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Review Article

Urticaria and comorbidities

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ABSTRACT

Urticaria is a mast cell (MC)-driven skin disease. Degranulation of these cells is triggered by the activation of several receptors on its surface. The activation of MC in chronic spontaneous urticaria (CSU) appears to be associated with an autoimmune etiology. Certain comorbidities such as autoimmunity, infections, allergy, emotional stress, and metabolic syndrome are frequently associated with chronic urticaria (CU). The objective of this review is to highlight the frequent association between CU and several comorbidities, which can lead to a worse prognosis for the underlying disease. We searched for original and review articles on CU and comorbidities in PUBMED, abstracts published in AAAAI and EAACI; all of them in English. Our review reinforced how CSU, being itself an autoimmune disease, is strongly linked to several other autoimmune diseases. Besides autoimmunity, emotional stress was considered another frequent comorbidity associated with CU and also a trigger factor for urticaria exacerbation. Some studies recently considered CU as a low-grade chronic inflammatory condition and may be associated with metabolic syndrome. In conclusion, CU is considered a heterogeneous disease with distinct clinical features. It is worth remembering that CU should not be considered just a skin disease and its complete control could minimize a worse clinical outcome.

Keywords: Chronic urticaria, Comorbidities, Autoimmunity

INTRODUCTION

Urticaria is a mast cell (MC)-driven skin disease. Degranulation of these cells is triggered by the activation of several receptors on their surface. All MC express high-affinity immunoglobulin (Ig)E receptors (FcεRI) and, increasingly, the IgE-FcεRI complex appears to have role in the autoimmune etiology of chronic spontaneous urticaria (CSU), through the presence of IgG anti-FcεRI/anti-IgE or IgE against autoallergens.[1,2]

Besides FcεRI-IgE complex, MC expresses numerous G protein-coupled receptors. Several drugs and other substances including antimicrobial host defense peptides, neuropeptides, and eosinophil peroxidase activate this type of receptor.[3,4] MRGPRX2 receptor on MCs, basophils, and eosinophils associated with IgE-independent degranulation is highly expressed on cutaneous MCs in severe CSU.[5]

MCs are multifunctional cells which play an important role in several diseases including allergic diseases, gastrointestinal disorders, certain malignancies, and cardiovascular diseases.[5-8] Comorbidities can add layers of complexity and often lead to a worse prognosis for the underlying disease. Management of comorbidities can be challenging as one condition may contribute or be linked to another and treatments can conflict with each other resulting in the modification of response to the drugs used to control diseases.[9]

There are certain comorbidities, frequently associated with urticaria: Autoimmunity, infections, allergy, emotional stress, and metabolic syndrome with dietary factors that can aggravate chronic urticaria (CU).[1,2,10-19] Some patients have more than one concomitant disease. These patients are older, have longer duration of urticaria, and are more resistant to antihistamines. The presence of such factors may be associated with worse prognosis. The progressive increase in the number of comorbidities in same patient may support the view that CU is a low-grade systemic inflammatory disease.[20]

Netchiporouk *et al.* assessed comorbidities in children with CU, and they found that atopy was the most common comorbidity (28%); 4.32% of the patients was diagnosed as having autoimmunity; 20% had chronic inducible urticarial (CIndU); and almost 30% had at least one atopic condition.[21]

Turk *et al.* identified four distinct subgroups of CU using machine learning algorithms. The first group (7%) included only patients with CIndU, this was the smallest group, with the highest age and the lowest total serum IgE. All

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Table 1: Autoimmune endotypes of CSU.

Type	Mechanism	Biomarkers	Clinical indicators
TIaiCSU	Autoallergic IgE autoantibodies against autoallergens: TPO, TG, tissue factor, IL-24[1,32]	Total IgE↑[1,31] IgG anti-TPO↓Total IgE↑/IgG anti-TPO↓	Severe and longer duration of disease, response to omalizumab[1,31,34]
TIIbaiCSU	Autoimmune Specific IgG autoantibodies (probably IgM and IgA) against FcεRIα/IgE.[23,35]	IgG anti-TPO↑[1,31,30] Total IgE↓IgG anti-TPO↑/Total IgE↓+Test-ASST, BHRA, IgG anti-FcεRIα/IgE.[23] Higher rates of eosinopenia and basopenia[1] and highly expressed MRGPRX2 receptor on cutaneous MC associated with severity[5]	Decreased probability of response to omalizumab and a higher chance of response to cyclosporine treatment[1,30,31,34]

Table 2: Chronic urticaria (CU) and comorbidities.

CU and comorbidities	Some characteristics
Autoimmunity	Considering the risk of autoimmune disease in CSU patients, especially adult women with family history should be screened for the presence of autoimmune diseases, especially HT and vitiligo.[2,24] CSU often precedes the onset of other autoimmune diseases.[25,28,30-33] Thyroid diseases are the most common; associated with TIIbaiCSU
Infectious disease	*Helicobacter pylori*; bacterial, fungal, and viral infections, including COVID-19[38-46] were associated with CU, but more research is needed
Drugs	NSAIDs can exacerbate CU[1,49]
Atopy	Some studies showed a high frequency of atopic diseases in CSU that indicates association with TIaiCSU[26,50]
Metabolic syndrome (MetS)	MetS may be associated with more severe CU. From public health perspective, it is important to screen CU patients for metabolic syndrome in the appropriate clinical settings[14,18,19]
Emotional stress	CU belongs to the group of psychodermatological disorders, accompanied by itching that can worsen the QoL of patients. Screening for mental health problems among patients with CSU should be a necessity.[51] Neuroimmune cutaneous interaction may be associated with IgE-independent mast cell activation[51-54]

patients in the second group (42%) presented CSU, with the higher total serum IgE levels and the lowest rate of autoantibodies (anti-TPO and/or ANA). The third group (38%) included 100% CSU, highest percentage of women, and highest rate of autoantibodies. Moreover, the forth group (13%), consisted only by CSU patients, had high frequency of comorbidities.[22] According to this study, "CIndU cluster," "high IgE cluster," "autoimmune cluster," and "high comorbidity" clusters were identified. The "high comorbidity cluster" included high rates of hypertension, diabetes mellitus, and hypothyroidism (correspondingly 74%, 62%, and 38%) each at least twice as high as in any other cluster.[22]

We searched for original and review articles on CU and comorbidities in PUBMED, abstracts published in AAAAI and EAACI; all of them in English.

AUTOIMMUNITY

Indirect evidence that CU is an autoimmune disease is derived from its association with other autoimmune conditions, a strong association between serum functionality and the human leukocyte antigen-DR4 haplotype, and response to immunotherapies.[23]

Many studies in different populations indicate that CSU is strongly linked to Hashimoto's thyroiditis (HT), pernicious anemia, vitiligo, type 1 diabetes mellitus, Graves' disease, celiac disease, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, inflammatory bowel disease, Henoch-Schönlein purpura, and Kawasaki disease.[2,24-29] Patients with CSU, especially adult women with family history of autoimmune disease, should undergo screening for common autoimmune conditions, especially HT and vitiligo.[2,24] CSU often precedes the onset of other autoimmune diseases.[25,28,30-33]

Based on two types of MC degranulating signals, two endotypes of CSU, that is, **autoallergic** and **autoimmune** are proposed [Table 1]. The first one is known as type I autoimmune CSU mediated by IgE autoantibodies **(TIaiCSU)** and the second – **aiCSU,** known as type IIb autoimmune CSU **(TIIbaiCSU),** in which IgG autoantibodies, and probably IgM and IgA, are responsible for direct activation of MC through binding to high-affinity IgE receptors.[1,2,34,35] Thyroid peroxidase (TPO) is a common and relevant autoallergen in **TIaiCSU**, beyond TPO, there are IgE autoantibodies directed to another autoantigens: Thyroglobulin, tissue factor, and interleukin (IL)-24.[1,32]

Total IgE is a valuable marker to distinguish between TIaiCSU and TIIbaiCSU.[1,34] High levels of total IgE may suggest TIaiCSU. These patients may have high disease activity, longer disease duration, and high likelihood of response to omalizumab but rapid relapse after its discontinuation, while the likelihood of response to ciclosporin is lower.[34] On another hand, markedly

low IgE may indicate to TIIbaiCSU that accounts 8% of patients with CSU,[30] which have lesser chance of response to omalizumab and a better chance of response to cyclosporine treatment.[34] These patients have higher rates of eosinopenia and basopenia,[1] highly expressed MRGPRX2 receptor on cutaneous MC, especially in patients with severe CSU.[5]

The high IgE levels are seen in atopic patients with CSU,[32] CSU with gastroesophageal reflux disorder,[13] and CSU with high IL-33 serum levels.[36] These results suggest that the presence of atopy and concomitant disorders may affect serum total IgE levels in patients with CSU.[33] Scientific data indicate that in approximately 50% of patients with CSU, total serum IgE levels were >100 IU/mL, whereas IgE-low (<30 IU/mL) and very low levels (<2 IU/mL) levels were seen in 25% and 10% of patients, respectively.[34] Schoepke *et al*. recommended to use the ratio of IgG anti-TPO to total IgE, as marker for TIIbaiCSU.[30] In another study was suggested to use anti-TPO↑IgE↓ as a diagnostic marker for this type of aiCSU and indicator of low response to antihistamine than patients without aTPO↑IgE↓.[31]

Recent scientific data indicate that, 28% of patients with CSU had at least one autoimmune disease, mostly HT (≥21%) and vitiligo (2%). A total of 2% of CSU patients had ≥2 autoimmune comorbidities. In patients with autoimmune CSU type IIb, autoimmune disease markers: Antinuclear antibodies and/or IgG antithyroid antibodies have been associated with non-response to omalizumab therapy.[2]

A systematic analysis of autoimmune comorbidity, in CSU revealed that the rates of comorbidity were ≥2% for Graves' disease, ≥3% for vitiligo, and ≥5% for pernicious anemia and HT.[24] More than 15% of CSU patients had family history for autoimmune diseases.[2,28] The prevalence of hives in AIDS patients was noted in more than 1% of most studies.[24] In regard to thyroid dysfunction, hypothyroidism and HT are more common than hyperthyroidism and Graves' disease in patients with CSU; likewise, elevated levels of IgG against thyroid peroxidase (TPO) are often observed in those patients.[25,28]

INFECTIOUS DISEASES

Helicobacter pylori (HP) affects a high percentage of patients with CSU; eradication of HP is associated with a remission of urticaria, suggesting role in CSU pathogenesis.[37,38] The effectiveness of eradication of HP in suppressing CSU symptoms was evident;[39] however, resolution of CSU was not associated with successful eradication HP. Significant higher CSU remission with or without HP eradication was seen in CSU with antibiotic therapy for HP eradication.[39]

Some parasites, Toxocara, F*asciola, Ancylostoma, Strongyloides, Filaria, etc.,* have been associated with acute urticarial.[39] A*nisakis simplex* can also cause urticaria after eating of contaminated sushi fish with the parasites.[40]

Epidemiological studies and case reports suggest that some bacterial, fungal, and viral infections might be associated with the CSU, they are as follows: *Streptococcus*, *Staphylococcus*, *Mycoplasma pneumoniae*, *Salmonella*, *Brucella*, *Borrelia*, *Chlamydia pneumoniae*, *Yersinia enterocolitica*, *Herpesviridae*, *Parvoviridae*, *Caliciviridae*, *Flaviviridae*, *Hepadnaviridae*, etc.[41,42]

Chronic hepatitis B virus and hepatitis C virus are also reported to be comorbidities in patients with CSU. About <5% and 2% of patients with CSU have markers of hepatitis B and C. Urticarial rash including CSU occurs in ≤3% of patients with hepatitis C.[43]

The routine screening of infections in CU is not recommended, however, testing for certain infections can be done on case-to-case basis according to patients characteristics.[44]

The COVID-19 pandemic is significantly disrupting health-care systems around the world. Skin manifestations predominate and can sometimes be the first symptom of a COVID-19.[45] It is noted that acral lesions and vesicular rash are the most common types of rash that precede non-cutaneous symptoms of COVID-19; however in rare cases, urticarial rash can also appear before other non-cutaneous symptoms of COVID-19.[45]

A cross-sectional, international, and questionnaire-based study by Kocatürk *et al*., 2021, evaluated impact of the pandemic on CU and its management.[46] It was concluded that the COVID-19 pandemic severely impairs CU patient care resulting in <50% reduction of numbers of weekly treated patients, due to restricted patients' referrals in clinics and decreased clinic hours. This study showed that CU does not affect the COVID-19, but COVID-19 may exacerbate CU.[46]

DRUGS

Type I immediate IgE-mediated allergic reactions often involve acute urticaria, which is usually seen within minutes to 2 h of exposure to the allergen (food and food additives, insect venoms, etc.). These causes include also medications: Beta-lactams/penicillins, cephalosporins, and other drugs, latex, blood products, and rarely – vaccines. Allergic reactions may be presented by the skin manifestations or maybe a part of a systemic allergic reaction (e.g., anaphylaxis). Generalized urticaria/angioedema after exposure to an allergen should be considered as a systemic reaction with a potential risk of anaphylaxis after subsequent exposure.[47]

Certain drugs (narcotics, muscle relaxants, vancomycin, and radiocontrast media), and plants (stinging nettle – *Urtica dioica*), as well as some food (tomatoes, strawberries, etc.) can cause urticaria due to MC degranulation through a non-IgE-mediated mechanism.[48]

Nonsteroidal anti-inflammatory drugs (NSAIDs) can trigger urticaria and/or angioedema by two distinct mechanisms: Due to underlying abnormalities in arachidonic acid metabolism (aspirin exacerbated cutaneous/or respiratory disease) and allergic reactions to NSAIDs that may be both very severe.[49]

IgE-mediated Type I allergic reactions are extremely rare causes of CSU, on the another hand, pseudo-allergic to NSAIDs or food may be more relevant for CSU.[1,49]

ATOPIC DISEASES

The association between CU and atopic diseases (asthma, atopic dermatitis, and allergic rhinoconjunctivitis) was investigated through a cross-sectional study and observed significantly higher frequency of atopic diseases in patients with CU compared than control group.[50]

The significant associations between CU and atopic and autoimmune diseases was observed in a retrospective cohort study suggesting important role of autoimmunity in CU pathogenesis and possibility of sharing common genetic components and etiological pathways by CU and comorbid atopic and autoimmune diseases.[26]

METABOLIC SYNDROME (METS)

MetS is associated with cardiovascular disease including the increased risk for coronary heart disease and other cardiovascular atherosclerotic diseases. MetS includes glucose intolerance, dyslipidemia, hypertension, and central obesity.[14] Thirty percent of patients with CU also had MetS, and this comorbidity was associated with a more severe and uncontrolled CU.[18]

In a literature review, authors showed that MetS is becoming increasingly valued in patients with autoimmune skin diseases, including CU. Chronic inflammation may explain the link between autoimmune disease and MetS.[16]

The association between CU and MetS was investigated through a cross-sectional study that included 11261 patients with CU and matched 67216 controls.[19] In this study, patients were predominantly young women. The authors found that CU was significantly associated with MetS and its components: Diabetes, obesity, hyperlipidemia, and hypertension. These data are in agreement with the growing concept that CU is a chronic, low-grade inflammatory condition, indicating importance of the early detection and treatment of MetS or its components in CU to prevent further complications. From Public Health perspective, it is important to screen CU patients for MetS in the appropriate clinical settings.[19]

EMOTIONAL STRESS

In CSU, recurrence of symptoms several times a week or even daily has a strong impact on quality of life (QoL) and psychological state. CU belongs to the group of psychodermatological disorders, the disease itself due to itching, can worsen the QoL of patients.[51-53] There is a neuroimmune interaction that involves the secretion of neurohormones and neuropeptides. Emotional stress is an important trigger and risk factor for psychiatric disorders, which account for more than 30% of patients with CSU. Screening for mental health problems among patients with CSU should be a necessity.[51]

A comprehensive neuro-immunocutaneous model including multiple neuropeptides and neurokinins, inflammatory mediators and cells, hypothalamic-pituitary-adrenal, and skin hormones may explain the underlying pathophysiological mechanisms in urticaria. In addition, increased levels of psychological stress, strongly associated with CSU/chronic idiopathic urticaria (CIU), may be related to imbalances or disturbances in this neuro-immunocutaneous circuit. It is still not clear, whether any psychological stress leads to CSU/CIU in addition to pre-existing neuroimmune dysregulation.[51]

The depression and anxiety were evident in nearly half of the 50 CSU patients and both measures significantly positively correlated with the urticaria activity score.[52] Patients with CSU often experience sleep disturbances (SDs) due to pruritus. However, SDs may also contribute to CSU development.[54]

Investigation of the effects of stress and pruritus on the QoL of women with CU revealed that in these patients the stress level was significantly higher than in the control group.[53] With regard to the overall pruritus score, all parameters of the Urticaria QoL questionnaire (CU-Q2oL) were affected, with the exception of the edema/mental status subscale.[53]

CONCLUSION

CU is considered a heterogeneous disease with distinct clinical and pathophysiologic features. It is worth remembering that CU should not be considered just a skin disease and, in addition to the systemic symptoms, associated comorbidities could worsen CU evolution [Table 2]. The complete control of CU could minimize a worse clinical outcome for patients. Further investigations are required to determine sensitive biomarkers that can predict course of development of CU and its comorbidities associated with various phenotypes, or clusters of CU and overall effective response to adequate therapy.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Maurer M, Eyerich K, Eyerich S, Ferrer M, Gutermuth J, Hartmann K, *et al.* Urticaria: Collegium internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol 2020;181:321-33.
2. Kolkhir P, Altrichter S, Asero R, Daschner A, Ferrer M, Giménez-Arnau A, *et al.* Autoimmune diseases are linked to Type IIb autoimmune chronic spontaneous urticaria. Allergy Asthma Immunol Res 2021;13:545-59.
3. Espinosa E, Valitutti S. New roles and controls of mast cells. Curr Opin Immunol 2018;50:39-47.
4. Subramanian H, Gupta K, Ali H. Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. J Allergy Clin Immunol 2016;138:700-10.
5. Krystel-Whittemore M, Dileepan KN, Wood JG. Mast cell: A multi-functional master cell. Front Immunol 2015;6:620.
6. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, 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.
7. Xu Y, Chen G. Mast cell and autoimmune diseases. Mediators Inflamm 2015;2015:246126.
8. Rojas J, Delgado MJ, Chávez C, Chávez-Castillo M, Mejía L, Salazar J, *et al.* Mast cell activation disease associated with autoimmune thyroid disease: Case report and review of literature. Arch Venez Farmacol Ter 2016;35:92-9.
9. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970;23:455-68.
10. Gieler U, Gieler T, Schut C, Niemeier V, Peters EM, Kupfer J. Quality of life and comorbidities in urticaria: What is know? Curr Derm Rep. 2015;4:77-82.
11. Konstantinou GN, Konstantinou GN. Psychiatric comorbidity in chronic urticaria patients: A systematic review and meta-analysis. Clin Transl Allergy 2019;9:42.
12. Pawłowicz R, Wytrychowski K, Panaszek B. Eradication of *Helicobacter pylori*, as add-on therapy, has a significant, but temporary influence on recovery in chronic idiopathic urticaria: A placebo-controlled, double blind trial in the Polish population. Postepy Dermatol Alergol 2018;35:151-5.
13. Aitella E, De Bartolomeis F, Savoia A, Fabiani M, Romano M, Astarita C. The overlap syndrome of urticaria and gastroesophageal reflux disease. PLoS One 2018;13:e0207602.
14. Vena GA, Cassano N. The link between chronic spontaneous urticaria and metabolic syndrome. Eur Ann Allergy Clin Immunol 2017;49:208-12.
15. Darlenski R, Kazandjieva J, Zuberbier T, Tsankov N. Chronic urticaria as a systemic disease. Clin Dermatol 2014;32:420-3.
16. Boguniewicz M. The autoimmune nature of chronic urticaria. Allergy Asthma Proc 2008;29:433-8.
17. Kocatürk E, Grattan C. Is chronic urticaria more than skin deep? Clin Transl Allergy 2019;9:48.
18. Ye YM, Jin HJ, Hwang EK, Nam YH, Kim JH, Shin YS, *et al.* Co-existence of chronic urticaria and metabolic syndrome: Clinical implications. Acta Derm Venereol 2013;93:156-60.
19. Shalom G, Magen E, Babaev M, Tiosano S, Vardy DA, Linder D, *et al.* Chronic urticaria and the metabolic syndrome: A cross-sectional community-based study of 11 261 patients. J Eur Acad Dermatol Venereol 2018;32:276-81.
20. Fernandes M, Argolo P, Gehlen B, Batalha A, Kalil J, Motta A, *et al.* Comorbidities in patients with chronic urticaria. J Allergy Clin Immunol 2021;147 Suppl: AB27.
21. Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M. Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with chronic urticaria. JAMA Dermatol 2017;153:1236-42.
22. Türk M, Ertaş R, Zeydan E, Türk Y, Atasoy M, Gutsche A, *et al.* Identification of chronic urticaria subtypes using machine learning algorithms. Allergy 2022;77:323-6.
23. Konstantinou GN, Asero R, Ferrer M, Knol EF, Maurer M, Raap U, *et al.* EAACI taskforce position paper: Evidence for autoimmune urticaria and proposal for defining diagnostic criteria. Allergy 2013;68:27-36.
24. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review. Autoimmun Rev 2017;16:1196-208.
25. 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.
26. Ghazanfar MN, Kibsgaard L, Thomsen SF, Vestergaard C. Risk of comorbidities in patients diagnosed with chronic urticaria: A nationwide registry-study. World Allergy Organ J 2020;13:100097.
27. Chiu HY, Muo CH, Sung FC. Associations of chronic urticaria with atopic and autoimmune comorbidities: A nationwide population-based study. Int J Dermatol 2018;57:822-9.
28. Gonzalez-Diaz SN, Sanchez-Borges M, Rangel-Gonzalez DM, Guzman-Avilan RI, Canseco-Villarreal JI, Arias-Cruz A. Chronic urticaria and thyroid pathology. World Allergy Organ J 2020;13:100101.
29. Kolkhir P, Pogorelov D, Olisova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus a systematic review. Clin Exp Allergy 2016;46:275-87.
30. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, Grattan CE, *et al.* Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST study. Allergy 2019;74:2427-36.
31. Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, *et al.* Autoimmune chronic spontaneous urticaria detection with IgG anti-TPO and total IgE. J Allergy Clin Immunol Pract 2021;9:4138-46.e8.
32. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, *et al.* IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 2018;142:876-82.
33. de Montjoye L, Darrigade AS, Giménez-Arnau A, Herman A, Dumoutier L, Baeck M. Correlations between disease activity, autoimmunity and biological parameters in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol 2021;53:55-66.
34. Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, *et al.* Total IgE as a marker for chronic spontaneous urticaria. Allergy Asthma Immunol Res 2021;13:206-18.
35. Altrichter S, Zampeli V, Ellrich A, Zhang K, Church MK, Maurer M. IgM and IgA in addition to IgG autoantibodies against FcεRIα are frequent and associated with disease markers of chronic spontaneous urticaria. Allergy 2020;75:3208-15.
36. Lin W, Zhou Q, Liu C, Ying M, Xu S. Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. Sci Rep 2017;7:17797.
37. Di Campli C, Gasbarrini A, Nucera E, Franceschi F, Ojetti V, Sanz Torre E, *et al.* Beneficial effects of *Helicobacter pylori* eradication on idiopathic chronic urticaria. Dig Dis Sci 1998;43:1226-9.
38. Kim HJ, Kim YJ, Lee HJ, Hong JY, Park AY, Chung EH, *et al.* Systematic review and meta-analysis: Effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria. Helicobacter 2019;24:e12661.
39. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites a systematic review. Allergy 2016;71:308-22.
40. Del Pozo MD, Audícana M, Diez JM, Munoz D, Ansotegui IJ, Fernández E, *et al.* Anisakis simplex, a relevant etiologic factor in acute urticaria. Allergy 1997;52:576-9.
41. Minciullo PL, Cascio A, Barberi G, Gangemi S. Urticaria and bacterial infections. Allergy Asthma Proc 2014;35:295-302.
42. Nettis E, Foti C, Ambrifi M, Baiardini I, Bianchi L, Borghi A, *et al.* Urticaria: Recommendations from the Italian society of allergology, asthma and clinical immunology and the Italian society of allergological, occupational and environmental dermatology. Clin Mol Allergy 2020;18:8.
43. Kolkhir P, Pereverzina N, Olisova O, Maurer M. Comorbidity of viral hepatitis and chronic spontaneous urticaria: A systematic review. Allergy 2018;73:1946-53.
44. Gotua M, Kulumbegov B, Chanturidze N, Devidze M, Lomidze N, Rukhadze M. Association between urticaria and infections (review). Georgian Med News 2019;288:97-101.
45. Pagali S, Parikh RS. Severe urticarial rash as the initial symptom of COVID-19 infection. BMJ Case Rep 2021;14:e241793.
46. Kocatürk E, Salman A, Cherrez-Ojeda I, Criado PR, Peter J, Comert-Ozer E, *et al.* The global impact of the COVID-19 pandemic on the management and course of chronic urticaria. Allergy 2021;76:816-30.
47. Saini S. Chronic Spontaneous Urticaria: Clinical Manifestations, Diagnosis, Pathogenesis, and Natural History. UpToDate; 2021.
48. Cummings AJ, Olsen M. Mechanism of action of stinging nettles. Wilderness Environ Med 2011;22:136-9.
49. Doña I, Pérez-Sánchez N, Eguiluz-Gracia I, Muñoz-Cano R, Bartra J, Torres MJ, *et al.* Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Allergy 2020;75:561-75.
50. Shalom G, Magen E, Dreiher J, Freud T, Bogen B, Comaneshter D, *et al.* Chronic urticaria and atopic disorders: A cross-sectional study of 11 271 patients. Br J Dermatol 2017;177:e96-7.
51. Konstantinou GN, Konstantinou GN. Psychological stress and chronic urticaria: A neuro-immuno-cutaneous crosstalk. A systematic review of the existing evidence. Clin Ther 2020;42:771-82.
52. Tat TS. Higher levels of depression and anxiety in patients with chronic urticaria. Med Sci Monit 2019;25:115-20.
53. Ograczyk-Piotrowska A, Gerlicz-Kowalczuk Z, Pietrzak A, Zalewska-Janowska AM. Stress, itch and quality of life in chronic urticaria females. Postepy Dermatol Alergol 2018;35:156-60.
54. He GY, Tsai TF, Lin CL, Shih HM, Hsu TY. Association between sleep disorders and subsequent chronic spontaneous urticaria development: A population-based cohort study. Medicine (Baltimore) 2018;97:e11992.

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