

Short communication

The autologous serum skin test in the follow-up of patients with chronic urticaria

Background: The presence of anti-FcεRI and anti-IgE autoantibodies in a subset of patients with chronic urticaria suggests their aetiopathogenetic role. In clinical practice, the presence of these antibodies is usually considered when the autologous serum skin test (ASST) is positive.

Aims: To evaluate if the positive ASST follows up the activity of chronic urticaria.

Methods: Autologous serum skin test and thyroid autoantibody detection were performed in 82 patients with chronic urticaria and repeated 1 year later, when the vast majority of patients were symptom-free. Twenty patients with Hashimoto thyroiditis (HT), who had never suffered from urticaria, represented the control group.

Results: At the start of the study, the prevalence of positive ASST was 46.6%. The association of HT–urticaria was 29.3%. ASST was positive in 62 and 39% of patients with and without HT, respectively ($P > 0.05$ ns). One year later, 28 of 34 patients with a positive ASST were symptom-free, but 50% of them were positive for ASST. The ASST was positive in 86.7 and 8% of patients with and without HT, respectively ($P < 0.001$). In the control group, ASST was always negative.

Conclusions: The co-existence of autoimmune thyroiditis with chronic urticaria seems to induce a significant difference in the persistence of a positive ASST. Consistent with previous reports, a positive ASST correlates with disease exacerbation in chronic urticaria patients without thyroiditis. In patients with thyroiditis and urticaria, positive ASST persists even after the urticaria has disappeared, thus questioning whether a positive ASST to be a surrogate marker of the functional role of anti-FcεRI and anti-IgE autoantibodies.

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Chronic urticaria is characterized by the recurrence of transient and itching maculopapular skin lesions with or without angioedema for more than 6 weeks (1, 2).

The presence of IgG anti-FcεRI and anti-IgE autoantibodies capable of activating mast cell and basophil degranulation suggests that the autoimmune aetiopathogenesis of the disease in a subset of patients (1–3). In particular, the presence of these autoantibodies is consistent with the exacerbation of the disease (4).

A further aspect suggesting an autoimmune cause of the chronic urticaria is its association with autoimmune thyroiditis (5). A correlation between the presence of anti-FcεRI and anti-IgE autoantibodies and positive ASST was documented. As a result, in clinical practice, a positive autologous serum skin test (ASST) is assumed to be suggestive of the autoimmune pathogenesis of the urticaria (6).

The aim of the study was to evaluate the follow-up of positive ASST in chronic urticaria patients as a surrogate marker of the functional role of these autoantibodies.

Methods

Patients and study design

Eighty-two patients with chronic urticaria diagnosed by the presence of hives for more than 6 months were enrolled. Sixty patients were female, and mean age was 39 ± 15 years (DS). In the first step, in patients with active urticaria, the ASST and the detection of thyroid autoantibodies were performed [time 0 (T0)].

One year later [time 1 (T1)] the same diagnostic protocol was repeated in positive ASST patients independent of the persistence of symptoms of urticaria.

As a high prevalence of positive ASST in urticaria patients with autoimmune thyroiditis was documented at the first step, ASST was carried out in 20 patients with autoimmune thyroiditis who had never suffered from urticaria, in order to evaluate if the positive ASST was related to autoimmune thyroiditis irrespective of coexisting urticaria (the control group). The ethics committee of our hospital approved the study protocol. All patients gave their informed consent before starting the study.

Skin test and thyroid function

Antihistamines were avoided 5 days before the skin test. An intradermal test with 0.05 ml of fresh, undiluted, autologous serum and saline control was performed and evaluated 30 min later (6).

A difference of > 1.5 mm between the wheal diameter elicited by autologous serum and that by saline was considered as a positive ASST (6).

In the same patients, circulating thyroid autoantibodies (antibodies antithyroglobulin and antithyroperoxidase) were investigated (BRAHMS Diagnostica GMBH, Hennigsdorf, Germany). Thyroid autoimmune disease was diagnosed on the basis of the presence of circulating antibodies antithyroglobulin and antithyroperoxidase.

Statistical analysis

Statistical analysis was performed on a Macintosh computer using an Instat 2.03 (GraphPad Software 1994, San Diego, CA, USA) software package. The chi-squared test was used in descriptive analysis of patients and a P -value < 0.05 was considered significant.

Results

At the beginning of the study (T0), ASST was performed in 73 of the 82 enrolled patients, with the exclusion of nine patients taking antihistamines.

The prevalence of positive ASST in our chronic urticaria patients was 46.6%. The autoimmune thyroiditis-urticaria association was 29.3%. The prevalence of positive ASST was 62% in patients with autoimmune thyroiditis and 39% in patients without autoimmune thyroiditis ($P > 0.05$ ns). One year later (T1), 28 of the 34 positive ASST patients were symptom-free (two males; age 40 ± 16 years). The ASST was positive in the six patients with the active disease and in 50% of the symptom-free patients. A positive ASST was present in

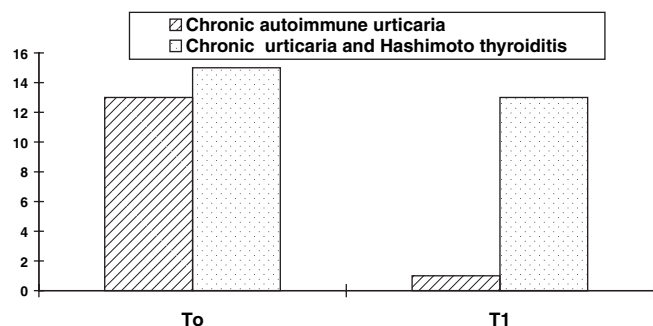


Figure 1. Follow-up of positive ASST. At time 0 (active disease) the distribution of positive ASST in 28 patients suffering from chronic idiopathic urticaria with or without Hashimoto thyroiditis is shown. One year later (time 1), the distribution of positive ASST in 14 patients suffering from chronic idiopathic urticaria with or without Hashimoto thyroiditis in spite of the remission of urticaria; 14 patients with negative ASST are not shown.

13 of the 15 patients with urticaria and autoimmune thyroiditis (86.7%) and in one of the 13 patients with urticaria without autoimmune thyroiditis (8%) ($P < 0.001$) (Fig. 1).

In controls, i.e. patients with thyroiditis without a positive case history for urticaria, ASST was always negative.

Discussion

At the first step of the study, the sample of chronic urticaria patients is quite similar to populations examined in other studies. In particular, the markedly high prevalence of females (73%) and the prevalence of the ASST positivity (46.6%) were consistent with results of analogous studies (7). Although other investigators reported a lower level (8), the prevalence of the autoimmune thyroiditis (29.3%) was very close to results of a study performed in Italy (7).

The prevalence of the positive ASST in patients with comorbidity urticaria-thyroiditis was similar to that reported in a previous study (56%) (9) but higher than that reported by other authors (25%) (10).

A significant difference in the follow up of chronic urticaria using ASST was documented. A positive ASST is consistent with the clinical course of symptoms in patients with urticaria without autoimmune thyroiditis, whereas the ASST continued to be positive in patients with urticaria and autoimmune thyroiditis, in spite of the remission of urticaria.

The high prevalence of positive ASST in patients suffering from urticaria and thyroiditis already at step one of the study and its persistence even after remission of cutaneous symptoms seems to suggest that some factor related to thyroid disease can enhance a positive ASST.

However, the negative ASST detected in all patients with autoimmune thyroiditis with no history of urticaria clearly indicates that the presence of some anomaly at a cutaneous level is necessary to induce a positive ASST. The significance of such a result is unclear.

We speculate that the decrease of anti-FcεRI and anti-IgE IgG autoantibody serum level could be involved in spontaneous urticaria remission, as suggested by a negative ASST in symptom-free autoimmune urticaria patients (4). The intracutaneous injection of an unknown histamine release factor present in serum of thyroiditis patients, could restore the degranulation of sensitive mast cells. The low level of autoantibodies present on mast cells surface, unable to cause the degranulation by themselves, could be the enhancing factor of mast-cell sensitivity.

If the two factors (histamine releasing factor from thyroiditis serum and skin abnormality) are not combined, as in the control group of thyroiditis patients, the phenomenon does not appear.

The presence of histamine-releasing factors or a component of the complement pathway in thyroiditis patients could be involved in this. In patients with urticaria, the presence of unknown histamine-releasing factors other than autoantibodies were documented (11, 12). Unfortunately, the presence and the role of coexisting autoimmune thyroiditis in such patients have not been investigated.

Therefore we cannot exclude that such histamine releasing factors was linked to co-existing thyroiditis. The role of the complement pathway in the skin mast cell degranulation has been recently emphasized (3, 11, 12, 13).

The previous model of functionally active autoantibodies in urticaria is thought to cause mast cell degranulation by a direct ligation and cross-link of α chain of Fc ϵ RI (Anti-Fc ϵ RI) or adjacent receptor-bound IgE (anti-IgE) (3). The evidence that these autoantibodies belong to IgG₁ and IgG₃ (13) complement-activating isotypes suggests a different mechanism in mast cell degranulation, i.e. autoantibodies can directly activate histamine release by combining with their receptors, but the amount of histamine released is increased by com-

plement activation with a broad variability within patients (3).

In particular, complement activation liberates component C5a, which directly participates in skin mast cell degranulation in urticaria patients with anti-Fc ϵ RI autoantibodies (12). This effect is selective because C5a receptors are expressed by mast cells in the skin but not by those in the lung (14).

A similar ability in activating the complement pathway *in vitro* by thyroid peroxidase autoantibodies, belonging to the IgG₁ and IgG₃ isotypes, has been documented, although the role of complement activation in the extent and progression of thyroid damage in Hashimoto and post-partum thyroiditis is under investigation (15).

In conclusion, our results seem to indicate that autoimmune thyroiditis can represent a relevant factor enhancing a positive ASST, thus questioning the role of this test as a surrogate marker of circulating anti-Fc ϵ RI and anti-IgE autoantibodies.

Further studies are necessary in order to verify the presence and the level of anti-Fc ϵ RI and anti-IgE autoantibodies and complement components in patient with thyroiditis and urticaria comorbidity.

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