, Psychiatric Disorders; GID, Gastrointestinal Disorders; DM, Diabetes Mellitus; AID, Autoimmune Diseases.

Authors' contributions

Rosana Câmara Agondi: Statistical analysis; approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Paula Natassya Argolo: Statistical analysis; approval of the final version of the manuscript; design and planning of

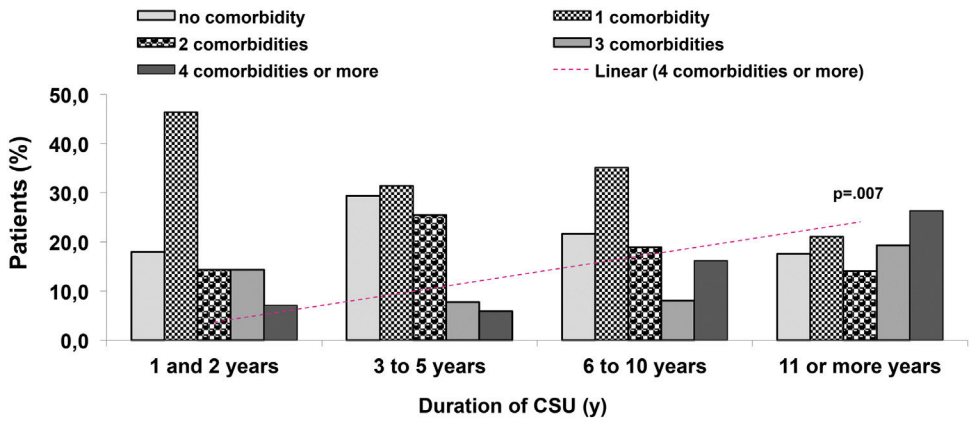

Figure 2 Frequency of comorbidities according to the duration of CSU; y, year; χ^2 test, p = 0.007.

the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Mariana Mousinho-Fernandes: Statistical analysis; approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Bruna Gehlen: Statistical analysis; approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Jorge Kalil: Statistical analysis; approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Antonio Abílio Motta: Statistical analysis; approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Conflicts of interest

None declared.

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References

1. Zuberbier T, Aberer W, Asero R, Latiff AHA, Baker D, Ballmer-Weber B, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73:1393–414.
2. Espinosa E, Valitutti S. New roles and controls of mast cells. Curr Opin Immunol. 2018;50:39–47.
3. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we don't know. J Allergy Clin Immunol. 2017;139:1772–81.
4. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. Allergy. 2017;72:1440–60.
5. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: association found in a large population study. J Allergy Clin Immunol. 2012;129:1307–13.
6. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 2015;278:369–95.
7. Kim DH, Sun NH, Lee AY. Effect of levothyroxine treatment on clinical symptoms in hypothyroid patients with chronic urticaria and thyroid autoimmunity. Ann Dermatol. 2016;28:199–204.
8. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb. 2005;12:295–300.
9. Darlenski R, Kazandjieva J, Zuberbier T, Tsankov N. Chronic urticaria as a systemic disease. Clin Dermatol. 2014;32:420–3.
10. Grzanka R, Damasiewicz-Bodzek A, Kasperska-Zajac A. Interply between acute phase response and coagulation/fibrinolysis in chronic spontaneous urticaria. Allergy Asthma Clin Immunol. 2018;14:27.

Rosana Câmara Agondi [a,b,*], Paula Natassya Argôlo [a], Mariana Mousinho-Fernandes [a], Bruna Gehlen [a], Jorge Kalil [a,b], Antonio Abílio Motta [a]

[a] *Clinical Immunology and Allergy Division, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil*
[b] *Laboratory of Immunology (LIM19), Instituto do Coração (InCor), Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil*

Corresponding author.
E-mail: rosana.agondi@hc.fm.usp.br (R.C. Agondi).

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Parrot beak nails: a Latin American case series☆

Dear Editor,

Parrot Beak Nail (PBN) deformity consists of a forward over the curvature of the distal nail plate, which gives the nail the appearance of this birds beak. Here in, we present three cases of PBN dystrophy, we describe a new association, and include a brief literature review.

A 75-year-old man with a medical history of leprosy diagnosed 20 years ago, who received complete treatment, came to the dermatologic clinic due to stasis dermatitis. On physical examination, as a coincidental finding, several and significant sequelae were found. He presented PBN with involvement of all his fingernails, chromonychia and onycholysis on diverse nails, contracture of the fingers sparing the thumb, and atrophy of the thenar and hypothenar muscles. He denied any symptoms, or history of trauma, and had not noticed this deformity (Fig. 1).

The second case was a 54-year-old woman with a diagnosis of rosacea, who consulted due to a recent flare. As a coincidental finding, PBN deformity of the fifth left fingernail was recognized. She had a history of left-hand trauma with a knife when she was eight years old (Fig. 2).

The third patient was an 80-year-old man with a personal history of hypertension, diabetes, and cerebrovascular disease, hospitalized due to gait disturbance. During his evaluation, his thumb and second right finger were partially amputated, and the third fingernail had a PBN deformity. He stated these changes were caused by the explosion of homemade fireworks at the age of thirteen (Fig. 3).

Kandil was the first one that described this deformity back in 1971, naming it due to its resemblance to a parrot beak. He reported an idiopathic over the curvature of two fingernails in a 38-year-old woman.[1] Chen and Cohen reported a prevalence of 2.1% of 436 patients who consulted a dermatology clinic. Marie et al. observed this condition in 2.5% of 80 healthy individuals. Other case series have shown that 31% of patients with systemic sclerosis can present this nail dystrophy.[2,3] This deformity has been found in 11 to 89-year-old patients, without sex predominance. We found nine articles reporting this clinical finding, with a total of 78 patients (Table 1).

Its etiology remains unknown. PBN has been associated with several conditions, including collagen vascular diseases, such as systemic lupus erythematosus and systemic sclerosis, where it may be the first finding and has been related to disease activity. Additional associations include cocaine abuse, and trauma, among other disorders.[4,5] The most accepted theory proposes that it is the result of an abnormal phospholipid distribution, which causes hydrophobic interactions between different zones of the nail plate.[1] Authors who support this theory claim the over curvature seen in PBN can be temporarily corrected after submerging the affected nail in water for some minutes, since it would overcome those hydrophobic interactions.[2] An injury could be the main cause, as in the present study's second and third cases. It would generate a chronic imbalance of growth and alter the content of hydrophobic phospholipids, leading to a pronounced longitudinal curvature.

Other theories include chronic vasoconstrictive ischemia as a key factor, based on a case series of eight women with chronic cocaine abuse who developed this deformity.[6] Furthemore, PBN is common in patients with systemic sclerosis, when associated with vascular impairment.[7,8] It could also be secondary to bone or soft tissue disorders, which may be congenital.

Repeated trauma is in certain cases the main cause. PBN dystrophy is found in patients with peripheral neuropathy who are prone to unnoticed nail bed traumatisms. Digital amputation and tight surgical closure in fingertip surgery are causes of pulp atrophy and extensive scarring, which could lead to a hooked-nail deformity that resembles PBN. Some surgical techniques have been described for its prevention: nail relocation, and hypodermic needles for tension-free closure, among others.[1]

When it is associated with chronic cocaine abuse, a triad of PBN, perniosis, and finger pulp atrophy has been reported.[6] Other comorbidities mentioned in the literature, whether they are coincidental or unassociated findings, include bony dystrophy, coronary artery disease, lymphoplasmacytic sclerosing pancreatitis, multiple system atrophy, digit deformity (hammer toe, overlying the fifth toe), and soft tissue hypoplasia.

Neuropathy-associated cases were previously reported by Forouzan et al., who described a patient unaware of his toenail elongation, due to an androgen deprivation therapy-induced peripheral neuropathy.[2] Other neuropathy-associated cases described by Chen et al. include diabetes and spinal stenosis-induced neuropathy. The present study's first patient had leprosy neuropathy; an association not described to the date in the revisited literature.

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