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# Effect of arterial hypertension on chronic urticaria duration

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**Background:** Reliable clinical or laboratory markers of chronic idiopathic urticaria (CIU) duration are not available. Angioedema, autologous serum skin test (ASST) results, and antithyroid antibodies have been inconsistently associated with longer urticaria duration.

**Objective:** To investigate the association of clinical and laboratory parameters with CIU duration, including systemic hypertension, because activation of the coagulation cascade pathway may contribute to the pathogenesis of CIU.

**Methods:** We performed a prospective study of a cohort of 228 consecutive adult patients with CIU of moderate to severe intensity referred to 2 outpatient allergy clinics and followed up for a 3- to 5-year period. The association of clinical and laboratory parameters (sex, atopy, markers of autoimmunity, antithyroid antibodies, positive ASST result, *Helicobacter pylori* infection, and hypertension) with urticaria duration was analyzed using semiparametric multivariable proportional hazards models (Cox regression) using remission as main outcome measure.

**Results:** Apart from systemic hypertension (hazard ratio, 0.71; 95% confidence interval, 0.53–0.95;  $P=.02$ ), none of the considered parameters influenced CIU remission of our patients; 74% and 54% of our patients with and without hypertension, respectively, still had CIU after 5 years.

**Conclusions:** Our results show, for the first time to our knowledge, that hypertension is associated with extended duration of CIU. This observation, together with the previous findings that point to vascular and coagulation involvement in CIU, may suggest a new approach to antihistamine-refractory CIU treatment, including adequate treatment of hypertension.

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## INTRODUCTION

Chronic urticaria (CU) is defined by the presence of hives, usually on most days of the week, for a duration of 6 weeks or longer. A careful history may occasionally identify external triggers, such as a physical trigger, food, medication, or topical allergen; however, in 80% to 90% of adults and children with CU, no external cause can be identified, which is termed *chronic idiopathic urticaria* (CIU).<sup>1,2</sup> In the last 2 decades, up to 40% of patients have been found to have an autoimmune component to their CU, based on antithyroid antibodies (ATA),<sup>3</sup> autoantibodies directed against the IgE or its receptor,<sup>1,4</sup> or, more simply, a positive autologous serum skin test (ASST) result.<sup>5</sup> A possible role of *Helicobacter pylori* infection in the pathogenesis of CU has also been suggested, with controversial results.<sup>6,7</sup>

The natural history of CIU is only partially known, and reliable clinical or laboratory markers of urticaria duration are not currently available. It has been reported that up to 40% of

patients with urticaria beyond 6 months will still have symptoms at 10 years.<sup>8</sup> In a prospective study, Toubi et al<sup>9</sup> reported that urticaria severity, defined according to Breneman et al,<sup>10</sup> angioedema, ASST results, and ATA were associated with longer urticaria duration. In a retrospective study, Kulthanan et al<sup>11</sup> found that median disease duration was nonsignificantly longer in autoimmune urticaria, defined according to ASST results, compared with CIU (450 and 390 days, respectively). The aim of the study was to investigate the effect of clinical and laboratory parameters on urticaria duration in a prospective study of a large cohort of adults with CIU of moderate to severe intensity. We decided to consider the hypertensive comorbidity as a factor that potentially influences urticaria duration. This is based on 2 considerations. The first is that systemic hypertension is a common condition known to be associated with a procoagulant state.<sup>12</sup> The second is the increasing evidence that activation of the coagulation cascade pathway may contribute to the pathogenesis of CIU, particularly in antihistamine-refractory cases in which anticoagulants have been reported to be useful in a few mentions in the literature since 1977.<sup>13,14</sup>

## METHODS

### Patients

A total of 228 consecutive white patients referred to 2 outpatient allergy clinics from January 2003 to December 2005

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for spontaneous CU (defined by the presence of hives, usually on most days of the week, for a duration of longer than 6 weeks, associated or not with angioedema) were included provided that urticaria was moderate to severe based on the evaluation of wheals and pruritus. Pure physical urticaria (such as cold or heat contact urticaria), delayed pressure or vibratory urticaria, solar, aquagenic, or cholinergic urticaria, and factitia or dermatographic urticaria were excluded. Viral and parasitic infections were excluded on the basis of a detailed history, physical examination, and related laboratory analyses, including stool culture for parasites. Food and food additive hypersensitivity was excluded on the basis of history and skin prick test results or specific IgE level for a wide panel of food allergens and, when highly suspected, on the basis of oral food additive elimination diet and/or food additive provocation test results.

The following investigations were performed in all the patients: skin prick tests or specific IgE measurement for a panel of the most common inhaled and food allergens, urine analysis, full blood cell count, erythrocyte sedimentation rate (ESR), liver function tests (and viral hepatitis screen if necessary), thyroid function and ATA measurement, antinuclear antibodies (ANA) measurement, C1 inhibitor assays (C3, C4, and C1 esterase), and serologic testing or enzyme fecal immunoassay (Meridian Diagnostics, Cincinnati, Ohio) for the diagnosis of *H pylori*.

Atopy was defined as a positive result on at least 1 skin prick test or specific IgE test for inhaled allergens; the presence of atopic respiratory diseases (rhinitis and asthma) was also recorded. Systemic hypertension, defined on the basis of antihypertensive drug treatment, was included in the statistical analysis as a possible influence on urticaria duration. The follow-up length ranged from 3 to 5 years. Written informed consent was obtained from each patient, and the study protocol was approved by the local ethics committee.

#### *Urticaria Severity*

A simple scoring system, based on the evaluation of wheals and pruritus, was used.<sup>15</sup> Briefly, the number of wheals (0, none; 1, <20 wheals per 24 hours; 2, 21–50 wheals per 24 hours; and 3, >50 wheals per 24 hours), their duration (0, none; 1, <11 hours per day; 2, 1–3 hours per day; and 3, >3 hours per day), and the severity of pruritus (0, none; 1, mild; 2, moderate; and 3, intense) were recorded by the patients every day for 1 week, and the mean values were calculated. To be included in the study, patients had to have a urticaria severity score greater than 6 (moderate to severe).

#### *ASST Results*

ASSTs were performed in all the patients after antihistamine washout of at least 2 days as previously described.<sup>5</sup> Briefly, 0.1 mL of sterile autologous serum was injected intradermally, and the wheal size was determined at 30 minutes and followed up for a total of 60 minutes. Saline was used as the negative control, and histamine (1 mg/mL) served as the positive control. The ASST result was considered positive

when the wheal attained was at least 1.5 mm greater than the negative control.

#### *Patient Treatment*

Patients were treated with antihistamine drugs associated with oral methylprednisolone when needed.

#### *Follow-up*

Follow-up visits were scheduled every 4 months by telephone interview for patients who could not attend the visit. During the visits urticaria severity, medication consumption, and adverse effects were reviewed. Urticaria remission was defined by the absence of hives and angioedema in the last 3 months, while the patients were not undergoing therapy.

#### *Statistical Analysis*

To evaluate the effect of predictors on the probability of urticaria remission, we used proportional hazard Cox regression models,<sup>16</sup> considering age, sex, atopy, angioedema, ESR, ASST result, liver test results, ATA, *H pylori*, ANA, C3, C4, and systemic hypertension as predictor variables and using remission as the main outcome measure and time from the onset of the urticaria to remission or to last visit (censored in that case) as the observation period (during which urticaria could or could not undergo remission). The observation time was truncated at 60 months, and events after this point were considered censored. The final model was based on the appropriate Akaike and Schwarz criterion.<sup>17</sup> Estimates of hazard ratio (HRs) and 95% confidence intervals (CIs) for true HRs were reported for each independent variable (predictor) in the regression model. A predictor with an HR significantly less than 1 would be indicative of extended duration of CIU associated with that predictor. Conversely, a predictor with an HR significantly greater than 1 would be indicative of attenuated duration of CIU. Significance of an HR was determined as  $P < .05$  in a 2-directional test. Kaplan-Meier curves were constructed for the relationship between urticaria duration and the significant predictor variables.<sup>18</sup>

## **RESULTS**

Clinical and demographic characteristics of the patients are reported in Table 1. The mean age of the patients (166 female, 62 male) was 48.2 years (age range, 16–85 years). There were 92 atopic patients (40.3%), and 65 (28.5%) of them reported allergic diseases (rhinitis combined or not with asthma).

Angioedema was found in 39.9%, a positive ASST result in 33.3%, ATA in 34.2%, ANA (low titer, 1:80, mostly homogeneous pattern) and minimal elevation of ESR in 21%, and *H pylori* infection in 32% of patients. Systemic hypertension was present in 42 of 228 patients (18.9%). Full blood cell count, liver function test results, and C3, C4, and thyroxine levels were normal in all the patients.

#### *Relationship Between Urticaria Duration and Considered Parameters*

Remission probability was based on 7,855 total patient-months and 82 events, giving a remission rate of 1.04% per

Table 1. Clinical and Demographic Characteristics of Study Patients

| Characteristic                                      | No. (%) of patients <sup>a</sup><br>(N = 228) |
|-----------------------------------------------------|-----------------------------------------------|
| Age, mean (range), y                                | 48.2 (16–85)                                  |
| Sex, F/M                                            | 166/62                                        |
| Duration, mean (range), mo                          | 33.3 (6–60)                                   |
| Duration from the onset of urticaria, mean (SD), mo | 44.5 (40.8)                                   |
| Duration of the study period, mean (SD), mo         | 31.8 (19.1)                                   |
| Atopy                                               | 92 (40.3)                                     |
| Allergic diseases                                   | 65 (28.5)                                     |
| Angioedema                                          | 91 (39.9)                                     |
| Positive ASST result                                | 76 (33.3)                                     |
| Arterial hypertension                               | 42 (18.4)                                     |
| ATA                                                 | 78 (34.2)                                     |
| ANA                                                 | 48 (21.0)                                     |
| <i>Helicobacter pylori</i> infection                | 73 (32.0)                                     |

Abbreviations: ANA, antinuclear antibodies; ASST, autologous serum skin test; ATA, antithyroid antibodies.

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

month. The median duration of CIU was 33 months (range, 6–60 months), and the mean (SD) duration was 44.5 (40.8) months starting from the onset of symptoms and 31.8 (19.1) months considering only the study period. Apart from systemic hypertension (HR, 0.71; 95% CI, 0.53–0.95;  $P = .02$ ), none of the considered parameters, including positive ASST results, statistically influenced urticaria remission and were excluded from the final model. The estimated effect of each single factor is reported in Table 2. The proportion of patients still having urticaria at each observation time was significantly higher in patients with hypertension compared with patients without hypertension. CIU persisted in 81% and 74% of hypertensive patients up to 24 and 60 months, respectively. On the other hand, in normotensive patients CIU persisted up to 24 months in 63% and up to 60 months in 54% of them (Fig 1). No significant effect of antihypertensive drugs class was found on urticaria duration (15 patients received angiotensin-converting enzyme inhibitors, 16 calcium blockers, 12 angiotensin receptor blocking drugs, and 30 diuretics).

Table 2. Summary Statistics for Cox Regression Analysis of Time Until Urticaria Remission

| Predictor    | Hazard ratio<br>(95% CI) | Robust<br>SE | z     | P value |
|--------------|--------------------------|--------------|-------|---------|
| Angioedema   | 0.96 (0.86–1.08)         | 0.06         | −0.61 | .54     |
| ASST         | 0.99 (0.99–1.01)         | 0.01         | −0.08 | .93     |
| ATA          | 1.00 (0.99–1.00)         | 0.02         | 0.68  | .495    |
| ANA          | 0.99 (0.99–1.01)         | 0.01         | −0.12 | .90     |
| Atopy        | 1.12 (0.44–3.28)         | 0.61         | 0.35  | .72     |
| Hypertension | 0.71 (0.53–0.95)         | 0.11         | −2.26 | .02     |

Abbreviations: ANA, antinuclear antibodies; ASST, autologous serum skin test; ATA, antithyroid antibodies; CI, confidence interval.

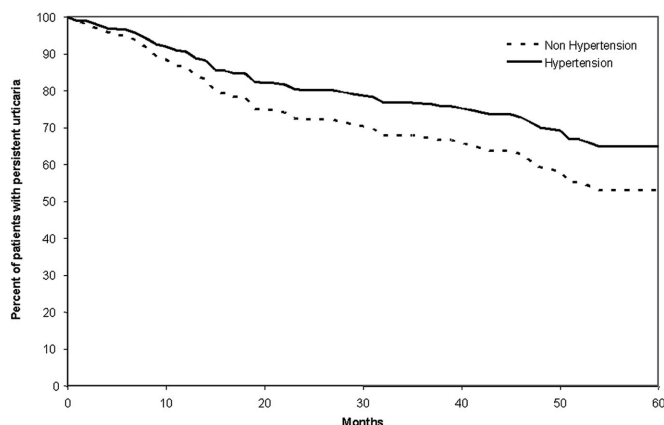


Figure 1. Kaplan-Meier curve demonstrating the relationship between chronic urticaria duration and the presence (continuous line) or absence (dotted line) of hypertension.

## DISCUSSION

Our results show that CIU persisted in more than half (64%) of adult patients who were prospectively evaluated for 5 years, and its duration was significantly longer in patients with systemic hypertension, irrespective of specific drug therapy (eg, angiotensin-converting enzyme inhibitors) than in normotensive patients. The high percentage of persistent urticaria we observed in our patients is similar to that reported by Sibbald et al,<sup>8</sup> but it is much higher than the value of 14% of persistent urticaria at 5-year follow-up reported by Toubi et al.<sup>9</sup> All the factors potentially involved in urticaria duration, including positive ASST results, did not significantly affect urticaria duration in our study population. This is in contrast with the results of Toubi et al,<sup>9</sup> who reported that urticaria severity, angioedema, ASST results, and ATA were associated with longer urticaria duration. Some differences in patient selection may help to explain our different results. We did not enroll patients with mild urticaria, which may explain the lack of influence of urticaria severity on its duration in our series. Furthermore, the mean age and female prevalence of our study population were higher than in the previous study, for which defined criteria for urticaria remission had not been clearly indicated.

The influence of systemic hypertension on CU duration has not been previously reported, probably because hypertension had never been taken into account as a factor that could affect urticaria duration. The biological link between systemic hypertension and CU is not currently known. Recently, activation of the extrinsic pathway of the coagulation cascade has been found in CIU, for which increased serum levels of prothrombin fragments and D-dimer<sup>19,20</sup> have been observed. Thrombin and fibrin degradation products have pleiotropic immunomodulatory and proinflammatory properties, such as enhancement of vascular permeability and provocation of mast cell degranulation.<sup>21</sup> Thrombin is also able to generate C5a in the absence of C3, thus bypassing the entire first part of the complement cascade.<sup>22</sup> C5a has been demonstrated to

amplify IgG-dependent histamine release from basophils in CU.<sup>23</sup> Systemic hypertension, even in its early stages, may cause blood vessel wall injury and activation of the coagulation system.<sup>24,25</sup> Alterations in the fibrinolytic-hemostatic balance have been reported in hypertension, predisposing patients to a procoagulant state,<sup>12,26</sup> and increased serum levels of prothrombin fragments and D-dimer<sup>25,27,28,29</sup> may be found in patients with hypertension. No specific therapy for CU, except antihistamine drugs, is supported by evidence.

Our results show, for the first time to our knowledge, that hypertension is significantly associated with prolonged duration of CIU. Whether adequate treatment of hypertension may be helpful in the management of CIU remains to be investigated. Our observation, together with the previous findings that point to vascular and coagulation involvement in CIU, may suggest a new approach to antihistamine-refractory CIU treatment, such as anticoagulants.<sup>30</sup>

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