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Mast cell activation in acquired chronic urticaria-angioedema

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Abstract

Mast cells play a central role in the pathogenesis of many allergic disorders. They can be activated in different ways. The present study was focused to evaluate the role of mast cells in acquired chronic urticaria-angioedema induced by gastroesophageal reflux. Tryptase, an important marker of mast cell activation, was detected with UniCap™ Tryptase Fluoroenzymeimmunoassay (Pharmacia & Upjohn AB, Uppsala, Sweden). Eight subjects were studied: four males and four females, aged between 29 and 71 years (mean age: 45 yrs.), suffering from acquired chronic urticaria-angioedema. Results were compared with the results of seven healthy control subjects. Moreover, data were compared with those of 13 subjects (10 males and 3 females, mean age: 24.7 years) suffering from allergic rhinitis. In acquired chronic urticaria-angioedema, serum tryptase levels (mean ± S.D.: 9.6 ± 4.3 μg/l) were significantly higher ($P < 0.007$) than those of the controls (mean ± S.D.: 3.0 ± 1.2 μg/l) and higher also than in allergic rhinitis (mean ± S.D.: 6.1 ± 2.4 μg/l, $P < 0.03$). The results underline the central role of mast cells in the inflammation of acquired chronic urticaria-angioedema.

Keywords: Tryptase; Mast cell; Urticaria-angioedema; Allergic inflammation; Gastroesophageal reflux

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1. Introduction

In a high number of cases the origin of the acquired chronic urticaria-angioedema is not known (Kaplan, 1993; Greaves, 1996). Our previous studies demonstrated that idiopathic acquired chronic urticaria-angioedema syndrome (UAS) may be often induced by unusual different factors that have been underestimated or slightly considered for too long a time. These are the focal diseases, exercise-induced anaphylaxis, or gastroesophageal reflux (Serafini and Coari, 1945; Bruno et al., 1981; Bruno, 1982, 1984; Bruno et al., 1993, 1996, 1997a). Independent of the kind of trigger factors, the inflammation of acquired chronic UAS is characterized by the involvement of several cells and different mediators that are released by immunological or non-immunological mechanisms. Mast cells play a central role in the pathogenesis of many allergic disorders and they can be activated in different ways. Recent studies have stressed the potential of the neutral proteases to act as important mediators of allergic inflammation (Schwartz and Huff, 1998), as our previous studies showed also in allergic rhinitis (Andreozzi et al., 1998, 1999).

Tryptase is considered to be an important specific marker of mast cell activation induced by several and different triggers. Up to now few data are available that concern the role of mast cells in pathophysiological events that characterize inflammation of acquired chronic UAS. The present study was devoted to evaluate mast cells activation in acquired chronic UAS.

2. Patients and methods

Eight subjects were studied: four males and four females, aged between 29 and 71 years (mean age: 45yrs.), suffering from acquired chronic idiopathic UAS. Results were compared with the results of seven healthy control subjects and with 13 subjects (10 males and 3 females, mean age: 24.7 years) suffering from perennial allergic rhinitis which was diagnosed by characteristic history, skin prick test and RAST.

Tryptase FEIA test. Ten millilitres peripheral blood venipuncture sample was collected from each patient with acquired chronic UAS, from each subject with perennial allergic rhinitis, and from healthy control subjects. The samples were centrifuged at 1500 rev./min for 10 min at room temperature in order to aliquot sera which were stored at -20°C. The test (Schwartz, 1994) was performed by UniCap^{TM} tryptase fluoroenzymeimmunoassay (Pharmacia & Upjohn AB, Uppsala, Sweden). Anti-tryptase, covalently coupled to immunoCap, reacted with tryptase in the patient serum sample. After washing, enzyme-labelled antibodies against tryptase were added to form a complex. After incubation, unbound enzyme-anti-tryptase was washed away and the bound complex was then incubated with a developing agent. After the reaction was stopped, the fluorescence in the eluate was measured. Fluorescence was directly proportional to the concentration of tryptase in the serum sample. A UniCap 100 instrument was programmed to calculate data automatically from the UniCap tryptase assay.

2.1. Statistical analysis

The blood samples were collected always at the same time to avoid possible variables owing to the circadian change. Results were analyzed by 'unpaired *t*-test'. Probability (P) values ≤ 0.05 were considered to be significant.

3. Results

No one of the patients with acquired chronic UAS showed factors related to the most common causes of urticaria-angioedema (such as drugs, foods, insect venom, complement deficiency, etc.). However, the evaluation of other 'unusual' trigger factors showed that all the subjects were also suffering from characteristic symptoms related to gastroesophageal disorders, such as heartburn, pyrosis, epigastric pain, and regurgitation, alone or in any combination. The upper intestinal endoscopy in all the cases showed the presence of gastroesophageal reflux (GER) with or without esophagitis of the lower tract, which was related to the incompetence of the lower sphincter or

Table 1
Clinical features and upper intestinal endoscopy in the patients with acquired chronic aUAS

Patient	Age	Sex	Diagnosis	Endoscopy
01. R.S.	52	M	UAS	LES incompetence, antrum gastritis, HP +
02. L.G.	32	F	UAS	LES incompetence, esophagitis
03. M.R.C.	39	F	UAS	LES incompetence, gastritis
04. E.Z.	62	F	UAS	Hiatal hernia, esophagitis
05. S.Z.	47	M	UAS	LES incompetence, duodenal ulcer,
06. C.P.	45	F	UAS	LES incompetence
07. R.T.	29	M	UAS	LES incompetence, esophageal diverticulum
08. G.S.	71	M	UAS	Hiatal hernia, antrum gastritis, HP +

hiatal hernia. GER was associated to antrum gastritis in two cases, to duodenal peptic ulcer in one case, and to esophageal diverticulum case. Two out of eight cases showed the presence of *Helicobacter pylori* (Table 1).

The healthy control subjects (mean age 30.4 years, range 17–35, 3 males and 2 females) did not have a personal or relative history of atopy and the allergic tests for IgE-mediated diseases were negative in vivo and in vitro.

In perennial allergic rhinitis patients, diagnosis was based on the characteristic history with symptoms of sneezing, nasal obstruction, rhinorrhoea, nasal itching. The skin prick test and the RAST showed a high degree of sensibility to Dermatophagoides pteronyssinus (D.pt.) in all patients.

As shown in Fig. 1, basal values of tryptase (mean $\pm$ S.D.: 9.6 ± 4.3 $\mu g/l$) were significantly higher ($P < 0.007$) than the values detected in the controls (mean $\pm$ S.D.: 3.0 ± 1.2 $\mu g/l$) and also than in the allergic rhinitis (mean $\pm$ S.D.: 6.1 ± 2.4 $\mu g/l$, Δ: $P < 0.03$). These had values significantly higher ($P < 0.02$) than those detected in the controls.

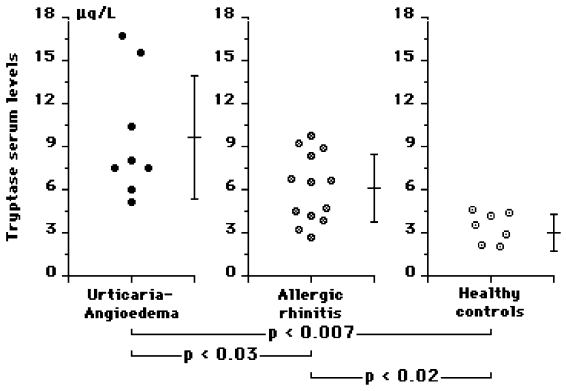

Fig. 1. Basal values of tryptase of allergic patients and controls. Values are expressed as mean $\pm$ S.D.

4. Discussion and conclusions

Acquired chronic urticaria-angioedema often causes considerable domestic, personal, recreational, social, and emotional handicaps (O'Donnell et al., 1997). Moreover, the causes of acquired UAS are considered unknown in a high percentage of cases. For these reasons urticaria and angioedema are often frustrating for patients as they go from one physician to another in hope of finding an extraordinary physician who will be able to identify the cause, eliminate the culprit, and thus cure their hives (Charlesworth, 1996). However, our previous study (Andreozzi et al., 1996; Bruno et al., 1997b,c, 1998) demonstrated that the occurrence of idiopathic urticaria-angioedema is not so frequent as it is reported (Kaplan, 1993; Greaves, 1996).

The patients selected for the study should be in the big group of idiopathic UAS, because the usual findings to ascertain this etiology were negative. But other symptoms reported by patients were typically to relate with a disorder of the gastroesophageal tract, as was demonstrated by the upper intestinal endoscopy. It is well known that GER is often the cause of a spectrum of diseases, including UAS (Bruno et al., 1998;

Castell, 1994; Debonne et al., 1994; Heading, 1994), and it is induced often by physical exercise (Clark et al., 1989). In predisposed individuals, inflammation induced by GER is similar to that mediated by immune reactions. The participation of several and different cells characterize inflammation, they release many biologically active substances. Also, mast cells are involved in inflammation. Our results confirmed the central role of mast cells also in the pathophysiology of acquired chronic urticaria-angioedema, as the increase of tryptase serum levels showed. Moreover, in acquired chronic UAS, mast cell activation seems to be significantly greater than in allergic rhinitis. Our data showed that mast cells can be activated in a way different from non-IgE-mediated mechanisms. In our patients the trigger factor of acquired chronic UAS was GER. It must be considered that low molecular weight peptides, including neuropeptides, complement components, nerve growth factor, opioid peptides and histamine releasing cytokines could activate mast cells independently of FCεRI. These may well have an amplifying role (Greaves and O'Donnell, 1997).

In skin there is good evidence that the wheal and flare response may be mediated by an axon reflex involving retrograde release of sensory neuropeptides such as Substance P. This is localized to afferent nerves in skin, and intradermal injection of this peptide causes a flare (due to local vasodilatation) and also a wheal, which may be due to histamine release from mast cells, confirmed by a rise in plasma histamine in the draining vein (Heavy et al., 1985; Barnes, 1986). There is evidence that axon reflexes can also be involved in the gastrointestinal tract, as they occur in 'gastric asthma' (Mays, 1976; Bruno et al., 1999). Since airways are derived embryologically from the gut, and there are many similarities in innervation, it would not be surprising if axon reflexes also operated in airways, skin and mucosa.

The neuropeptides like substance P and neurokinin A, members of the tachikinins, both released by sensory nerves, own potent effects on inflammation that involve different patterns of cells including immune cells (Maggi et al., 1995). Moreover, mast cells have been shown to release nerve growth factor or brain-derived neurotrophic factor, which are potent regulators of neuropeptide synthesis (McGillis et al., 1987; Fischer and Hoffmann, 1996). The high number of immunocompetent cells in the vagus nerve and in the vagal sensory ganglia indicate further functional interactions, that so far are only poorly understood (Fischer and Kummer, 1998).

Finally the occurrence of *Helicobacter pylori* is also considered. *Helicobacter pylori* could act as an inducer or an amplifying agent of neurogenic inflammation. Recently *Helicobacter pylori* has been related to acquired C1-INH deficiency in a patient with angioedema (Farkas et al., 1999). Further studies are necessary to evaluate the role of neurogenic inflammation and *Helicobacter pylori* in acquired chronic UAS induced by GER.

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