

Original article

Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients

Background: Despite the disabling nature of chronic urticaria (CU), little is known about the disease's duration or the efficacy of adopting aggressive therapeutic regimens such as cyclosporine A.

Objectives: The aim of this study was to evaluate whether parameters such as angioedema, autologous serum test, anti-thyroid antibodies, and total IgE could predict both CU duration and severity.

Patients and methods: One hundred and thirty-nine patients suffering from CU were prospectively followed over a 5-year period for disease duration, severity and the presence of angioedema. Also investigated was the association between these clinical parameters and the subsequent detection of autologous serum test, anti-thyroid antibodies, and total IgE.

Results: CU lasted over 1 year in more than 70% of cases and in 14% it still existed after 5 years. Angioedema co-existed or appeared during the course of CU in 40% of patients and was associated with disease duration. Autologous serum test and anti-thyroid antibodies were found positive in 28 and 12% of patients, respectively, compared to none of normal individuals, $P = 0.001$. CU duration was associated with the presence of both autologous serum test and anti-thyroid antibodies; however, autologous serum test and not anti-thyroid antibodies was found in association with CU severity.

Conclusion: We demonstrate for the first time that CU duration is associated with clinical parameters such as severity and angioedema, and with laboratory parameters such as autologous serum test and anti-thyroid antibodies. The ability to predict CU duration may facilitate decisions regarding the possible early initiation of cyclosporine A as a means by which to reduce disease severity and duration.

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Chronic urticaria (CU) is a common disabling disorder occurring in 0.1% of the population, with an average duration of 3–5 years in adults (1). Physical urticaria and intolerance to food additives account for 20% and nearly 5% of such patients, respectively, with the remaining defined as chronic idiopathic urticaria (CIU). Nevertheless, in 40% of patients, physical urticaria such as delayed pressure urticaria and dermatographism were shown to co-exist with CIU (2–4).

In 1986, Grattan et al. (5) reported the presence of a serum factor that caused whealing upon autologous intradermal injection (autologous serum test, AST) in some patients with CIU. However, the autoimmune dimension of CU became apparent only in 1993 when Greaves and colleagues (6) identified this factor as an IgG with specificity for the α -chain of the high-affinity IgE receptor (Fc ϵ RI α). The presence of anti-Fc ϵ RI α , ranging from 25 to 45% of the total patients with CIU, was demonstrated by many to be the causative autoantibody that results in mast cell degranulation (7, 8). The

possibility that CU is at least partially autoimmune is consistent with previous findings of increased frequency of anti-thyroid antibodies (ATA) and other autoimmune markers such as rheumatoid factor (9, 10).

Although most investigators concur that laboratory tests such as CBC, chemistry panel, complement levels and skin test are noncontributory, autoimmune markers such as anti-nuclear (ANA), AST, ATA, and total IgE are worthy of consideration and were subsequently obtained routinely by most clinicians for the evaluation of CU. In practice, most specialists who deal with this disabling disorder are mainly concerned with the management of these patients. H1 anti-histamine treatment is beneficial for mild–moderate CU patients. However, when CU is severe and short courses of corticosteroids are unavoidable, low dose of cyclosporine A (CsA) was reported by many to be both safe and beneficial (11–13). The natural history of CIU becomes particularly important when such forms of treatment are considered, given that the efficacy of such treatment modalities are

likely to vary with the disease course. Yet, reports on the natural history of CU are very limited, and for the most part fail to cover the possible association between the clinical course of CU and laboratory analyses (14–17). Consequently, we still know little about the average duration of CU and the prevalence of CU lasting longer than 1 year. We also know little about the efficacy of CsA treatment among severe patients symptomatic for longer than 1 year, not to mention the efficacy of early initiation of CsA in particularly severe cases.

The current study was designed to analyze whether urticaria duration could be predicted by various clinical and laboratory parameters such as AST, ANA, ATA, total IgE, and others in a large cohort of patients who were prospectively followed in our referral outpatient clinic over a period of 5 years.

Patients and methods

This prospective study included 145 CIU patients (92 females and 53 males, age range 17–66 years, mean 41 years) who were followed by four senior allergists in two large referral outpatient allergy clinics from 1998 until 2003. The follow-up time ranged between 3 and 5 years. Exclusion criteria included pure physical urticaria, infectious diseases, and food or food additive hypersensitivity. Chronic infection was excluded on the basis of a detailed history, physical examination, and related laboratory analyses such as stool culture and eosinophils for parasites, C-reactive protein, and antibodies to *Helicobacter pylori* when suspected (18). Food and food additive hypersensitivity were excluded on the basis of skin prick tests for a wide panel of food allergens and a trial of mono-allergen elimination diet. When highly suspected, oral food additive provocation tests were initiated (19, 20).

All patients underwent the following laboratory workup: CBC, chemistry panel, protein-electrophoresis (PEP) and complement levels. ANAs were detected by using indirect fluorescent antibody technique on HEP-2 commercial slides (Zeus Scientific, Inc., New Jersey, USA), anti-thyroglobulin and thyroid microsomal antibodies were detected by ELISA commercial kits (Orgentec Diagnostika, GmbH, Mainz, Germany), and total IgE was detected by a Ridascreen, ELISA kit (Darmstadt, Germany). AST was detected upon entry in only 127 patients. All laboratory tests were compared with those analyzed in 60 age- and sex-matched healthy individuals (employees of both medical centers), who served as normal controls. During follow-up, six patients dropped out, leaving a sample of 139 patients for whom complete information was available.

Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Bnai Zion Medical Center Human Research Committee.

Urticaria score

All patients were scored on a four-point scale as detailed previously by Breneman et al. (21). Briefly, this scale takes into account the number of lesions, number of separate episodes, average size of lesions, average duration of lesions and pruritus as follows: 0 = no symptoms; 1 = mild urticaria (1–4 points); 2 = moderate urticaria (5–9 points); 3 = severe urticaria (=10 points).

Autologous serum test

AST was performed in all the individuals studied (in patients after antihistamine washout) as previously described (22). Briefly, 0.1 ml of sterile autologous serum was injected intradermally, and the wheal/flare size was determined at 30 min and followed for a total of 60 min. Saline was used as a negative control and histamine (1 mg/ml) served as a positive control. The wheal/flare diameter was measured and scored from 0 to +3 as follows: 0 = negative control; +1 = wheal 1.5 mm > negative control, flare = 15 mm; +2 wheal = 3–5 mm, flare > 15 mm; +3 = wheal = 6–10 mm. A widely used simplification of this test was suggested by the same group, that is, AST is considered positive when the wheal attained is at least 1.5 mm greater than the negative control (23).

Statistical analyses

Associations between categorical groups were assessed using the chi-square test or Fisher's exact test as appropriate. The relation between urticaria duration and disease severity, angioedema, AST and ATA was evaluated using the log-rank test. Kaplan–Meier curves were constructed and displayed for the relation between urticaria duration and each of the above variables. Two-tailed *P*-values of 0.05 or less were considered to be statistically significant.

Results

Patient characteristics

At commencement of the study and during the following 3 months of follow-up, 28/139 (20%) patients were scored as mild CU, whereas 45/139 (32%) and 66/139 (47%) were scored as suffering from moderate to severe CU, respectively. Angioedema (at least three episodes of angioedema during a month) co-existed or appeared during the course of CU in 56/139 (40%) of patients. Patients with mild CU were treated periodically with antihistamines, whereas most patients with moderate to severe CU were on antihistamines most of the time and frequently needed short courses of corticosteroids.

Duration of CU

After 6 months of follow-up, 94% of patients were still found to be CU-positive. At the end of 12 months CU was still ongoing in 75% of patients, whereas towards the end of 24 months CU was present in 52% of patients. After 36 months of follow-up CU was still present in 43% of patients, and by the end of the study (5 years) 14% of patients were still suffering from CU.

Laboratory analyses

All patients presented normal chemistry panel, CBC, PEP, and complement levels. ANA were found positive in 6/139 (4%) of patients compared to 1/60 (1.7%) of normal controls, *P* = 0.6. Both duration and severity were not associated with ANA positivity. ATAs were detected positive in 17/139 (12%) of patients compared to

none of the normal controls $P = 0.004$. In three of these patients disthyroidism was detected by low TT4 and high TSH; however, thyroid replacement did not change the course of CU. Total IgE was found elevated (considered elevated only when $>200 \text{ U} + 2 \text{ SD}$) in 32/139 (23%) compared to 3/60 (5%) in the control group $P = 0.02$.

The association of CU duration with clinical parameters (angioedema and severity), and laboratory parameters (AST, ATA, and total IgE) was analyzed in all patients studied as follows:

Relation between CU duration and severity: Whereas urticaria resolved in all patients with mild CU within 24 months, moderate to severe CU persisted in 59% of patients up to 24 months, and in 32% up to 60 months, $P < 0.0001$ (Table 1).

With angioedema: At 12 months of follow-up, 88 and 80% of angioedema-positive and angioedema-negative patients were still suffering from urticaria attacks, respectively. However, at 24 months of follow-up 64% of angioedema-positive patients in contrast to 43% of angioedema-negative patients were still presenting CU hives. When this association was analyzed further up to 5 years 45% of patients with existing angioedema were still having CU as compared to only 12% of angioedema-negative patients, $P = 0.002$ (see Fig. 1).

Table 1. Rates of urticaria duration in relation to disease severity

Severity	Rates of urticaria duration (months)				P value
	12	24	36	60	
Mild ($n = 23$)	68%	0%	—	—	<0.0001
Moderate to severe ($n = 116$)	86%	59%	50%	32%	

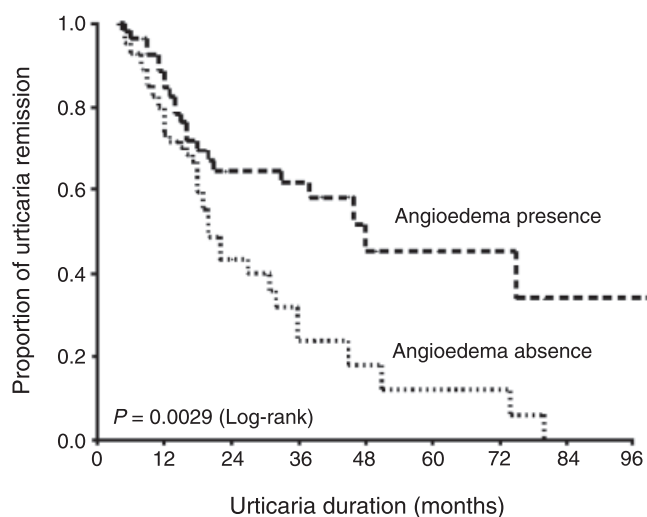


Figure 1. A Kaplan–Meier curve demonstrating the relationship between chronic urticaria duration and the presence of angioedema during the course of disease in these patients.

In relation with AST: AST was defined positive in 36/126 (28%) of patients and in none among the normal individuals, $P = 0.0001$. In this regard, when CU duration was analyzed in relation to AST, significant differences were already present at 12 months of follow-up: CU still existed in 94% of AST-positive patients, in contrast to 78% of AST-negative patients. At 24 months, 72% of AST-positive patients were still suffering from CU, in contrast to 43% of AST-negative patients. Of interest is that at 5 years of follow-up both AST-positive and AST-negative patients presented similar rates. Differences in CU duration between AST-positive and AST-negative were significant when considering the whole period, $P = 0.004$ (see Fig. 2). Also, we could not demonstrate a correlation between CU duration and AST score among patients with positive AST.

CU duration in relation to ATA: At 12 months differences in CU rates between ATA-positive and AST-negative patients were noticed (94 vs 82%, respectively). At 24 months, 70% of ATA-positive patients (as opposed to 50% of ATA-negative patients) still suffered from CU. At 5 years of follow-up, 52% of ATA-positive patients vs 16% of ATA-negative presented CU attacks, $P = 0.02$ (see Fig. 3).

Though relative to normal individuals, total IgE was found to be elevated among CU patients, this elevation was not found to have a significant association with either disease duration or CU severity.

The association of CU severity with other parameters

Angioedema was documented in 47/111 patients suffering from moderate to severe CU, and in 9/28 of mild CU patients. ATA was found positive in 3/28 mild CU patients and in 14/111 of moderate to severe CU patients.

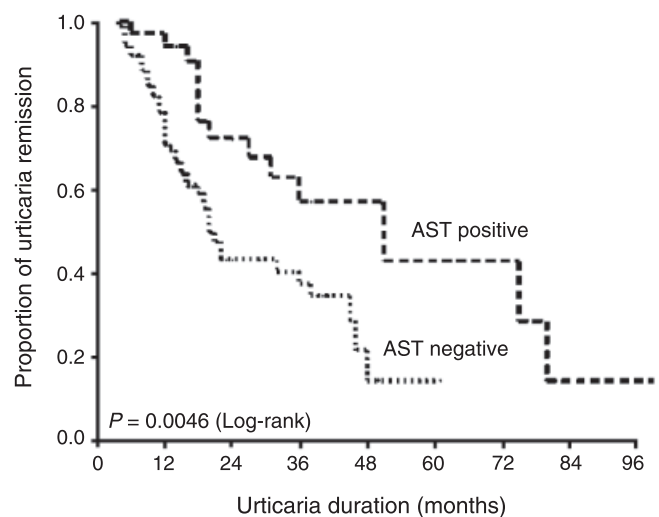


Figure 2. A Kaplan–Meier curve demonstrating the relationship between chronic urticaria duration and the detection of autologous serum test in these patients.

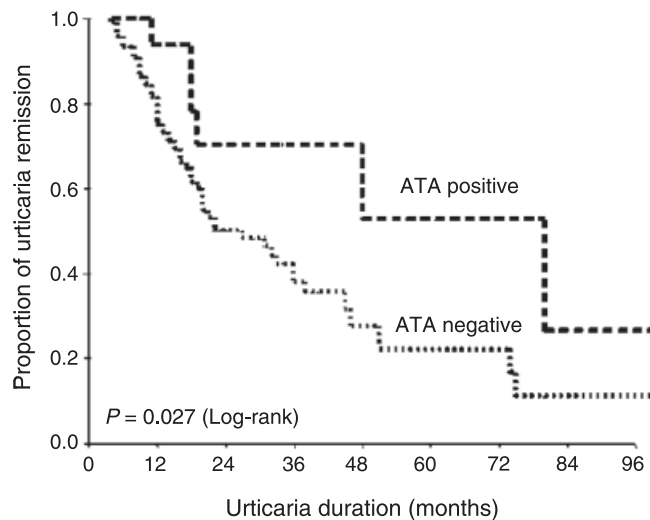


Figure 3. A Kaplan-Meier curve demonstrating the relationship between chronic urticaria duration and the detection of anti-thyroid antibodies.

Whereas neither parameter was found in association with CU severity, both were found to have a significant association with CU duration. Positive AST was documented in 33/104 moderate to severe CU patients; however, only 3/22 patients with mild CU were AST positive, thus AST positivity presents a trend towards a significant association with CU severity, $P = 0.08$.

Discussion

The wide clinical spectrum of urticaria (i.e. distribution of hives, the invariable intensity of itch, and the duration of disease) indicate that multiple mediators are involved in the polymorphism and variable behavior of this disorder (24, 25). The occasional appearance of angioedema during the course of CU occurred in approximately 50% of patients. However, neither angioedema nor CU severity, have been evaluated in conjunction with other laboratory parameters as possible predictors of CU duration or as means by which to distinguish between autoimmune and nonautoimmune CU.

The reports of Leznof (26) were the first to show an association between thyroid autoimmunity and CU. Such an association was further supported in other studies in which both thyroglobulin and thyroid microsomal antibodies were found increased (27). The prevalence of thyroid function alterations in such patients as well as the efficacy of correcting these alterations has been discussed in many studies but remains questionable (9). In a most recent report (28), higher incidence of ATA was found in CU patients in whom anti-IgE receptor antibodies were positive. This is compatible with our finding of the association between AST positivity and the presence of ATA. However, the association between thyroid autoim-

munity and CU severity and duration has not been investigated in the past.

Interest in the possible autoimmune origin of CU was further strengthened with the identification of IgG autoantibodies directed against $\text{Fc}\epsilon\text{RI}\alpha$ or IgE on mast cells (29, 30). But since these disease-specific histamine-releasing autoantibodies were found in not more than 50% of cases, other circulatory factors were proposed to play a role in mast cell degranulation such as metalloproteinases and cytokines such as $\text{TNF-}\alpha$ and IL-10 (31, 32). The production of various and unrelated autoantibodies in CU (AST and ATA) might be driven by polyclonal T-helper-cell activity, rather than distinct monoclonal auto-reactive T-cells and therefore were suggested to be only associate autoimmune markers. We propose that our current finding of total IgE elevation is a part of this polyclonal activity rather than due to a specific trigger. This is consistent with our previous documentation of increased proliferation and over-expression of Bcl-2 in both B and T lymphocytes derived from CU patients (33). Following this understanding of CU being a T-cell-dependent disorder, the beneficial effects of CsA in severe CU become highly reasonable, in addition to its histamine-releasing inhibitory effect.

In this study, we demonstrate that CU lasted over 1 year in more than 70% of patients. After 36 months of follow-up, 43% of patients were still suffering from CU, and by the end of the study, 14% of patients were still suffering from CU. In this regard, the natural history of urticaria reveals that management should be directed toward allowing the patient to maintain an acceptable quality of life, until the episode resolves. Since most reports on CsA treatment suggest its initiation only when severe CU lasts over 1 year, we propose that, as it is customary in the management of autoimmune diseases, the early initiation of CsA be considered in severe CU cases.

The early identification of patients in whom urticaria is expected to be long lasting and/or severe is desirable. A significant contribution of the current study is that our findings suggest a strong association between CU duration with the presence of angioedema, AST, and ATA. Whereas our results reinforce earlier findings suggesting an association between AST and CU severity (34), the current study is the first to associate AST with CU duration. Based on these findings, the early initiation of CsA among patients exhibiting severe CU along with AST positivity may be considered, especially when angioedema and ATA are also present, since in such patients one may predict CU to also be long standing.

Just how autoimmunity is related to CU duration and severity remains unclear and requires further investigation. One possibility is that long-lasting CU is the result of a prolonged stimulation of T-cells followed by prolonged polyclonal activation, and the production of various cytokines that could possibly induce the secretion of the autoantibodies discussed above. We are cognizant of the high incidence of moderate to severe CU among

our study population which could be explained by the higher referral rate of such patients to specialized outpatient clinics. Additional studies should be conducted

in order to further confirm the efficacy of utilizing immunological indices as a basis for therapeutic decision-making.

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