

Clinical and Laboratory Examinations in the Subgroups of Chronic Urticaria

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Key Words

Antihistamine therapy · Autoimmune urticaria ·
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Abstract

Background: The aetiology of chronic urticaria is heterogeneous. Physical urticaria (PU) is estimated at around 35%, autoimmune urticaria (AIU) at 25% and chronic idiopathic urticaria (CIU) at 35% of all chronic urticaria cases. **Methods:** Differences in clinical and laboratory parameters among AIU, PU and CIU groups were examined. AIU was diagnosed if the basophil CD63 assay was positive. Demographic data, severity of symptoms and association with allergic and autoimmune diseases were analysed by the aid of a questionnaire. Immunoassays were carried out and the effectiveness of therapy was also investigated. **Results:** Concerning the urticaria score, AIU patients had significantly higher total urticaria scores than patients with CIU ($p = 0.013$), dermatographic urticaria ($p = 0.05$) or cholinergic urticaria ($p = 0.038$). Between CIU and dermatographic urticaria and between CIU and cholinergic urticaria patients, we found insignificant differences in the urticaria score ($p = 0.707$ and $p = 0.336$, respectively). AIU was more frequently associated with autoimmune diseases in the personal history ($p < 0.001$) and with other types of urticaria in the family history ($p < 0.001$). Also, anti-thyroid antibodies were more frequently detected in

the AIU group. Antihistamine therapy was less effective in the AIU group (12.8%) than in the PU (70.3%) and CIU groups (68.6%), but there were no significant differences between the CIU and PU groups regarding the effectiveness of antihistamine therapy. **Conclusion:** The autoimmune subgroup represents the most severe form of chronic urticaria. On the other hand, there were no significant differences between the CIU and PU groups neither in urticaria scores nor in response to antihistamine therapy.

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Introduction

When wheals occur for more than 6 weeks with daily or almost daily appearance, the diagnosis is chronic urticaria. The continuously itching and burning skin lesions with the consequent sleeping disorders distract patients from their daily activities and are responsible for impairment in their quality of life.

The aetiology of chronic urticaria is heterogeneous [1, 2]. In some cases, urticaria may develop on a pseudoallergic or focal infection-related basis, while the aetiological role of real food allergy is minimal in chronic urticaria [3]. The urticaria-provoking effects of additive substances are frequently discussed in the literature. Greaves [4] found that food additives could be substantiated to be

causative in not more than 5% of cases, while others reported higher figures [5, 6]. A few years ago chronic focal infections, especially *Helicobacter pylori* infection, were regarded as having a major role in the aetiology of chronic urticaria. Recently, some authors demonstrated that the provoking effect of *Helicobacter pylori* infection in chronic urticaria was insignificant and only limited to a few cases [4, 7, 8].

Grattan et al. [9] reported that 35% of chronic urticaria cases were physical urticarias (PUs). PUs frequently occur together, and their symptoms develop just after exposure to physical stimuli and disappear not more than 1–2 h later, except in delayed pressure urticaria (DPU) [10]. PUs are traditionally included in the non-restrictive definition of chronic urticaria, although they are commonly intermittent and form a diverse disease group, having little resemblance to chronic idiopathic urticaria (CIU) and autoimmune urticaria (AIU) [2].

In the last decade, several research teams have investigated a special form of chronic urticaria, AIU, which presumably constitutes 20–35% of all cases [9, 11]. AIU patients have antibodies in their serum that react with the α -chain of the high-affinity IgE receptor (Fc ϵ RI α) or with IgE itself. These pathogenic antibodies, which belong to the IgG1 and IgG3 subclasses, were demonstrated to cause histamine release by directly cross-linking the IgE receptor and this activation was augmented by complement [12–16].

In the diagnosis of AIU, the autologous serum skin test (ASST) is frequently used, although this method does not identify patients with autoantibodies but rather those with serum autoreactivity [17]. For a definitive diagnosis, further examinations are usually needed, either by functional or binding assays. One of them, the gold standard, is the basophil histamine release (HR) test [18]. In recent studies, a new method, the modified CD63 expression assay, was found to be a reliable method for the diagnosis of AIU [19–22].

If no aetiological factors are found in spite of extensive investigations, the diagnosis is CIU [9].

In the present study, our aim was to further investigate the usefulness of the CD63 assay in clinical practice. We differentiated AIU from CIU on CD63 assay positivity. Our further objective was to study demographic data, urticaria score parameters, other accompanying diseases, the presence of autoantibodies and the effectiveness of therapy in patients with AIU and CIU. Although the PU group includes diverse diseases, this form of chronic urticaria was also investigated.

Patients and Methods

Patients

We examined 109 patients with chronic urticaria. The mean age was 39.8 ± 15.8 years (range 13–74 years), there were 82 females and 27 males (female to male ratio 3:1). From the history of the 109 patients the mean duration of skin symptoms was 24.7 ± 36.4 months (range 2–231 months).

After informed consent had been obtained, the patients were subjected to a diagnostic protocol which included detailed history taking, physical examination, routine laboratory tests and provocation tests for PU. Urticaria patients with focal infection or a drug or food allergy as aetiological background were excluded. Biopsy was performed if the possibility of urticaria vasculitis existed. The ASST and CD63 assays were performed on every patient. The 109 patients suffering from PU, CIU and AIU were then asked to fill in an internationally accepted questionnaire. Patients suffering from more than 1 form of chronic urticaria were excluded.

Symptomatic dermatographic urticaria (DU) was diagnosed in 48.1% (13/27) of the PU patients, cholinergic urticaria (CU) in 33.3% (9/27), DPU in 11.1% (3/27) and cold urticaria in 7.4% (2/27). DPU patients with associated AIU were excluded from the study. The skin symptoms of patients suffering from DU and CU appeared several times a week. Because of the heterogeneity of the PU group, we divided the group into subgroups and the urticaria score parameters were counted separately. As only the 13 patients with DU and the 9 patients with CU fulfilled the criteria of continuously existing chronic urticaria and patients with DPU and cold urticaria were rather considered as intermittent urticaria forms, only patients with DU and CU were analysed in the urticaria score measurements.

Antihistamines were withdrawn 72 h before provocation tests, while corticosteroids and other immunosuppressant drugs were withdrawn at least 4 weeks prior to provocation tests, ASST and laboratory examinations. After the completion of the aforementioned investigations, a treatment protocol was started on all patients. The protocol was approved by the local ethics committee.

Questionnaire

All patients filled in a questionnaire, which was kindly provided by M. Kozel (Department of Dermatology of the Academic Medical Center, University of Amsterdam) [23], and which was supplemented with a few questions of ours. From this form, more accurate information was gained about the sexual distribution, the severity of symptoms and the disease course. Personal and family history were thoroughly investigated regarding the occurrence of other types of urticaria as well as allergic and autoimmune diseases.

Measurement of Urticaria Score Parameters

The urticaria score introduced by Breneman et al. [24], with slight modification in order to be suitable for scoring PUs, was used for assessing the severity of the disease. A 4-grade scale was used for describing the localization, the size of lesions, the duration of lesions, the frequency of episodes and the intensity of pruritus. Localization of wheals was classified as follows: 0 = no wheals; 1 = wheals were localized to 1 part of the body; 2 = 2–3 parts of the body were involved; 3 = generalized wheals. Average size of lesions was categorized as follows: 0 = no wheals; 1 = 1–

2 cm; 2 = 3–4 cm; 3 = >4 cm. Average duration of lesions: 0 = no symptoms; 1 = <60 minutes; 2 = 1–4 h; 3 = >4 h. The frequency of lesions was scored as follows: 0 = no wheals; 1 = lesions appearing 2 times a week; 2 = 3 times a week; 3 = >4 times a week. Intensity of pruritus: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Severity of pruritus was measured using a visual, analog 10-point scale, and the results were converted into the above mentioned 4-point scale. By summing up the points we reached the total severity score of a patient.

Autologous Serum Skin Test

The ASST was carried out according to the literature [17]. Positive reaction was defined when the serum-induced wheal was red and had a diameter that was ≥ 1.5 mm wider than the saline-induced response at 30 minutes.

CD63 Surface Expression Assay

The CD63 expression on the surface of donor basophils was determined as described earlier [20]. Briefly, after incubation with chronic urticaria sera, the cells were labelled with goat anti-human IgE FITC and R-phycoerythrin conjugated anti-human CD63 monoclonal antibody (both from Caltag, Burlingame, Calif., USA) and the percentage of IgE and CD63 double-positive basophils was measured on a Becton Dickinson FACSCalibur flow cytometer. Values above the 95th percentile of CD63-positive cells induced by 20 control sera were considered as positive (cut-off values were 5.1% for atopic donors (D_A) and 2.2% for non-atopic donors (D_{NA}).

Detection of Autoantibodies

Levels of autoantibodies against thyroglobulin (a-TG), thyroid peroxidase (a-TPO) and extractable nuclear antigen (a-ENA) were measured by a commercial enzyme-linked immunosorbent assay (ELISA; Hycor Biomedical GmbH, Kassel, Germany) according to the instructions of the manufacturer. The serum concentrations of anti-endothelial cell antibody (AECA) was analysed by ELISA (Cogent Diagnostic, Edinburgh, UK) according to the manufacturer's instructions [25].

Therapeutic Protocol

All patients got antihistamines as a first line of therapy. Patients received low-sedation, second-generation H1 receptor antagonist antihistamine (cetirizine 10 mg/day) monotherapy first. In case of inadequate response, cetirizine was given in a higher dose (20 mg/day), then sedative antihistamine (hydroxyzine 25 mg twice a day) and H2 receptor antagonist (cimetidine 400 mg twice a day) were combined [26, 27]. We regarded the therapy ineffective if the patient's severe complaints persisted or the urticaria score index did not show a reduction of at least 50%. In CIU and AIU patients, a short course of oral corticosteroid treatment (methylprednisolone 32 mg/day, reduced by 4 mg every 5 days to zero) was used as a second line of therapy. If this therapy resulted only in temporary improvement, cyclosporine (3 mg/kg/day for 3 months) was added as a third line of therapy for AIU patients [28].

Statistical Analysis

Fisher's exact test was used to analyse the relationship between categorical variables. One-way analysis of variance was used to test for differences in the means of continuous dependent variables broken by the levels of categorical independent variables.

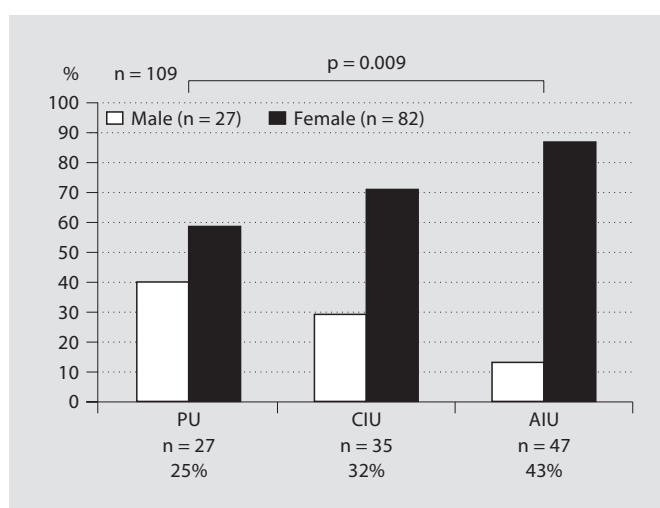


Fig. 1. The 3 subgroups of chronic urticaria patients and their distribution by gender. A female predominance was found in all the 3 subgroups: female/male ratio was 6.9:1 in the AIU group, 2.5:1 in the CIU group and 1.5:1 in the PU group. The difference was significant between the AIU and PU groups ($p = 0.009$).

Results

Laboratory Tests

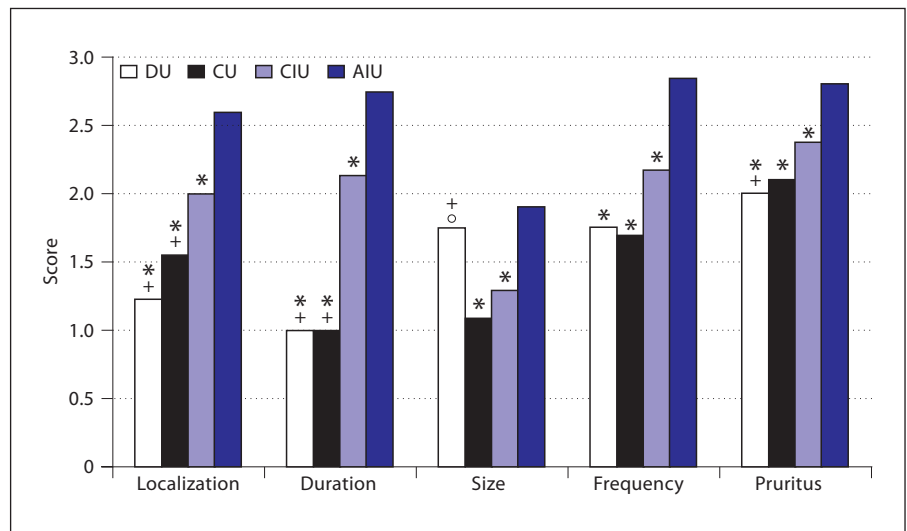
Among the 109 patients, 58 (53.2%) had a positive ASST and 47 (43%) a positive CD63 assay. Positivity of the CD63 assay was needed for a diagnosis of AIU.

Demographic Data

Among the 109 patients with chronic urticaria, 47 patients (43%) had AIU, 35 (32%) CIU and 27 (25%) PU (fig. 1). The mean age of patients with chronic urticaria was 39.8 ± 15.8 years (range 13–74). The mean age in the AIU subgroup was 43.1 ± 15.8 years, in the CIU subgroup 38 ± 13.7 years and in the PU subgroup 32.7 ± 17.8 years. There was no significant difference in the mean age of the subgroups.

The female/male ratio in the whole group was 3.0:1 (82/27), which meant a statistically significant female preponderance ($p = 0.02$). The female/male ratio in the AIU group was 6.9:1 (41/6), in the CIU group 2.5:1 (25/10) and in the PU group 1.5:1 (16/11). We found that the female preponderance was significantly different only between the AIU and PU groups ($p = 0.009$). Among the female patients, 50% had AIU, 30.5% CIU and 19.5% PU, while 22.7% of the male patients had AIU, 37% CIU and 40.8% PU (fig. 1).

Fig. 2. Evaluation of urticaria score parameters in chronic urticaria patients. Urticaria score was determined for every patient (localization, duration, size and frequency of wheals as well as severity of pruritus). The AIU group was significantly different from the CIU and CU groups with regard to all 5 parameters, while between AIU and DU patients significant differences could be observed with regard to only 4 parameters (localization, frequency and duration of wheals as well as severity of pruritus). Between CIU and DU patients and between CIU and CU patients significant differences were detected less frequently. * Significant differences from AIU group. + Significant differences from CIU group. ° Significant differences from CU group.



Evaluation of Urticaria Score Parameters

The localisation of wheals was examined. In patients with AIU, 93.6% of the cases had symptoms on the whole body surface, while in the CIU subgroup wheals were widespread in 85.7% of patients. Among DU patients 7.7% and among CU patients 44.5% had generalized symptoms. The localization score was 2.6 for AIU patients, 2.0 for CIU patients, 1.23 for DU patients and 1.55 for CU patients (fig. 2). The differences were significant between AIU and CIU patients ($p < 0.001$), between AIU and DU patients ($p < 0.001$), and between AIU and CU patients ($p < 0.001$). We also found significant differences between CIU and CU patients ($p = 0.043$) and between CIU and DU patients ($p < 0.001$). The results showed insignificant differences between CU and DU patients ($p = 0.381$).

We investigated the duration of wheals (from appearance to vanishing). The mean duration was 9 h in the AIU subgroup, with a mean score of 2.74. Among CIU patients, the mean duration of wheals was 4.45 h with a mean score of 2.14, while for DU patients it was 0.81 h with a score of 1.0, and 0.79 h with a 1.0 score in CU patients (fig. 2). The results show significant differences between AIU and CIU ($p < 0.001$), between AIU and DU ($p < 0.001$), and between AIU and CU ($p < 0.001$) patients. Also, differences were significant between CIU and DU ($p < 0.001$), and between CIU and CU ($p < 0.001$) patients. Comparing patients with DU and CU, no significant difference was detected ($p = 0.662$).

We also measured wheal sizes. The mean size of lesions was 2.36 ± 1.54 cm for all patients enrolled. It was

3.1 ± 1.8 cm for patients with AIU (score: 1.91), 1.9 ± 1.1 cm for patients with CIU (score: 1.3), 2.4 ± 1.5 cm for patients with DU (score: 1.76) and 1.1 ± 0.7 cm in CU patients (score: 1.1) (fig. 2). The differences were significant between AIU and CIU ($p < 0.001$) and also between AIU and CU patients ($p = 0.015$), but the results showed insignificant differences between AIU and DU patients ($p = 0.672$). Comparing CIU to DU patients, the size of wheals was significantly higher in DU patients ($p = 0.035$) and no significant differences were detected between CIU and CU patients ($p = 1.000$). The differences were significant between DU and CU patients ($p = 0.038$).

The frequency of urticaria episodes showed significant differences between AIU and CIU patients on one hand ($p < 0.001$) and between AIU and DU as well as CU patients on the other (both $p < 0.001$). Comparing CIU to DU and to CU patients, we did not find significant differences ($p = 0.162$ and $p = 0.125$, respectively) between the groups. There were no significant differences between DU and CU patients ($p = 1.000$). Eighty-five percent of patients with AIU, 46% of patients with CIU, 15.4% of patients with DU and 11.1% of patients with CU experienced skin symptoms more than 4 times a week. Accordingly, the frequency of urticaria episodes score for AIU patients was 2.85, while it was 2.17 for CIU, 1.7 for DU and 1.7 for CU patients (fig. 2).

We also investigated pruritus. According to the pruritus scale, the AIU patients' mean score was 2.80, while for CIU, DU and CU patients it was 2.37, 2.0 and 2.1, respectively (fig. 2). The differences were significant between AIU and CIU patients ($p < 0.001$), between AIU and DU

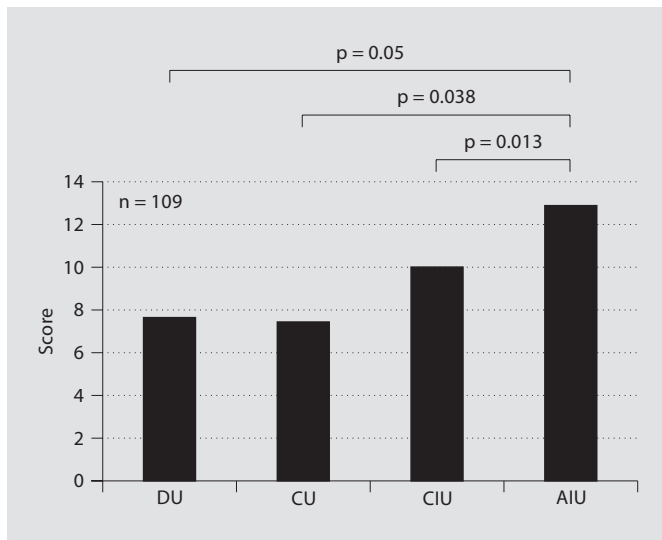


Fig. 3. Total urticaria score of patients. The total urticaria score was significantly higher in the AIU group than in the CIU, DU and CU groups ($p = 0.013$, $p = 0.05$ and $p = 0.038$, respectively), but no significant difference was found between CU, DU and CIU patients.

patients ($p < 0.001$) and also between AIU and CU patients ($p = 0.001$). The pruritus score was significantly different between CIU and DU patients ($p = 0.030$), but no statistically significant difference was found between CU and DU patients ($p = 0.845$) and between CIU and CU patients ($p = 0.178$).

Total scores counted from the parameters mentioned above were summed up to give the individual score index of each patient (the severity of disease). This mean score index was 12.89 for AIU patients, 9.98 for CIU patients, 7.69 for DU patients and 7.45 for CU patients. The total urticaria score was significantly different between AIU and DU patients ($p = 0.05$), between AIU and CU patients ($p = 0.038$) and between AIU and CIU patients ($p = 0.013$), but no statistically significant difference was found between CIU and DU patients ($p = 0.707$) and between CIU and CU patients ($p = 0.336$; fig. 3).

Accompanying Diseases and Autoantibodies

Prevalence of urticaria in patients' families was also investigated. Twenty-three percent (25/109) of chronic urticaria patients mentioned the occurrence of some type of urticaria in their family history. In AIU patients, 48.9% (23/47) had a positive family history of urticaria, while this was the case in 5.7% (2/35) of CIU patients and 3.7% (1/27) of PU patients. This meant a significant difference

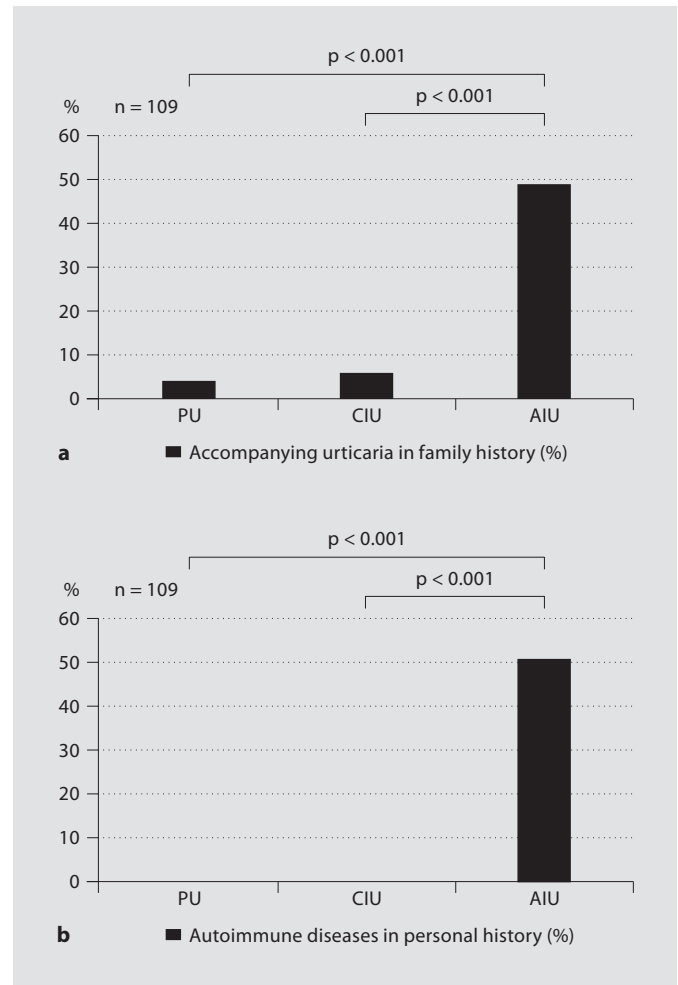


Fig. 4. Occurrence of accompanying diseases. **a** Significantly more patients with AIU had a positive family history of urticaria than patients with PU and CIU ($p < 0.001$ and $p < 0.001$, respectively). **b** Autoimmune diseases were significantly more frequent in the personal history of AIU patients than in the history of CIU and PU patients.

between the AIU and CIU groups ($p < 0.001$) and between the AIU and PU groups ($p < 0.001$; fig. 4). Among our chronic urticaria patients, drug allergy was observed in 11% (12/109), bronchial asthma in 5.5% (6/109), allergic rhinitis in 9.1% (10/109) and eczema in 2.7% (3/109). The occurrence of these diseases was nearly the same among AIU, CIU and PU patients.

Twenty-two percent (24/109) of patients reported autoimmune diseases in their history. Autoimmune disease was present in the history of 51% (24/47) of AIU patients but not in the history of CIU and PU patients. This meant a significant difference between these groups ($p < 0.001$;

Table 1. Detection of autoantibodies in chronic urticaria patients

	a-ENA	a-TG	a-TPO	AECA
PU (n = 27)	1 (3.7%)	0	0	2 (7.4%)
CIU (n = 35)	2 (5.7%)	0	1 (2.8%)	2 (5.7%)
AIU (n = 47)	2 (4.2%)	3 (6.3%)	8 (17%)	2 (6.3%)

Significantly higher occurrence of anti-thyroid antibodies was detected in the AIU group than in the other subgroups ($p < 0.001$). Differences between the subgroups while investigating other autoantibodies (a-ENA and AECA) were not observed.

Table 2. Effectiveness of different treatment modalities in chronic urticaria

	First line	Second line	Third line
PU (n = 27)	19/27 (70.3%)	–	–
DU (n = 13)	10/13 (77%)	–	–
CU (n = 9)	7/9 (77.7%)	–	–
CIU (n = 35)	24/35 (68.57%)	7/11 (63.6%)	–
AIU (n = 47)	6/47 (12.8%)	22/41 (53.6%)	15/19 (78.9%)

First-line therapy consisted of antihistamines, second-line therapy of oral corticosteroids and third-line therapy of oral cyclosporine.

fig. 4). Most often, autoimmune thyroiditis (44.6%, 21/47), rheumatoid arthritis (4.2%, 2/47) and vitiligo (17%, 8/47) were associated with AIU.

The presence of autoantibodies was also examined in all patients. Patients with AIU had a significantly higher occurrence of autoantibodies against the thyroid gland than patients with chronic urticaria of any other origin. We found anti-thyroid autoantibodies (a-TG, a-TPO) in 11% (12/109) of chronic urticaria patients and in 23% (11/47) of AIU patients. Among CIU patients, we detected a-TPO positivity in only 1 case (2.8%, 1/35), but no anti-thyroid antibodies were found in the sera of PU patients. This meant a significantly higher occurrence of anti-thyroid antibodies in AIU than in the other subgroups ($p < 0.001$). We did not observe any differences between the subgroups while investigating other autoantibodies (a-ENA and AECA; table 1).

Response to the Therapeutical Protocol

Antihistamine therapy (cetirizine monotherapy, cetirizine higher dose, cetirizine and hydroxyzine combina-

tion, cetirizine and cimetidine combination) was effective in 45% (49/109) of chronic urticaria patients. To the first line of therapy, 70.3% (19/27) of PU patients and 68.6% (24/35) of CIU patients responded, in contrast to a 12.8% (6/47) response rate in AIU patients. In the PU group, antihistamine therapy was equally effective in DU (77%) and CU (77.7%) patients, but DPU (33%) and cold urticaria (50%) patients responded poorly. Oral corticosteroids were used in 31.4% (11/35) of CIU patients and in 87.2% (41/47) of AIU patients, and were found to be effective in 63.6% (7/11) of CIU patients and 53.6% (22/41) of AIU patients. Nineteen AIU patients were ultimately given oral cyclosporine therapy, which relieved the symptoms in 15/19 patients (78.9%; table 2). Corticosteroid and cyclosporine therapy were not introduced in the PU patient group.

Discussion

Our current study was aimed at comparing the most common forms of chronic urticaria (PU, CIU and AIU) regarding demographic data, urticaria score, accompanying diseases, presence of autoantibodies and the effectiveness of different treatments. In the literature, AIU is usually defined on the basis of the results of ASST and HR assay [4, 21], but in our present study the CD63 assay was used instead of the HR assay. On the basis of recent investigations, the CD63 expression assay seems to be a convenient and reliable functional assay in the diagnosis of AIU, as it is less expensive and less time consuming than the HR assay [19–22].

Most authors agree that the proportion of PU in chronic urticaria is 30–35%, while AIU represents 27–35% [9, 17]. In the current study of chronic urticaria patients, 43% had AIU, 32% CIU and 25% had PU. This higher proportion of the AIU group and lower proportion of the PU group among our patients could be explained by the fact that mild forms of urticaria were treated by local general practitioners or at dermatology outpatient units. More severe or treatment-resistant urticaria cases were generally referred to the allergy follow-up clinic run by our Department of Dermatology (tertiary care institution).

In our study we found a 75% female preponderance (3.0:1) in the total chronic urticaria patient group, and an even more significant female preponderance was detected in the AIU group (87.2%). Several other studies have confirmed our results. For example, Sabroe et al. [29] also detected a 61% (66/107) female predominance in the pa-

tient group with autoantibodies, while in the CIU group 73% female patients were found in by others [24].

To assess the severity of disease we applied the urticaria score introduced by Breneman et al. [24] with slight modifications in order to be suitable for scoring PUs. This urticaria score for assessing the severity of symptoms was used not only for the AIU and CIU groups, but also for the PU group. Because of the heterogeneity of PUs, this group was further divided into subgroups when urticaria score was calculated, and only DU and CU patients with persistent urticaria were compared to AIU and CIU patients. In the case of PU, the urticaria score is generally difficult to apply, although it can also provide valuable information about how the disease adversely affects the quality of life in this subgroup of chronic urticaria patients. In the present study, one of our aims was to determine how symptoms influence quality of life, so we used a modified urticaria score for the AIU, CIU, DU and CU groups. According to our results, there were significant differences in the total score between AIU and CIU patients, between AIU and DU patients and between AIU and CU patients. Sabroe et al. [29] also demonstrated that the patients with detectable serum autoantibodies had significantly higher urticaria scores with more wheals ($p = 0.005$), a wider distribution ($p = 0.009$) and higher itch scores for the most severe episodes of itching ($p = 0.002$) than patients without autoantibodies. On the basis of our results, the CIU group was significantly different from the CU group with regard to only 2 urticaria score parameters, while between CIU and DU patients significant differences could be observed with regard to only 4 parameters. Due to this, CIU, CU and DU patients' total urticaria scores did not differ significantly, although some of the parameters were higher in the CIU subgroup. This insignificant difference may also come from the fact that only the most severe forms of DU and CU patients are referred to our department.

Several studies have investigated the presence of different autoantibodies in AIU. Originally, Leznoff et al. [30] observed an increased incidence of anti-thyroid antibodies (a-TG, a-TPO) in chronic urticaria patients and since then several groups have detected these types of autoantibodies. In a recent article, Kikuchi et al. [31] found anti-thyroid antibodies in 27.7% of histamine release-positive chronic urticaria patients and 10.9% of histamine release-negative patients. In conformity with their findings we also detected a significantly higher occurrence of anti-thyroid antibodies in the AIU group than in the other 2 subgroups. However, there is no evidence that in the presence of both autoimmune thyroid gland

and urticaria diseases, the anti-thyroid antibodies have a pathogenetic role in the development of chronic urticaria. Other authors have demonstrated autoantibodies against ENA, cardiolipin, 2-glycoprotein, rheumatoid factor, endothelial cell and myeloperoxidase in chronic urticaria patients [32–34]. Our results showed no significantly increased prevalence of a-ENA or AECA in either subgroup of chronic urticaria patients.

Caproni et al. [35] and Sabroe et al. [29] also investigated the presence of atopic diseases and urticaria in the family or personal history of chronic urticaria patients, but did not observe significant differences between patients with and without autoantibodies. In the present study, the occurrence of urticaria in the family history of AIU patients was significantly more frequent compared to CIU or PU subgroups. Concerning atopic diseases or drug allergy, there were no significant differences between the 3 subgroups. Among our chronic urticaria cases we observed drug allergy in 11%, while Humphreys and Hunter [36] reported a 9.8% frequency in similar circumstances.

Regarding the therapy of chronic urticaria, we applied a 3-line therapy protocol [2, 11, 27]. All chronic urticaria patients were treated first with antihistamines (cetirizine monotherapy at doses of 10 and 20 mg/day, cetirizine and hydroxyzine combined therapy, cetirizine and cimetidine combined therapy) and 45% (49/109) responded well. The efficacy of cetirizine monotherapy and cetirizine and H₂ antihistamine combined therapy was investigated independently in several studies. In a study with 97 CIU patients, Handa et al. [37] found cetirizine monotherapy to be effective in 88.4% (51.9% became symptom free, 36.5% showed partial improvement). On the other hand, Harvey et al. [38] demonstrated that the hydroxyzine-cimetidine combination was favored by 58% of CIU patients, but the total effectiveness of the different modes of antihistamine treatments in the 3 subgroups of chronic urticaria was not reported earlier. In our present study, the first-line therapy was effective in 68.6% of CIU, in 70.3% of PU and in 12.8% of AIU patients, which suggests that AIU is not just the most severe form of chronic urticaria, but also responds less to conventional antihistamine therapy.

For patients in whom first-line therapy was ineffective, oral corticosteroid treatment was started. Seven of the 11 (63.6%) CIU patients and 22 of the 41 (53.6%) AIU patients who had to be treated with oral corticosteroids responded to the second line of therapy. Although there are no double-blind, placebo-controlled trials of the use of corticosteroids in chronic urticaria, there is truly no

question regarding their efficacy [39]. Various regimens of corticosteroid treatment have been suggested in review articles, but it is usually recommended that H1 receptor antagonists should be continued and prolonged corticosteroid therapy should be avoided because of side effects [40]. Of the remaining 19 AIU patients not responding to oral corticosteroids, ciclosporin therapy was introduced and among them 15 (78.9%) became symptom free. Ciclosporin has been shown to be effective both in antibody-positive and antibody-negative chronic urticaria patients, and Greaves [4] reported a >75% response rate with one third of patients remaining in remission, one third relapsing mildly and one third relapsing seriously [4, 41, 42].

In conclusion, when the CD63 assay instead of the HR test was used in the diagnosis of AIU, the autoimmune form was also found to be the most severe form of chronic urticaria, as it was shown in earlier studies when the HR assay was utilised [29]. These results also support our previous findings that the CD63 assay is a reliable test in

the diagnosis of AIU. When comparing clinical parameters between ASST-positive and ASST-negative groups of CIU patients, Nettis et al. [43] did not find significant differences between the subgroups and concluded that ASST cannot be used alone either to predict the severity of urticaria or to define it as autoimmune. On the other hand, there was no significant difference between the CIU, DU and CU subgroups in their total urticaria score and in their response to antihistamine therapy. Other forms of urticaria were observed significantly more frequently in the family history of AIU patients, while in their personal history autoimmune disease occurred more often.

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