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Plasma levels of metalloproteinase-9 are elevated in patients with chronic autoimmune urticaria

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SIR, It has recently been suggested that chronic idiopathic urticaria (CIU) has an autoimmune aetiology in a major subpopulation of patients, who show a positive autologous serum skin test (ASST) and *in vitro* histamine release test (HRT).¹ This type of chronic urticaria is conventionally designated as chronic autoimmune urticaria (CAU).

Matrix metalloproteinases (MMPs) are essential both for physiological and for pathological processes, including arthritis, cardiovascular diseases and cancer.² MMP-2 has been implicated in the pathogenesis of some skin conditions, such as psoriasis and contact dermatitis.³ MMP-9 is augmented in several inflammatory and autoimmune diseases,² where it may play a pathogenetic role. In particular, MMP-9 degrades collagen type IV, enabling immune cell invasion of injured tissue.² Moreover, MMP-9 mediates terminal cleavage of interleukin (IL)-8, thus potentiating IL-8-induced neutrophil activation.⁴ This suggests that MMP-9 can be involved as a mediator of the recruitment of neutrophils, which represent the main infiltrating cell population in urticarial lesions.⁵ It is also possible that the MMP-9 cleavage function may produce a variety of neo-epitopes that induce an immune response and thus participate in the pathogenesis of the disease.² The action of MMPs is controlled by their natural inhibitors, known as tissue inhibitors of metalloproteinases (TIMPs).⁶ To understand the possible involvement of the MMP system in the pathogenesis of urticaria, serum levels of MMP-2, MMP-9 and their inhibitors TIMP-1 and TIMP-2 were investigated in patients with CAU and CIU and in healthy controls.

Study subjects included 15 patients with urticaria who showed positivity to ASST and HRT, performed as previously described,⁷ and were classified as having CAU (12 women and three men, age range 19–58 years), and 15 patients with urticaria with negativity to ASST and HRT who were classified as having CIU (10 women and five men, age range 27–64 years). Both groups showed a severe form of the disease, with similar mean $\pm$ SD Breneman score⁸ (patients with CAU, 12.83 ± 0.41 ; patients with CIU, 12.33 ± 1.47). Patients with clinical evidence of urticarial vasculitis or physical urticaria were excluded. No patient had been taking corticosteroids or immunosuppressant drugs for at least 4 weeks. As controls, 10 age- and sex-matched healthy subjects were included in the study. The present trial was approved by the medical ethical committee of our hospital and was conducted according to the Declaration of Helsinki; all patients provided written informed consent.

Blood samples were collected from patients and controls and centrifuged for 20 min at 10 000 *g* (5417R microcentrifuge; Eppendorf, Hamburg, Germany). Then, solid-phase enzyme-linked immunosorbent assay kits were used to determine serum levels of MMP-2, MMP-9, TIMP-1 and TIMP-2 (R&D Systems, Minneapolis, MN, U.S.A.), according to the manufacturer's instructions. Samples and standards were analysed in duplicate and only coefficients of variation < 15% were accepted. Statistical analysis was performed using the Wilcoxon rank sum test. Differences were considered as statistically significant when $P < 0.05$.

Plasma levels of MMP-2 were similar in both groups of urticarial patients and in controls (Table 1). TIMP-1 levels were similar in CAU, CIU and controls, as were TIMP-2 levels. In contrast, MMP-9 was found to be significantly higher in patients with CAU than in those with CIU and in healthy controls, while no differences were found between patients with CIU and healthy controls (Table 1). Interestingly, all

Table 1 Matrix metalloproteinase (MMP)-2, MMP-9, tissue inhibitor of metalloproteinases (TIMP)-1 and TIMP-2 concentrations (mean $\pm$ SD, ng mL⁻¹) in chronic autoimmune urticaria (CAU), chronic idiopathic urticaria (CIU) and healthy controls

	CAU	CIU	Healthy controls	p1	p2	p3
MMP-2	103.88 $\pm$ 15.42	109.03 $\pm$ 23.05	109.61 $\pm$ 19.39	NS	NS	NS
MMP-9	284.33 $\pm$ 53.09	108.27 $\pm$ 49.85	100.2 $\pm$ 34.09	0.001	0.0007	NS
TIMP-1	191.03 $\pm$ 31.37	174.84 $\pm$ 38.23	176.25 $\pm$ 41.02	NS	NS	NS
TIMP-2	123.33 $\pm$ 24.99	132.00 $\pm$ 38.95	96.25 $\pm$ 11.29	NS	NS	NS

p1, CAU vs. CIU; p2, CAU vs. healthy controls; p3, CIU vs. healthy controls; NS, not significant.

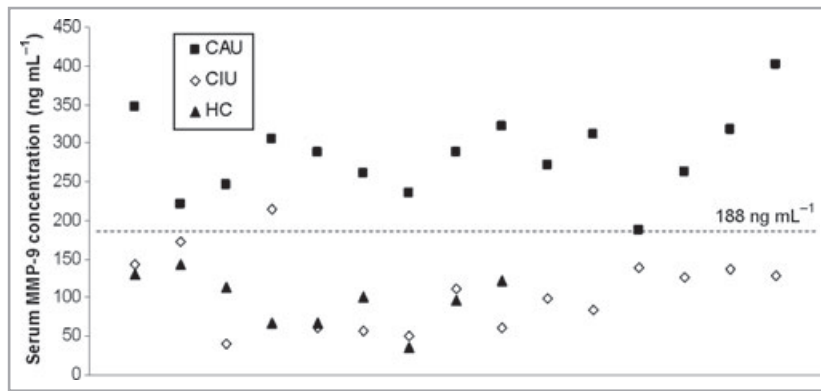


Fig 1. Matrix metalloproteinase (MMP)-9 values in patients with chronic autoimmune urticaria (CAU), chronic idiopathic urticaria (CIU) and in healthy controls (HC). Interestingly, all the patients with CAU showed MMP-9 levels higher than 188 ng mL⁻¹, while all the patients with CIU but one (215 ng mL⁻¹) and all the healthy controls had MMP-9 values lower than this cut-off level.

the patients with CAU showed MMP-9 levels higher than 188 ng mL⁻¹ (Fig. 1).

CAU represents about a third of all the forms of CIU, and its pathogenesis involves both autoantibodies and infiltrating inflammatory cells. MMPs play a crucial role in the transmigration of inflammatory cells, and their serological levels are augmented in several inflammatory diseases,² while their inhibitors, namely TIMPs, often show lower concentrations in pathological conditions.⁹ Our data showed that serum levels of MMP-2 as well as TIMP-1 and TIMP-2 were similar both in patients with CAU and CIU and in healthy controls, suggesting that such molecules may not play a central role in the pathogenesis of urticaria.

By contrast, interesting results were found regarding MMP-9. MMP-9 has been previously investigated in patients with urticaria only once, without distinction between CAU and CIU.¹⁰ The authors found higher MMP-9 levels in patients with CIU than in controls and a significant correlation between MMP-9 and severity of urticaria.¹⁰ Our data showed that MMP-9 concentrations were higher in patients with CAU than with CIU, independently of severity of urticaria. Such findings suggest that MMP-9, probably secreted by infiltrating cells, is related to the autoimmune form of urticaria, while it is not involved in the pathogenesis of CIU. Finally, we found MMP-9 concentrations above the level of 188 ng mL⁻¹ in all the patients with CAU, suggesting that MMP-9 might be used as a diagnostic marker for CAU.

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Conflicts of interest: none declared.