Introduction

Chronic urticaria is a disease characterized by the development of itching hives, angioedema, or both for six weeks or more (1). Among its different presentations, chronic spontaneous urticaria (CSU) is the most common, with a point prevalence of 0.4 to 1.0% in the general population (2). CSU's average duration ranges from 6 months to 5 years but may be longer in patients with angioedema or autoimmune thyroid disease (3–5).

Currently, there are potential biomarkers of CSU activity and response to treatment (6). Still, a definitive blood biomarker to predict CSU duration or prognosis is lacking, and anti-thyroid antibodies have been studied for this purpose. However, its use is controversial since the frequency of this association is variable in different populations (3,7,8). Therefore, this study aimed to evaluate anti-thyroid autoantibodies' association with disease duration, presence of angioedema, and response to antihistamines treatment.

Materials and Methods

This retrospective and cross-sectional study analyzed data from CSU patients followed at the Federal University of Sao Paulo from January 2012 to December 2019. The study was conducted in accordance with Declaration of Helsinki and all participants or their legal guardians have given their written informed consent to file their records for clinical research. The registry was approved by the ethics committee of the Federal University of Sao Paulo (CAAE: 94104318.0.0000.5505).

All patients with a clinical diagnosis of CSU and tested for anti-thyroglobulin (anti-TGB) IgG or anti-peroxidase (anti-TPO) IgG antibodies were included. Patients with isolated inducible chronic urticaria or incomplete data charts were excluded.

To access the presence of anti-thyroid antibodies (ATA) in CSU patients, we considered the positivity for any or both anti-TGB/Anti-TPO IgG antibodies. We statistically analyzed this data with different prognostic aspects of CSU according to the nature of variables. The chi-square or Fisher's exact test were used to analyze associations between categorical groups and compare distributions. The median test was used to compare medians, and a p-value ≤ 0.05 was considered statistically significant. The time from the onset of symptoms until the last visit presenting urticaria was chosen to assess disease duration. The response to treatment criteria was met based on the second-generation antihistamines (anti-H1) doses necessary to control symptoms (UAS7 ≤ 6 and/or UCT > 12) or the refractoriness to these drugs, defined by UAS7 > 6 and/or UCT < 12 with 4-times the standard anti-H1 dose (1).

Results

In this study, 147 patients were tested for ATA and included for analysis. The mean age of patients was 36.4 years (SD: 17.21), and females were predominant (5:1). Only 42 patients had positive ATA (14 anti-TPO + / 14 anti-TGB + / 14 positive for both), 85% were women and the mean age was 38.43 years (SD: 16.42); however, there was no association between gender and age with ATA (p=0.86 and p=0.36, respectively). CSU duration was variable, with a median of 36 months (range: 2 to 360 months). In ATA positive patients, the median CSU duration was 31 months, while in ATA negative was 36 months. There was no significant difference in CSU duration between ATA groups (p= 0.58) as shown in figure 01, even when comparing isolated positiveness to Anti-TPO or Anti-TGB (p=0.58 and p=0.68, respectively). Sixteen patients had autoimmune thyroid diseases but only nine of them had positive ATA. These diseases were not associated with CSU duration as well (p=0.73).

Angioedema was more frequent in patients with ATA (64.2%), but not significantly (p=0.45). Also, ATA's association with angioedema did not influence CSU duration compared with ATA positiveness and angioedema only (p = 0.63).

The majority of CSU patients had a good response to anti-H1 treatment (107/147), but only 15% controlled with standard doses. One quarter of patients controlled with 2-fold the standard dose, and 32% with 4-fold dose. When comparing ATA groups, ATA positive patients responded to anti-H1 treatment in 69% of cases (29/42), while ATA negatives responded in 74%. Regarding the anti-H1 dose regimen, a standard dose was able to control symptoms in 12% of ATA positives and 16% of negatives; a 2-fold dose in 29% of positives and 24% of negatives; and a 4-fold dose in 29% positives and 26% negatives. In ATA positives, 30% did not respond to the 4-fold dose anti-H1 treatment, while in ATA negatives 26%. Although the ATA positive patients used nonstandard doses more frequently, we found no association of positivity to ATA and response to anti-H1 treatment (p=0.54) or the necessary dosage to control symptoms (p=0.79).

Discussion/Conclusion

The prevalence found of positive ATA in CSU patients (29%) was similar to the literature (5), which was up to 53.6% in some studies (11). The exact mechanism that explains this association is still unknown, but autoimmunity has been discussed and could explain part of the physiopathology (11).

The higher prevalence of CSU and positive ATA in women were previously observed and involved the role of adipokines and other cytokines in promoting an inflammatory state capable of compromise the

innate immune response to triggers. This erratic response contributes to the inflammatory cascade and breaks the tolerance to thyroid autoantigens (5).

A strong association between ATA presence and CSU duration has been discussed since 2004 when a study reported that in 70% of ATA patients, the urticaria lasted for more than one year (4). Furthermore, anti-TPO seems to have a more critical role in predicting CSU duration than anti-TGB (5). However, in our sample, anti-thyroid antibodies were not statistically associated with CSU duration.

In a Thai study, angioedema was not associated with autoimmune thyroiditis or the presence of autoantibodies alone (5). Although angioedema was more frequent in patients with positive autoantibodies in our study, there was also no statistical association between these two variables. The same Thai study described a higher use of nonstandard doses of second-generation anti-H1 in CSU patients with positive ATA than in ATA negatives (61.2% versus 37.8%). However, this association was not statistically different in their study (5). Similarly, in our sample, ATA patients used nonstandard doses more frequently but without statistical difference. Therefore, we believe it is not possible to say that positive ATA has an actual interference in response to treatment with anti-H1.

Limitations of this study were a lack of information about CSU activity and control scores in all medical records, preventing the inclusion of these variables in the analyses. Also, 15 patients lost follow-up, and we considered the last registered outcome to evaluate response to treatment. However, strong points in our study are the size of our sample and the fact this is the first study to evaluate the role of ATA in a population of CSU Brazilian patients.

Therefore, we concluded anti-thyroid autoantibodies might not be suitable biomarkers to predict CSU duration, disease severity, or response to anti-H1 treatment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

References

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse U and W. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy Eur J Allergy Clin Immunol. 2018;73(7):1393–414.
2. Maria-Magdalena Balp, Karsten Weller, Veruska Carboni, Alexandra Chirilov, Charis Papavassilis, Thomas Severin, Haijun Tian, Torsten Zuberbier MM. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. Pediatr Allergy Immunol. 2018;29(6):630–6.
3. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. Allergy. 2017 Oct 1;72(10):1440–60.
4. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: A prospective study of 139 patients. Allergy Eur J Allergy Clin Immunol. 2004;59(8):869–73.
5. Chanprapaph K, Iamsumang W, Wattanakrai P, Vachiramon V. Thyroid autoimmunity and autoimmunity in chronic spontaneous urticaria linked to disease severity, therapeutic response, and time to remission in patients with chronic spontaneous urticaria. Biomed Res Int. 2018;2018.
6. Jie Shen Fok, Pavel Kolkhir, Martin K Church MM. Predictors of treatment response in chronic spontaneous urticaria. Allergy. (doi: 10.1111/all.14757. Online ahead of print).
7. Kolkhir P, André F, Church MK, Maurer M, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. Clin Exp Allergy. 2017;47(1):19–36.
8. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging Biomarkers and Therapeutic Pipelines for Chronic Spontaneous Urticaria. J Allergy Clin Immunol Pract. 2018;6(4):1108–17.
9. Alen Coutinho I, Regateiro FS, Fernandes RA, Pita JS, Gomes R, Coelho C, et al. Refractory chronic urticaria in adults: clinical characterization and predictors of severity. Allergy, Asthma Clin Immunol. 2020;16(1):1–9.
10. Folci M, Heffler E, Canonica GW, Furlan R, Brunetta E. Cutting edge: Biomarkers for chronic spontaneous urticaria. J Immunol Res. 2018;2018:
11. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. J Allergy Clin Immunol. 2017;139(6):1772-1781.e1.

Figure Legends

Fig. 1. CSU duration in patients with positive and negative anti-thyroid antibodies (ATA).