The Utility of Serum Tryptase as a Marker in Chronic Spontaneous Urticaria

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Chronic spontaneous urticaria (CsU) is defined as recurrent episodes of spontaneous pruritic wheal and flare skin lesions that occur daily, or on most days of the week, for at least 6 weeks (1). CsU is characterized by an unpredictable clinical course with varying degrees of frequency and severity. Mast cell activation may play a role in the pathogenesis of chronic urticaria as mast cells release a variety of mediators, including histamine and tryptase (2).

Elevated tryptase levels can be identified in the setting of mast cell degranulation (i.e. IgE-mediated reactions, such as anaphylaxis) and/or increased mast cell burden (i.e. mastocytosis) (3, 4). Elevated total serum tryptase (tST) has been demonstrated in a subset of patients with CsU compared with controls (5–7). The aim of this study was to identify clinical features of a subset of patients with CsU and elevated tST compared with those with normal tST.

MATERIALS AND METHODS

We performed a retrospective chart review of subjects with CsU who underwent tST evaluation via fluorescent enzyme immunoassay from 2004 to 2011. Elevated tST was defined as a value ≥ 13.5 μg/l, the upper limit of normal at our facility. Patients with acute urticaria, urticarial vasculitis, incomplete medical records or possible systemic mastocytosis (i.e. tryptase level >20 μg/l without bone marrow biopsy) were excluded from data analysis. Categorical variables were analysed using χ^2 or Fisher's exact tests. Continuous variables were analysed using Wilcoxon rank-sum or Student's *t*-tests. Statistical significance was set at $p < 0.05$. The study was conducted with Institutional Review Board approval.

RESULTS

A total of 205 subjects with CsU who had been tested for tST were identified. The male:female ratio was 1:2 (69 males and 136 females). Of these, 18 had elevated tST (≥ 13.5 μg/l) and 187 subjects with normal tryptase levels (Table SI; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1486). The mean ± SD age was significantly greater for CsU subjects with elevated tST compared with those with normal tST (50 ± 19 years vs. 40 ± 18 years; $p = 0.02$). Otherwise, there were no statistically significant demographic differences among the 2 groups. The duration of urticaria was not statistically different between patients with elevated tryptase and those with normal tryptase (5.5 months (range 3–20 months) vs. 12.0 months (range 4–36 months) ($p = 0.12$)), respectively.

Of the 18 subjects with elevated tST, a total of 8 subjects (44%) underwent bone marrow biopsy and none met World Health Organization (WHO) criteria for the diagnosis of systemic mastocytosis (4). Six of the 8 subjects had markedly elevated tST (>20 μg/l) yet no evidence of systemic mastocytosis on bone marrow biopsy. There were an additional 4 subjects with CsU who had tST >20 μg/l, but declined bone marrow biopsy and were therefore excluded from the data analysis. There were no differences found among CsU subjects with elevated vs. normal tST with regards to complete blood count, comprehensive metabolic panel, antinuclear antibody, thyroid stimulating hormone, sedimentation rate, C-reactive protein, anti-microsomal antibody or anti-thyroid peroxidase antibody.

There were no statistically significant differences between the two groups in the percentage of subjects with a concomitant atopic condition; autoimmune disease; angioedema or anaphylaxis. Subjects with CsU and elevated tST were found to have similar utilization of antihistamines; H2-receptor blockers; leukotriene antagonists; oral albuterol, and immunomodulators (cyclosporine) (for details see Appendix SI; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1486)). A greater percentage of subjects with CsU and elevated tST were prescribed oral corticosteroids (9/18 (50.0%) vs. 48/187 (25.7%); $p = 0.028$) and required more frequent use of oral steroids based on number of days per month ($p = 0.007$). Multivariate analysis controlling for age revealed an odds ratio of 2.43 (95% confidence interval 0.89, 6.62) for prescription of oral steroids in subjects with elevated tST, which was not statistically significant ($p = 0.08$), possibly due to the small sample size.

DISCUSSION

To date there are limited prognostic tests available to predict disease characteristics in CsU. Autologous serum skin testing or evaluation for anti-FcεRI or anti-IgE antibodies may identify a subset of patients with "autoreactive" urticaria (2, 8). The therapeutic implications of "autoreactive" urticaria remain unresolved.

A statistically significant increase in tST has been demonstrated in a subset of patients with CsU compared with controls, though in all previous studies the total tST remained in the normal range (5–7). Unlike prior studies, our study identified a subgroup of CsU subjects with elevated tST (≥ 13.5μg/l) that was out-

side the normal range. These subjects were found to be older and may have a more severe disease course as indirectly measured by a trend towards greater use of oral steroids for symptom control. Interestingly, in a retrospective study of patients seen in a dermatology clinic for possible allergic disease, anaphylaxis, and urticaria, elevated basal serum tryptase was also found to be correlated with increasing age (9). In the study by Schliemann et al. CsU subjects with elevated tST were not different from their counterparts with respect to other clinical characteristics or the use of conventional CsU medications (9).

In the present study retrospective study it was difficult to uniformly quantify disease burden, since the extent of active lesions, mean wheal and flare size, standardized urticaria activity score, and quality of life measures were not consistently recorded in the medical record. Therefore, data analysis of surrogate markers of severity, including specific steroid dosing, was not possible. We acknowledge that retrospective data collection poses a significant limitation to the results.

A tST > 20 μg/l is one of the minor WHO diagnostic criteria for systemic mastocytosis, and we found 6 CsU subjects with tST > 20 μg/l (4). All of these subjects had a bone marrow biopsy that was negative for systemic mastocytosis. There were 4 subjects with CsU and tryptase >20 μg/l who unfortunately declined a bone marrow biopsy and were therefore not included in the data analysis. Thus, one limitation of this retrospective study is that only 8 of 18 CsU subjects with elevated tST underwent more definitive testing to exclude the diagnosis of systemic mastocytosis. Although elevated tST levels may be due to underlying mastocytosis, CsU subjects with tryptase levels ≥13.5 μg/l had no other clinical or laboratory findings suggestive of mastocytosis, compared with controls.

tST measures both α preprotryptase (or immature tryptase) and β (or mature) tryptase. Immature tryptase is presumably constitutively expressed by mast cells, while mature tryptase is elevated in the setting of mast cell activation and degranulation (3). Thus, fractionation of tryptase could help distinguish mast cell burden from mast cell activation when the proposed mast cell activation syndrome is suspected; however, tryptase fractionation was not available in this retrospective chart review study. Therefore, it is not clear whether elevated tST in subjects with CsU implies mast cell activation, as steroid therapy does not prevent mast cell activation *in vitro* (10).

This study demonstrates that patients with CsU with elevated tST may require increased steroid therapy for disease control. The utility of tST as a biomarker to justify steroid use in the first place certainly has not been established, given that a minority of CsU subjects had tST ≥ 13.5 μg/l and only a subset of these subjects had a marrow examination. Future studies are needed to determine the utility of measuring tST in patients with CsU.

The authors declare no conflicts of interest.

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