
Natural course of physical and chronic urticaria and angioedema in 220 patients

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Background: Information about spontaneous remission of chronic urticaria is limited.

Objective: To investigate the natural course of urticaria, we followed up 220 adults in a prospective study.

Methods: Patients were followed up for 1 to 3 years to evaluate interventions, to detect latent causes, and to study the natural course of urticaria. The diagnosis was made by detailed history-taking as well as laboratory and provocation tests.

Results: Thirty-five percent of all patients were free of symptoms after 1 year. In 28.9% of patients, symptoms had decreased. Spontaneous remission occurred in 47.4% of the patients in whom no cause of their urticaria and/or angioedema could be identified and in only 16.4% of the patients with physical urticaria. A cause could be identified in 53.1% of the patients. Thirty-six percent of the patients had idiopathic urticaria. Chronic idiopathic urticaria combined with physical urticaria occurred in 10.9%.

Conclusion: In general, the prognosis for spontaneous remission is reasonable, with the exception of the subgroup (33.2%) with physical urticaria. (J Am Acad Dermatol 2001;45:387-91.)

Urticaria is characterized by a well-demarcated eruption of transitory, usually itchy, and sometimes even painful erythematous skin swellings that can recur for months or years. Previous investigators have defined chronic urticaria as episodes recurring for more than 6 weeks.¹ Urticaria and angioedema are common disorders.² Approximately 5% of patients with a bout of urticaria will be symptomatic for longer than 4 weeks.³ Thirty percent of patients with urticaria seen in a family practice have chronic urticaria.³ In clinical studies percentages of causes found for urticaria vary between 20% and 90%.^{2,4-7} The percentages of found causes differ because different inclusion and exclusion criteria (eg, inclusion of physical urticarias) were used.

Chronic urticaria may be caused by internal diseases or malignancies, but these underlying diseases are rarely found.^{2,4,8-10} In the past, extensive laboratory screening has been performed to exclude an underlying disease. Recent diagnostic guidelines recommend thorough history-taking and only a very limited amount of laboratory tests.^{11,12} In a prospective study we evaluated the benefit of extensive laboratory testing and concluded that tests not based on the history do not contribute to the detection of underlying causes of chronic urticaria.¹³ This study was performed in the same patient cohort.

Very little is known about the natural course of chronic idiopathic or physical urticaria. A literature search including articles from 1966 to 2000 revealed more than 5500 medical articles on urticaria or angioedema (or both), but only 13 articles referred to the natural course of the disease.

The aim of this prospective cohort study in consecutive patients was to investigate the natural course and prognosis of chronic urticaria and/or angioedema, including subtypes such as physical urticaria.

SUBJECTS AND METHODS

Patient recruitment, patient population, and study design

The study was performed at the outpatient Department of Dermatology of the Academic

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Medical Center in Amsterdam, The Netherlands, which is a secondary and tertiary care center. From January 1992 to July 1994, all consecutive patients older than 15 years with urticaria and/or angioedema of unknown origin and with at least a 6-week duration of the symptoms were included.

Two hundred twenty patients were investigated. One hundred thirty-two women and 88 men were enrolled in the study; their mean age was 38 years (range, 15-79 years). Forty-one patients (19%) had urticaria only, 64 patients (29%) had urticaria and angioedema, and 18 patients (8%) had angioedema without urticaria.

After informed consent had been obtained, the patients were subjected to a diagnostic protocol, which included a detailed questionnaire, physical examination, laboratory tests, provocation tests for physical urticaria, and adverse reactions to food and drugs. The protocol was approved by the Medical Ethical Committee.

Patient questionnaire

A detailed history was obtained from all patients, using a standardized questionnaire with particular attention to possible causes of urticaria, based on earlier published questionnaires¹⁴⁻¹⁶ and personal experiences.

Laboratory investigations and provocation tests

The study was part of a research project for the development of evidence-based clinical guidelines for laboratory investigations in patients with chronic urticaria and/or angioedema.¹³ Therefore many hematologic, immunologic, biochemical, and allergy tests; cultures; and x-rays were performed, as described in detail elsewhere.¹³ Provocation tests for physical urticaria were performed.^{17,18} To evaluate dermographism, firm stroking of the skin was performed, which induces itchy, linear hives within minutes. The test for pressure urticaria was performed with a special device that applied 3 different weights on the back of the patient for 20 minutes; the appearance of whealing was checked for during the day. Cold urticaria was tested with a steel container with ice cubes applied to the forearm for 20 minutes. Cholinergic urticaria was provoked by a hot shower or exercise until sweating. Screening for food allergy or intolerance was investigated by an elimination diet for at least 3 weeks. All drugs used were discontinued or replaced with chemically unrelated equivalents. Drug provocation tests and oral food rechallenge tests were performed if necessary.

Follow-up

After a follow-up period of at least 1 year, patients were asked whether they had remaining or new com-

plaints and whether they still used antihistamines, oral corticosteroids, or other drugs. Laboratory tests were repeated, if indicated. The follow-up was directed at detecting causes of urticaria not traced initially by the questionnaire, to evaluate the effect of interventions, and to obtain information about the natural course of the different subtypes of urticaria.

RESULTS

Patient questionnaire

Twenty-five percent of the patients had urticaria continuously, 30% of them had daily bouts, 22% had more than 2 bouts every week, and the remaining group less frequently had hives or only angioedema. In 94% of the patients the itch was the most important complaint. Sleeping disorders occurred in 25% of the patients with urticaria and in 4% of the patients with angioedema. Twenty-eight percent of the patients reported intense pruritic whealing from insect bites or stings. This was mainly seen in patients with chronic urticaria and urticaria factitia. Occurrence of urticaria in the family (parents, siblings, grandparents, aunts, uncles, cousins, or nieces) was reported by 10% of the patients, angioedema by 6%, and allergies (not further specified) by 45%. A history of atopy was reported in 40% of the study population.

A large percentage of the patients mentioned that factors such as stress (36%), warm environment (23%), dermographism (13%), and consumption of alcohol (9%) or analgesic drugs (8%) aggravated their urticaria.

Laboratory investigations and provocation tests

In 89% of the patients no abnormalities were found during the physical examination. Dermatologic problems (eg, tinea pedis, vaginal discharge, lipoma, different forms of eczema, acne, or folliculitis) were found and treated in 19 patients. Three patients had emphysema and 2 had arterial insufficiency of the lower legs.

In patients with more than one type of physical urticaria, the type which interfered most with normal life was used for the classification. Of all patients, 10.9% had a combination of physical urticaria and urticarial lesions of unknown origin. In Table I we described this group of patients as having a combination of (one type of) physical urticaria and idiopathic urticaria.

After discontinuation of suspected drugs, provocation tests were performed by reintroducing the drug in a symptom-free period, which resulted in a relapse of symptoms in all patients. The responsible drugs are listed in Table I.

In two patients exercise-induced, food-dependent urticaria was found. In both patients consumption of

Table I. Causes of physical urticaria (PU), chronic urticaria (CU), and/or angioedema (A) and type of reaction in 220 patients

	No. of patients	% Study population	Type of reaction
Physical urticaria	73	33.2	
Dermographism	37	16.8	PU
Pressure	7	3.2	PU
Cold	11	5.0	PU, PU + CU + A
Cholinergic	11	5.0	PU
Heat contact	1	0.5	PU
Solar	4	1.8	PU
Exercise-induced	2	0.9	CU + A
Combination of physical urticaria and chronic idiopathic urticaria	24	10.9	
Dermographism	10	4.5	PU + CU
Pressure	13	5.9	PU + CU
Cold	1	0.5	PU + CU
Drugs	20	9.0	
Aspirin	5	2.3	PU + CU, CU, A
NSAIDs	3	1.4	CU + A, A
Codeine	1	0.4	CU + A
Propyphenazone	2	0.9	PU + CU, A
Antibiotics	3	1.4	PU + CU, CU, A
Antidepressants	1	0.4	PU
ACE inhibitors	2	0.9	A
Oral contraceptives	2	0.9	CU + A
Methotrexate	1	0.4	CU
Food	15	6.8	
Normal hives and/or angioedema	10	4.5	CU + A, CU, A
Dermographism	3	1.4	PU
Exercise-induced, food-dependent	2	0.9	CU + A
Infections	4	1.8	PU, CU
Internal diseases	3	1.4	CU, CU + A
Contact urticaria	2	0.9	CU
Malignancies	0	0	
Hereditary angioedema	0	0	
Chronic idiopathic urticaria	78	36.0	CU + A, CU, A

ACE, Angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drugs.

cereals in combination with exercise resulted in urticaria and angioedema; radioallergosorbent tests (RASTs) to cereals were positive, and provocation tests confirmed the diagnosis. In two patients urticaria factitia developed after consumption of food containing vasoactive amines (eg, wine and cheese). RASTs were negative. One patient with severe hay fever had complaints of urticaria factitia after consuming apples and tomatoes. These 3 causes were found by means of the elimination diet followed by reintroduction of the particular food. Three patients developed severe reactions (eg, syncope and shock) after consuming crustaceans (in one patient), flour (in one), and sesame oil (in one). Scratch tests were highly positive and the oral allergy syndrome was present. Provocation tests would have been dangerous, and the patients were not willing to participate. In 7 patients, after following

the elimination diet and a period of food reintroduction, the following foods were found to be the most likely cause of the urticaria and/or angioedema: dairy products (3 times), eggs (1 time), alcohol (1 time), beef (1 time), and apples/pears (1 time). In one patient the specific RAST was positive (apple/pear). Continuation of the diet resulted in disappearance of the complaints and by reintroduction of the particular food, hives occurred.

In 4 of 10 patients with a parasitic infection, the complaints disappeared after treatment. Their complaints were urticaria factitia and pruritus, not classic hives or angioedema. In two patients an infection with *Trichuris trichiura* and in two other patients an infection with *Strongyloides stercoralis* were found. These patients were born or had lived for a long period in a tropical country.

Table II. Percentages of patients free of symptoms after 1 year

Idiopathic, all patients	47.4% (37/78)
Urticaria only	38.5% (10/26)
Angioedema only	20.0% (2/10)
Both urticaria and angioedema	59.5% (25/42)
Physical and idiopathic urticaria	20.8% (5/24)
Physical urticarias	16.4% (12/73)

The following internal diseases, probably related to the urticaria, were found: Sjögren's syndrome, systemic lupus erythematosus, and paraproteinemia. Hives are still present in them after 3 years' follow-up. Histopathologic evaluation of the skin biopsy specimens did not reveal urticarial vasculitis in this cohort, even in patients who had mentioned that they had wheals for longer than 48 hours. No other severe internal disease or malignancy associated with urticaria or angioedema was found.

Contact urticaria to latex and preservatives was found in two patients.

Follow-up

Follow-up data were obtained by interviewing the patient at the outpatient department, by telephone inquiry, or, in 3 cases, by contacting the general practitioner. The mean follow-up period was 2 years 4 months (range, 12-71 months). One patient was followed up for only 3 months because he moved. In this patient no cause of urticaria could be identified.

Ninety percent of the patients used nonsedating antihistamines during follow-up, 46% used sedating antihistamines as well, 16% occasionally used systemic prednisolone during severe bouts, and in 4% of the patients epinephrine for intramuscular use was prescribed.

After 3 months 14% of the 220 patients were free of complaints. After 6, 9, and 12 months, 26%, 30%, and 35%, respectively, were free of symptoms. At the end of the follow-up period, in 28.9% of the patients the symptoms had decreased, in 35% the symptoms remained the same, and in 1.4% the symptoms had worsened. In 25% of the 220 patients, a spontaneous remission occurred after 1 year.

For the entire patient group with idiopathic urticaria and/or angioedema, as well as for the different subtypes (idiopathic urticaria only, idiopathic angioedema only, idiopathic urticaria and angioedema, physical urticaria, and combination of physical and idiopathic urticaria), we investigated the number of patients who were free of symptoms after 1 year (Table II). In some patients with physical urticaria, a parasitic infection or an adverse event to

food or drugs was provoking dermographism. These patients were not included in Table II.

DISCUSSION

This study provides information about the natural course of different types of urticaria. In a disease in which it is often not possible for the clinician to determine the cause of patients' complaints, it is helpful to be able to inform them about their prognosis. In this study, 47.4% of the patients with idiopathic urticaria and/or angioedema were free of symptoms after 1 year, and only 16.4% of the patients with physical urticaria were free of symptoms.

A limitation of this study is that it was performed in a secondary and tertiary care center, and the results may not be applicable to other patient populations. Furthermore, by analyzing the number of patients with different forms of urticaria separately, the percentages are based on smaller numbers of patients.

An advantage of the study design is that we followed a well-defined cohort of 220 patients. A cohort study is considered to be the best study design to identify prognostic factors and to determine the relationship between a prognostic factor and disease duration.¹⁹

We performed extended laboratory investigations not because we believed that they are necessary to detect the cause of chronic urticaria, but to provide evidence that routine investigations are not useful if performed without an indication from history-taking or a questionnaire. This hypothesis could be confirmed and was presented in another article.¹³

Only a few studies deal with the natural course of chronic urticaria. Urbach²⁰ found in 500 patients with urticaria and/or angioedema the following percentages of durations: 3 to 12 months (19%), 1 to 5 years (20%), 6 to 10 years (4%), and after 11 to 20 years (1.5%). Humphreys and Hunter⁷ found that symptoms were present for more than 5 years in 5% of the patients when they first attended a general dermatology clinic and in 13% of patients who visited a specialized urticaria clinic. Quaranta et al²¹ investigated 86 patients with chronic idiopathic urticaria in whom 27 (31%) resolved, 48 (56%) continued to have symptoms, and in 11 (13%) the natural cause was unknown. It made no difference whether the patients had urticaria, angioedema, or urticaria and angioedema. In 32% of their patients, complaints resolved after a 3-year period. In our patient cohort, 47.4% of this subgroup of patients (having idiopathic urticaria and/or angioedema) were free of symptoms after 1 year. Information on the natural course of chronic urticaria in a large group of patients was given by Champion et al² in 1969. In their study approximately 45% of patients with idiopathic urticaria only still had com-

plaints after 1 year. In our study group 61.5% of the patients with idiopathic urticaria only still had complaints. Champion et al found that for patients with idiopathic angioedema only and for patients with idiopathic urticaria and angioedema, about 55% and 70%, respectively, still had symptoms after 1 year. We found this in 80% and 40.5% of our patients with idiopathic angioedema only and with idiopathic urticaria and angioedema, respectively. We could not confirm that patients with idiopathic urticaria and angioedema had the worst prognosis. In our study physical urticaria was the worst prognostic factor; 84% of the patients still had complaints after 1 year.

In many of the previously published studies the percentages of identified causes are smaller than in our study.^{2,4} In particular, the number of physical urticaria cases is high, probably because efforts were made to detect them with detailed questions and provocation tests. Physical urticaria was found in 12% to 57% of patients in different studies in the literature from 1937 to 1985, including 120 to 500 patients, depending on the care center.²²

In 3.6% of the patients the urticaria was caused by medication and not by the internal disease or infection for which the drugs were prescribed. One patient had a mesothelioma, but his angioedema was not related to his malignancy and it cleared after discontinuing medication.²³ In another patient with severe rheumatoid arthritis, methotrexate induced the urticaria. In some patients exacerbation occurred during viral infections. This was often related to the use of analgesic drugs.

An elimination diet followed by reintroduction of the food was helpful in a few patients motivated to find a cause, but the frequency of food reaction was very low. During the follow-up period all found infections (parasite infections, vaginitis, or cystitis) were treated, and only in 4 patients with a parasitic infection was there a probable relation with urticaria factitia.

In conclusion, spontaneous remission occurs in approximately 47% of the patients with chronic idiopathic urticaria and/or angioedema within 1 year after referral. Only 16% of the patients with physical urticaria were free of symptoms after 1 year. In patients referred to a tertiary care center for chronic urticaria, the prognosis is reasonable. This is another argument for adopting an attitude of waiting regarding extensive laboratory screening.

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