

Association of chronic urticaria with thyroid autoimmunity and Raynaud phenomenon with anticentromere antibodies

To the Editor:

It has been demonstrated that patients with chronic urticaria (CU) frequently have positive results on intradermal injection of autologous serum.¹ At least in a proportion of patients, this phenomenon is associated with circulating and functionally active IgG autoantibodies specific for the high-affinity IgE receptor (Fc ϵ RI) present on mast cells and basophils¹⁻⁵ or for IgE.^{6,7} Further indirect evidence of the autoimmune origin of CU comes from its frequent association with thyroid autoimmune disorders.⁸⁻¹⁴ The prevalence of thyroid autoimmunity with or without functional disturbances of thyroid function (defined as either increased or decreased free thyroxine [FT4] levels, thyroid-stimulating hormone [TSH] levels, or both) in patients with CU ranges from 12% to 27%.⁸⁻¹⁴ We report an association with thyroid autoimmunity, Raynaud phenomenon, and anticentromere antibodies (ACAs) in a subset of patients with autoimmune CU.

Two hundred fifty-seven consecutive patients with CU (69 male and 188 female patients; age range, 13-81 years) defined as recurrence of hives with or without angioedema for more than 6 weeks seen at the allergy center of Bollate Hospital during the last 3 years were studied. Patients were thoroughly interviewed and carefully visited to ascertain symptoms, signs, or both of diseases other than CU. Five days after antihistamine therapy (cetirizine, loratadine, or fexofenadine in all cases) was stopped, patients underwent intradermal testing with 0.05 mL of fresh autologous serum (autologous serum skin test [ASST]) and with saline as a negative control. ASST was carried out and read as previously described.¹ Finally, a standard panel of laboratory measurements, including erythrocyte sedimentation rate, blood counts, electrophoresis results, complement fractions, fluorescent antinuclear antibodies (using Hep2 cells as substrate), rheumatoid factor test results, Waaler-Rose test results, anti-thyroglobulin and anti-peroxidase antibodies, and thyroid hormones (free tri-iodothyronine, FT4, and TSH) was carried out.

Proportions were compared by means of the 2-tailed χ^2 test with the Yates correction. Means were compared by means of the 2-tailed Student *t* test. Probability values of less than .05 were considered significant.

Relative risk (RR) for independent samples was calculated as follows¹⁵:

$$RR = ad/bc,$$

where values are determined as in Table I.

One hundred sixty-seven (65%) patients had positive ASST results. Sixty-six (26%) of 257 patients were

TABLE I. Calculation of relative risk

	Patients	Control subjects
No. with risk factor	a	b
No. without risk factor	c	d
Total	a + c	b + d

found to have circulating thyroid autoantibodies. Thyroid function was normal in 46 of these subjects, 16 showed a reduction of thyroid function (defined as decreased FT4, increased TSH, or both), and 4 showed an increased thyroid function (defined as increased FT4, decreased TSH, or both).

Six (2%) of 257 patients (0 male and 6 female patients; age range, 38-64 years; mean age, 54.3 years) had unequivocal Raynaud phenomenon. All 6 (100%) had strongly positive ASST results. One of them had mixed connective tissue disease, with typical clinical and serologic features. Of the 5 remaining subjects (Table II), one showed a fine speckled pattern on immunofluorescence (titer 1:160) in the absence of other serologic abnormalities, and serum from another subject did not have antinuclear antibodies. Finally, 3 patients had positive ACA results. No patients with positive ACA results had clinical features of scleroderma (eg, sclerodactily, telangiectasias, or scleroderma skin lesions) or reported dysphagia; however, capillaroscopic examination showed a borderline aspect in all patients. All 3 (100%) patients with positive ACA results showed circulating thyroid antibodies ($P < .05$ in comparison with the prevalence of thyroid antibodies in the general population with CU). An *in vitro* histamine release assay was carried out by using basophils from normal donors as substrate, as previously described,¹⁶ before and after stripping of membrane-bound IgE with 10 mmol/L lactic acid (pH 3.9) for 3.5 minutes at room temperature.¹⁷ Basophil stimulation with an optimal dose of goat polyclonal anti-IgE (10 μ g/mL) and sera from patients with CU was carried out as previously described,¹⁶ and histamine concentration in the cell supernatant was measured by using an automated fluorometric method. Results were expressed as the net percentage of histamine release over total histamine content. A 5% net histamine release was used as the cut-off point.

Serum from only 1 in 3 patients with CU and positive ACA results induced a weak histamine release (5.5%) from untreated basophils; in contrast, after basophil treatment with lactic acid, sera from 2 of 2 patients with CU with ACA results induced significant histamine release (23.1% and 46.2%, respectively; Table II). Sera from the other 2 patients with CU with negative ACA results and Raynaud phenomenon induced a significant histamine release only after stripping of membrane-bound IgE (27.9% and 36.5%, respectively). In contrast, anti-IgE-induced histamine release was greatly reduced by lactic acid treatment (from 33% to 13%). These

TABLE II. Clinical and serologic features of patients with Raynaud phenomenon and CU

Patients	1	2	3	4	5
Sex	F	F	F	F	F
Age (y)	60	64	38	59	54
Urticaria duration (mo)	120	12	10	2	5
ASST	3+	4+	3+	4+	4+
RP duration (mo)	160	48	36	12	5
Capillaroscopy	ND	Positive	Positive	ND	Positive
Antinuclear antibodies	ACA	ACA	Fine Sp >1/160	Negative	ACA
Thyroid autoantibodies	Positive	Positive	Negative	Positive	Positive
Thyroid function (DD)	Normal	Normal	Normal	Low (36 mo)	Low (8 mo)
HR (%)	1.6	5.5	4.7	3.9	4.7
HR after IgE stripping (%)	ND	23.1	36.5	27.9	46.2

RP, Raynaud phenomenon; ND, not done; HR, histamine release; Sp, speckled; DD, disease duration.

results indicate that the sera from patients with Raynaud phenomenon tested contained functionally active anti-Fc γ RI autoantibodies.

Raynaud phenomenon precedes other symptoms of systemic sclerosis in most cases. ACAs are usually detected in the calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, telangiectasias (CREST) variant of limited systemic sclerosis.¹⁸ It is generally accepted that such autoantibodies are predictive of the CREST syndrome¹⁹ and might precede other symptoms of scleroderma by years.¹⁸ Notably, none of our patients with Raynaud phenomenon had clinical symptoms of scleroderma, although one patient had Raynaud phenomenon for as long as 15 years. The estimated prevalence of systemic sclerosis is 67 to 267 cases per 100,000 persons²⁰; however, because only 25% of patients with systemic sclerosis have a CREST variant,²¹ the estimated prevalence of ACAs in the general population should be 17 to 67 cases per 100,000 persons (approximately 0.035%). This means that in our population with CU, the prevalence of ACAs was approximately 60 times higher than the expected prevalence ($P < .0001$). The relative risk of having ACAs in the presence of CU was approximately 40. Furthermore, an association between ACA antibodies and anti-Fc γ RI antibodies might be postulated.

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