

Clinical and Laboratory Investigations

Clinical and aetiological aspects in urticaria and angio-oedema

E.NETTIS, A.PANNOFINO, C.D'APRILE, A.FERRANNINI AND A.TURSI

Department of Medical Clinics, Immunology and Infectious Diseases, Section of Allergy and Clinical Immunology, University of Bari, Piazza Giulio Cesare 11, Policlinico 70124, Bari, Italy

Accepted for publication 9 September 2002

Summary

Background Urticaria is a common disorder that affects as many as 20% of all people at some time during their lifetime.

Objectives To analyse the prevalence of various forms of urticaria according to an aetiological and clinical classification, we carried out a 4-year study in an outpatient clinic.

Methods The study was carried out on 562 consecutive patients (178 males and 384 females; mean age 35.4 ± 16), who had been referred to our unit for the study of urticaria and angio-oedema. Baseline investigations included: the patient's family and personal history of allergy; duration of symptoms, presence of associated symptoms and objective signs of the current episode; clinical, laboratory and instrumental investigations; assessment of response to antihistamine treatment.

Results A family history of atopy was present in 35% of patients and a personal history of allergy in 24%. We subdivided urticaria and angio-oedema into several groups on the basis of their clinical and aetiological aspects. Of the 562 patients, 424 (76%) presented with ordinary urticaria (43 acute urticaria, 311 chronic urticaria, 70 episodic urticaria), 80 (14%) physical urticaria, 49 (9%) angio-oedema without weals, six (1%) IgE-mediated contact urticaria and three (0.5%) urticarial vasculitis. In 64 cases (11%) urticaria/angio-oedema was associated with one or more symptoms. We identified 394 cases (82%) of idiopathic urticaria, 42 (9%) of immunological urticaria, 29 (6%) of non-immunological urticaria and 17 (3%) of urticaria secondary to infections. Of the treated subjects, 54% showed a good response to treatment with antihistamines.

Conclusions Our data provide an overview of urticaria/angio-oedema in a large series of patients, based on clinical–aetiological aspects, and related to recent diagnostic guidelines.

Key words: autologous serum skin test, epidemiology, H₁ antihistamines, urticaria/angio-oedema

Urticaria is a common disease which affects up to 20% of the general population at least once during their lifetime. Several conditions such as intolerance to certain foods, additives, drugs, as well as infection or internal diseases, have been found to be related to urticaria symptoms and have therefore been implicated as aetiopathogenetic factors.¹ A recent study² demonstrated that, although patients with acute urticaria often complained of an associated upper airways infection or had taken a particular drug, in over 50%

the eliciting cause was unclear. Other work^{3,4} has shown that the cause of chronic urticaria (CU) remained unknown in a high percentage (70–75) of cases, despite intensive clinical and laboratory investigations. In our study the characteristics of urticaria were documented in 562 patients by a careful history, including frequency of occurrence and clinical presentation, and associated symptoms, and a diagnostic evaluation, by means of clinical, laboratory and instrumental investigations, to reveal any possible cause of the disorder. The aim of our study, which was conducted at our outpatient clinic, was to analyse the prevalence of various forms of urticaria according to an aetiological and clinical classification⁵ and to evaluate the efficacy of antihistamine therapy in this disease.

Correspondence: Eustachio Nettis, MD.
E-mail: e.nettis@allergy.uniba.it

Subjects and methods

Our study population consisted of 562 consecutive patients suffering from urticaria and/or angio-oedema and examined in our study unit for urticaria and angio-oedema during 1996–99. All subjects signed informed consent to enrolment in the study. They were asked to complete a questionnaire detailing sex, age at presentation; family history of allergic rhinitis, asthma, atopic eczema and urticaria; any past history of allergic rhinitis, asthma and atopic eczema; any history of reactions to drugs and foods; duration of the illness; duration of weals; skin areas involved and associated symptoms. Data on the response to treatment with antihistamines were collected after a 0.5–3-month follow-up period.

At the first visit, after a careful history and detailed physical examination, all patients were submitted to clinical, laboratory and instrumental investigations tailored to the individual clinical history and findings in each patient:¹ tests included urinalysis, routine laboratory evaluation (including complement C3, C4 and C1 inhibitor antigenic level, thyroid function test, antithyroid autoantibodies, antinuclear antibodies, rheumatoid factor, serum immunoglobulins, circulating immune complexes, cryoglobulins, stool screening for blood, parasites and yeast, serology for viral, bacterial and parasite antibodies, serum electrophoresis, gastroscopy, biopsy and enzyme-linked immunosorbent assay for specific anti-*Helicobacter pylori* IgG antibodies), X-ray studies (including dental series, sinus series and chest X-ray) and sonography of the upper abdomen. A skin biopsy was done in three patients who had weals that lasted over 24 h.

Skin prick tests were performed with common available foods and inhalants (Bayropharm, Milan, Italy). In some cases, a 'prick-prick test' with the fresh raw food was made. Histamine hydrochloride (10 mg mL⁻¹) was used as positive control, and physiological saline as negative control. The prick test was considered positive if the weal was more than 3 mm larger than the weal of the negative control. Measurement of total IgE level was by the paper radioimmunosorbent (PRIST) test (Pharmacia, Uppsala, Sweden) and specific serum IgE by a fluorescence enzyme-linked immunoassay (CAP-FEIA system; Pharmacia, Uppsala, Sweden). Total IgE was measured according to the manufacturer's instructions and PRIST was considered positive at titres > 100 kU L⁻¹. The threshold of positivity for the FEIA was set at 0.35 kU L⁻¹. Intradermal skin tests (concentration

1 µg mL⁻¹) were performed by injection of 0.02 mL venoms (Bayropharm) from *Apis mellifera*, *Vespula*, *Polistes* and *Vespa crabro*. A negative (diluent) and a positive control (histamine 0.1 mg mL⁻¹) of venom skin tests were run concurrently. Skin tests were graded according to the system described by Norman.⁶ Reactions graded as 2+ or higher were considered positive. Drug-related aetiology was established on the basis of the criteria laid down by the protocols in literature.⁷ Briefly, the methods used to evaluate patients with suspected drug-induced urticaria were a detailed history, withdrawal of the suspected drug, and in some cases *in vivo* and *in vitro* testing. In order to evaluate the role of foods and additives, double blind placebo-controlled *in vivo* provocation tests (DBPCFC) with foods and additives were performed when necessary.^{8–11} The choice of foods and additives selected for the DBPCFC was determined by history, skin test, or radioallergosorbent test (RAST) test or by the results of an elimination diet; a 14-day diet in which all foods or additives suspected of causing an urticarial reaction were eliminated. Patients with a history consistent with an immediate reaction to a food or additive and a positive skin test (or RAST test) to foods were not challenged. Autologous serum skin tests, performed as previously reported,¹² were carried out on 125 subjects with CU. Physical challenge tests were used to confirm the diagnosis of physical urticaria.^{13–16} For the diagnosis of delayed pressure urticaria a 7-kg weight was suspended from the patient's shoulder for 15 min and the test was read at 30 min, 3, 6, 8 and 24 h.^{13,14} A diagnosis of dermatographism was based on the appearance of a linear red weal 5–10 min after light stroking of the skin.^{13–16} For cold urticaria the diagnosis was confirmed by applying an ice cube to the skin of the forearm for 10–15 min and, after allowing a few minutes for the skin to warm again, the development of weals was observed.^{13–16} Challenge procedures for the diagnosis of cholinergic urticaria were exercise (jogging up to 30 min) or a warm bath for 10–20 min.^{13,14} Solar urticaria was induced by exposure to natural or artificial sunlight and aquagenic urticaria by application of water compresses at body temperature for 30 min.^{13–16} All data regarding investigation results, questionnaire data, patient management and response to treatment were collected in a database in our unit. Data analysis and comparison of results were performed using Epi Info software, version 6 (Centers for Disease Control and Prevention, Atlanta, GA, U.S.A.). For comparison of antihistamine therapy in the different forms of urticaria and angio-oedema, on the basis

of their clinical aspects,⁵ χ^2 -tests with Yates' correction at a significance level of $P < 0.05$ was used.

Results

Prevalence and incidence

From January 1996 to December 1999, 562 consecutive patients with urticaria and/or angio-oedema, 178 males (32%) and 384 females (68%), ranging in age from 5 to 86 years (mean 35 ± 16 years) were evaluated. A constant increase of incidence was observed over the years of the study. Indeed, during 1999, 280 (50%) new cases of urticaria and/or angio-oedema were seen in our unit.

Atopic history

Among 562 patients, 197 (35%) reported a family history of atopy (rhinoconjunctivitis, asthma and atopic dermatitis) and 56 (10%) a family history of urticaria. One hundred and thirty-eight (24%) patients had a personal history of allergy. Ninety-eight (17%) reported respiratory symptoms: allergic rhinitis in 82 cases and asthma in 16 cases. Forty patients (7%) had a history of atopic dermatitis.

History of adverse reactions to drugs and foods

One hundred and five patients (19%) reported a history of reactions to drugs. Thirty-five of 105 patients (33%) presented a history of reaction to antimicrobial agents: penicillins (29 cases), cephalosporins (three), macrolides (two) and sulphonamides (one). Fifty-eight of 105 (55%) reported episodes of non-steroidal anti-inflammatory drug sensitivity; in 15 patients the reaction had apparently been provoked by salicylates, in 18 by propionic acid derivatives, in 13 by pyrazolone derivatives, in six by nimesulide, in five by paracetamol, in one by naproxen. The remaining 12 patients reported episodes due to different drugs. Finally, 66 subjects (12%) had a history of food reactions.

Clinical classification of urticaria and angio-oedema

We subdivided urticaria and angio-oedema into several groups on the basis of their clinical aspects, according to the diagnostic guidelines proposed by Grattan *et al.*⁵ Table 1 shows the clinical classification of urticaria and angio-oedema in the population studied. In our study 424 patients (75%) presented with ordinary urticaria

Table 1. Clinical classification of urticaria and angio-oedema seen in 562 subjects, many of whom showed more than one type of urticaria or angio-oedema

Type of urticaria or angio-oedema	Subjects	
	No.	%
Ordinary urticaria	424	75.4
Chronic	311	55.3
Episodic (intermittent)	70	12.5
Acute	43	7.6
Physical urticaria	80	14.2
Dermographism	50	8.9
Delayed pressure urticaria	17	3.0
Cold urticaria	6	1.1
Cholinergic urticaria	4	0.7
Aquagenic urticaria	1	0.2
Solar urticaria	1	0.2
Dermographism + pressure urticaria	1	0.2
Angio-oedema (without weals)	49	8.7
Contact urticaria	6	1.1
Urticarial vasculitis	3	0.5
Total types	1066	

(43 acute urticaria, 311 CU, 70 episodic urticaria). Angio-oedema occurred concurrently with urticaria in 150 (27%) of 562 patients, while urticaria alone was reported by 274 (49%) subjects. Eighty patients (14%) in our study group presented one or more forms of physical urticaria. Physical urticarias occurred alone in 27 subjects (5%) and in association with ordinary urticaria in 53 (9%). Finally, 49 patients (9%) presented angio-oedema without weals. In this group of patients we found one patient with C1 esterase inhibitor (C1INH) deficiency where insufficient C1INH synthesis occurred (hereditary angio-oedema type I), whereas the remaining 48 subjects had a normal C1INH value. In 199 patients who had angio-oedema alone or with urticaria, the disease was mainly localized on the lips (16%), eyelids (8%), face (11%) and larynx (4%). In 64 cases (11%) urticaria and/or angio-oedema was associated with one or more symptoms (Table 2). We identified six cases of IgE-mediated contact urticaria; in four patients the complaint was caused by latex and in two by tomatoes. Finally, three patients reported weals lasting over 24 h and urticarial vasculitis was diagnosed by means of skin biopsy.

Aetiology and associations of urticaria and angio-oedema

Urticaria and angio-oedema may be caused by a wide variety of factors. Table 3 shows the classification of urticaria and angio-oedema on the basis of its

Table 2. Symptoms associated with urticaria/angio-oedema in 562 subjects

Symptoms	Subjects	
	No.	%
Gastralgia	52	9.2
Asthma	39	6.9
Fever	23	4.1
Rhinitis	17	3.0
Lipothymia	16	2.8
Conjunctivitis	11	2.0
Arthralgia	6	1.1
Headache	4	0.7
Total symptoms	168	

aetiology.⁵ For this classification, we excluded patients with physical urticaria and evaluated the remaining 482 subjects. Idiopathic urticaria was diagnosed after exclusion of all possible causal factors; in our study, we could not demonstrate a cause for the urticaria and/or angio-oedema in 394 cases (82%). The pathogenesis of chronic idiopathic urticaria (CIU) is still unknown. As autoantibodies specific for IgE or high-affinity IgE-Fc receptors have been detected in some patients with this disease, autoimmunity has been hypothesized to play a role in its development.^{17,18} In our study 54 of the 125 patients (43%) submitted to the autologous serum skin test showed a positive response. A positive test is

Table 3. Aetiology of urticaria and angio-oedema in 482 subjects

	Subjects	
	No.	%
Idiopathic	394	81.7
Immunological	42	8.7
IgE dependent	38	7.9
Immune complex	3	0.6
Complement dependent (C1INH deficiency)	1	0.2
Non-immunological	29	6.0
Drugs	13	2.7
Aspirin	4	0.8
Propionic acid derivatives	4	0.8
Pyrazolone derivatives	3	0.6
Angiotensin-converting enzyme inhibitors	2	0.4
Foods (after placebo-controlled challenge testing)	6	1.2
Soya	4	0.8
Tomato	2	0.4
Additives (after placebo-controlled challenge testing)	10	2.1
Tartrazine	6	1.2
Sodium benzoate	4	0.8
Total causes	565	

suggestive but not diagnostic of an autoimmune basis for the patient's CU, which would require confirmation by *in vitro* testing of the patient's serum for anti-FcεRIα or anti-IgE autoantibodies.¹⁶ For this reason, we have not included the autoimmune classification in our study. In addition, urticaria may result from an IgE-mediated allergic reaction. In this study we identified 38 cases (8%) of IgE-mediated type I allergic reactions due to drugs, foods, inhalants, *Hymenoptera* and latex as shown in Table 4. Non-allergic hypersensitivity reactions to aspirin, other NSAIDs and drugs, as well as food or additives, cause urticaria by non-immunological pathways which have not so far been clarified. In our study we found 29 cases (6%) of non-immunological urticaria (Table 3), while exacerbation of CU after aspirin administration was reported in 55 patients (11%). All patients in whom a food or additive was identified as the culprit had the diagnosis confirmed by placebo-controlled challenge testing.

Urticaria and angio-oedema can also be the presenting symptom or an associated symptom of underlying systemic disease. In our study CIU was associated with thyroid disease in 10 subjects (2%). Seven patients suffered from a hypothyroid condition with positive antithyroid autoantibodies, and three from a hyperthyroid condition. Laboratory and instrumental investigations (gastroscopy and biopsy) revealed that *Helicobacter pylori* was the cause of urticaria in 10 patients, intestinal parasitic infections in four cases (two cases of *Giardia lamblia*, one case of *Ascaris lumbricoides*, one case of *Enterobius vermicularis*), streptococcal tonsillitis

Table 4. IgE-dependent urticaria to drugs, foods, inhalants, *Hymenoptera* and latex in 38 subjects, more than one cause per subject

Causative factors	Subjects	
	No.	%
Drugs	11	28.9
Penicillins	6	15.8
Cephalosporins	4	10.5
Macrolides	1	2.6
Foods	14	36.8
Nut	4	10.5
Peanut	3	7.9
Peach	3	7.9
Tomato	2	5.3
Hazelnut	2	5.3
Inhalants (pollens)	8	21.0
Hymenoptera	1	2.6
Latex	4	10.5
Total	63	

in two cases and urogenital tract infections in one case. In these patients the urticaria resolved on appropriate treatment.

Therapy

Therapy with antihistamines was attempted in 475 patients with active urticaria and/or angio-oedema. The efficacy of such therapies was not recorded in 124 patients, because of loss to follow-up. A good response was recorded in 191 (40%) patients, moderate response in 137 (29%), and a slight response or none in 23 (5%). According to the clinical classification, H₁ antihistamines were not shown to be effective in physical urticaria, while they induced a significant improvement in ordinary urticaria ($P < 0.05$). Statistical analysis was not performed in patients with urticarial vasculitis and contact urticaria because of loss to follow-up. Other types of drugs were administered in 221 patients: 144 were treated with steroids, 31 with cyclosporin A, 26 with disodium chromoglycate, 14 with antileukotrienes and six with adrenaline.

Discussion

In a study by Champion *et al.*¹⁹ a family history of allergic rhinitis, asthma and atopic dermatitis was observed in 35% of cases and a family history of urticaria in 10% of all subjects. The percentage of patients with a personal history of allergy is higher (25%) in our study than in the above (18%).

As to the aetiology, most cases (82%) were forms of idiopathic urticaria. In other studies the cause of CU was unidentified in 70–75% of patients,^{3,4} and that of acute urticaria in > 50% of cases.² Indeed, the tedious search for an underlying cause is often fruitless and, even when successful and appropriately dealt with, is not necessarily followed by complete resolution of the symptoms. Physical causes, drugs and food agents are most easily recognized as aetiological factors in acute urticaria. In CU, laboratory and instrumental evaluations (of step-by-step type) provide important clues for suspecting or confirming the effect of any agent that is likely to induce urticaria.

C1INH deficiency is an autosomal dominant defect causing an angio-oedema (hereditary angio-oedema) that characteristically occurs without urticaria. More than 90% of all angioedemas are idiopathic and hereditary forms account for less than 1% of all angioedemas.²⁰ In our study 0.2% of the subjects with angio-oedema had a C1 esterase inhibitor deficiency.

Food and drug additives include preservatives, colourings, stabilizers, antioxidants, sweeteners and flavourings. Because many adverse reactions to additives have not been verified by appropriate diagnostic challenge procedures, the true frequency of food and drug additive reactions in the general population remains unknown. Other authors have reported that food dyes, natural salicylates and/or benzoic acid derivatives may be causative factors in some cases of CU and angio-oedema;^{21–23} an incidence of adverse reaction to additives ranging between 3%²² and 5%²⁴ has been estimated. We report an extensive analysis of aetiological factors in urticaria and/or angio-oedema. An incidence of 2% in patients with CU, which may be attributed to tartrazine (six cases) and sodium benzoate (four cases), was documented and confirmed by a DBPCFC, the standard test for the definitive diagnosis of food and drug additive allergies.^{8–10}

Many patients with CU develop an obvious increase in weal size and swelling after administration of aspirin. The proportion of patients with CU who develop exacerbation after aspirin administration and other salicylates ranges from 20% to 40%,^{25–27} whereas aspirin administration causes urticaria and/or angio-oedema in a percentage ranging from 1% to 6%²⁷ of normal subjects. These exacerbations occurred in 10% of patients in our study, a lower value than that reported by other authors.¹⁹ It is thought that an imbalance in the arachidonic acid cascade, with inhibition of prostaglandin synthesis and increase of leukotrienes, may play a pathophysiological role, not only in aspirin-induced asthma, but also in aspirin-induced adverse skin reactions. It seems therefore that all patients with urticaria should avoid aspirin in any form.

First-line therapy for urticaria is based on H₁ antihistamines. Various antihistamines, especially those of newer generations, exhibit antiallergic and anti-inflammatory effects, which may be variable in their degree and target of action.^{28,29} Although these drugs do not always decrease the number of urticarial lesions or the frequency of eruptions, they may provide symptomatic relief. In this study, 54% of patients reported a good response after antihistamines, an outcome which is in contrast with other data.^{19–30} The positive effects induced in CIU by treatment with antileukotrienes³¹ and cyclosporin^{32,33} suggest that other mediators as well as histamine are involved in the pathogenesis of urticaria, even though use of H₁ antihistamines remains the main treatment of urticaria regardless of its aetiology. Finally, diagnostic clues can

be provided by patient history and confirmation by proper selection of diagnostic investigations and selected laboratory tests. Nevertheless, in this study we found that, despite intensive laboratory evaluations, the cause of urticaria cannot be ascertained in most patients with urticaria and/or angio-oedema.

In conclusion, our data provide an overview of urticaria/angio-oedema in a large series of patients, based on clinical-aetiological aspects, and related to recent diagnostic guidelines.

References

- Kaplan AP. Urticaria and angio-oedema. In: *Allergy: Principles and Practice* (Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, eds). St Louis, MO: CV Mosby, 1993: 1562–4.
- Zuberbier T, Iffländer J, Semmler C, Czarnetzki BM. Acute urticaria-clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996; **76**: 295–7.
- Champion RH. Urticaria: then and now. *Br J Dermatol* 1988; **119**: 427–36.
- Green GA, Koelsche GA, Kierland R. Etiology and pathogenesis of chronic urticaria. *Ann Allergy* 1965; **23**: 30–6.
- Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. *Br J Dermatol* 2001; **144**: 708–14.
- Norman PS. Skin testing. In: *Manual of Clinical Immunology* (Rose NR, Friedman H, eds). Washington DC: American Society of Microbiology, 1980: 789–93.
- Vervloet D, Pradal M. *Drug Allergy*. Uppsala: Kabi Pharmacia, 1992.
- Bock SA, Sampson HA, Atkins FM *et al.* Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; **82**: 986 (Abstr.).
- Pastorello EA. Evaluating new tests for the diagnosis of food allergy. *Allergy* 1995; **50**: 289–91.
- May CD. Are confusion and controversy about food hypersensitivity really necessary? *J Allergy Clin Immunol* 1985; **75**: 329–33.
- Simon RA, Stevenson DD. Adverse reactions to food and drug additives. In: *Allergy: Principles and Practice* (Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, eds). St Louis, MO: CV Mosby, 1993: 1687–704.
- Sabroe RA, Grattan CEH, Francis DM *et al.* The autologous serum skin test: A screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–52.
- Kontou-Fili K, Borici-Mazi R, Kapp A *et al.* Physical urticaria: classification and diagnostic guidelines. *Allergy* 1997; **52**: 504–13.
- Möller P, Henz BM. Physical urticaria. In: *Urticaria: Clinical, Diagnostic and Therapeutic Aspects* (Henz BM, Zuberbier T, Grabbe J, Monroe E, eds). Berlin: Springer-Verlag, 1998: 55–89.
- Jensen-Bindslev C, Finzi A, Greaves M *et al.* Chronic urticaria: diagnostic recommendations. *J Eur Acad Dermatol Venereol* 2000; **14**: 175–80.
- Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; **105**: 664–72.
- Niimi N, Francis DM, Kermani F *et al.* Dermal cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**: 1001–6.
- Tong LJ, Balakrishnan G, Kochan JP *et al.* Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; **99**: 461–5.
- Champion RH, Roberts SOB, Carpenter RG *et al.* Urticaria and angio-oedema. *Br J Dermatol* 1969; **81**: 588–97.
- Möller P, Henz BM. Angio-oedema. In: *Urticaria: Clinical, Diagnostic and Therapeutic Aspects* (Henz BM, Zuberbier T, Grabbe J, Monroe E, eds). Berlin: Springer-Verlag, 1998: 45–54.
- Iacobsen DW. Adverse reactions to benzoates and parabens. In: *Food Allergy: Adverse Reactions to Foods and Food Additives* (Metcalfe DD, Sampson HA, Simon RA, eds). Boston: Blackwell Scientific, 1991: 276–87.
- Volonakiis M, Katsaron-Kutsari A, Stratigos J. Etiologic factors on childhood chronic urticaria. *Ann Allergy* 1992; **69**: 61–5.
- Stevenson DD, Simon RA, Lumry WR *et al.* Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986; **78**: 182–91.
- Black AK, Greaves MW, Champion RK *et al.* The urticarias 1990. *Br J Dermatol* 1991; **124**: 100–8.
- Warin RP, Smith RJ. Chronic urticaria: investigations with patch and challenge tests. *Contact Dermatitis* 1982; **8**: 117–21.
- Juhlin L. Intolerance to food and drug additives. In: *Handbook of Experimental Pharmacology* (deWeck AL, Bundgaard H, eds). Berlin: Springer Verlag, 1983: 63, 643.
- Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: *Allergy: Principles and Practice* (Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, eds). St Louis, MO: CV Mosby, 1993: 1752–3.
- Monroe EW, Bernstein DI, Fox RW *et al.* Relative efficacy and safety of loratadine, hydroxyzine and placebo in chronic idiopathic urticaria. *Arzneimittelforschung* 1992; **42**: 1119–21.
- Kalivas J, Breneman D, Tharp M *et al.* Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol* 1990; **86**: 1014–18.
- Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998; **138**: 635–8.
- Nettis E, Dambra P, D'Oronzio L *et al.* Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol* 2001; **137**: 99–100.
- Loria MP, Dambra PP, D'Oronzio L *et al.* Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001; **23**: 205–13.
- Grattan CEH, O'Donnell BF, Francis DM. Randomized double-blind study of cyclosporin in chronic idiopathic urticaria. *Br J Dermatol* 2000; **143**: 365–72.