

Sex differences in the pathogenesis of chronic urticaria

To the Editor:

Chronic urticaria (CU) is characterized by the recurrence of hives with or without angioedema for more than 6 weeks.^{1,2} Recent studies have shown that CU is often an autoimmune disorder characterized by circulating IgG antibodies specific for the high-affinity IgE receptor (FcεRI) present on mast cells and basophils¹⁻⁵ or for IgE.^{6,7} The frequent association between CU and thyroid autoimmunity⁸⁻¹³ along with its prevalence in middle-aged women^{14,15} represent further indirect evidence of a possible autoimmune origin of this skin disease. This study looked for possible sex differences in the pathogenesis of CU.

Two hundred fifty-seven consecutive adult patients (69 men and 188 women) given a diagnosis of CU at this allergy center during the last 3 years were studied. CU was diagnosed on the basis of the recurrence of hives with or without angioedema for more than 6 weeks. Five days after antihistamine therapy (cetirizine, loratadine, or fexofenadine in all cases) was stopped, an intradermal test with 0.05 mL of fresh autologous serum (autologous serum skin test [ASST]) and with saline as a negative control was carried out. ASST was performed and read at 30 minutes, according to established methods.⁴ A skin prick test with 10 mg/mL histamine was carried out to exclude any residual effect of antihistaminic drugs. Patients having a wheal with a diameter at least 1.5 mm larger than that elicited by a control saline solution were considered as having significant autoreactivity.¹⁶ Moreover, circulating thyroid autoantibodies were sought, and thyroid function (T4 and thyroid-stimulating hormone) was assessed in all subjects. Patients were considered to have a thyroid autoimmune disease in the presence of either thyroglobulin or peroxidase antibodies; thyroid dysfunction was diagnosed in the presence of either increased or decreased thyroid-stimulating hormone or T4. Proportions were compared by using the χ^2 test with the Yates correction; *P* values of less than .05 were considered statistically significant.

Altogether, 167 (65%) of 257 patients had positive ASST results, but the prevalence of a positive ASST result was significantly different in male and female patients (24/69 [35%] vs 143/188 [76%], respectively; *P* < .001). Thyroid autoantibodies were detected in 66 (26%) of 257 patients, but patients with positive or negative ASST results showed a significant difference in the prevalence of such autoantibodies (60/167 [36%] vs 6/90 [7%], respectively; *P* < .001). Male and female patients with positive ASST results showed similar prevalences of thyroid autoantibodies (8/24 [33%] vs 52/143 [36%], respectively; *P* = not significant). Six (75%) of 8 male patients with positive thyroid antibody results had normal thyroid function, with the remaining 2 (25%) having increased function; among 52 female patients with thyroid autoim-

munity, thyroid function was normal in 37 (71%) patients, increased in 1, and reduced in 14 (27%).

The CU population studied here was similar to CU populations examined in other studies in several respects. Most patients were women, as previously observed.^{14,15} ASST results were positive in a proportion (65%) similar to that found in other studies,^{4,17-19} and the overall prevalence of thyroid autoimmunity (26%) and thyroid dysfunction (15%) were nearly identical to that reported by other authors.^{13,20} However, interestingly, ASST results were much more frequently positive in female patients than in male patients; notably, a strongly positive ASST result has been associated with the presence of circulating autoantibodies to FcεRI or IgE.¹⁶ Moreover, thyroid autoimmunity was strictly associated with autoreactivity on ASST results both in female and male patients, a finding that indirectly confirms that patients with positive ASST results have an autoimmune disorder. This study was carried out on a large number of patients with CU, and this should have reduced the risk of biased results. The findings of this study suggest that CU is probably autoimmune in the majority (about three fourths) of female patients. In contrast, most male patients (about two thirds) with CU appear to have an idiopathic disease.

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Structural similarity between the bee venom peptides and the immunodominant human myelin basic proteins: Role for pathogenesis of acute disseminated encephalomyelitis

To the Editor:

Acute disseminated encephalomyelitis (ADEM) or other related acute encephalitis-myelitis has been reported to develop after Hymenoptera sting.¹ There is, however, no evidence demonstrating how Hymenoptera venom peptides mediate an inflammatory demyelinating disorder of the central nervous system (CNS). A recent study identified T_H2 cells reactive to myelin basic protein (MBP) in peripheral blood of patients with ADEM.² Although these cells are observed only during the recovery phase of the disease, suggesting that they are not necessarily pathogenic themselves, they might play other roles in the pathogenesis of ADEM, such as regulation rather than induction of the disease. One possible mechanism of induction of ADEM is a molecular mimicry between the antigens of Hymenoptera venom peptides and the MBP of the human CNS.

Bee venom is a complex mixture of enzymes and peptides that are more well defined than those of wasp venom. Bee venom peptides are composed of many low-molecular-weight peptides. Of these peptides, melittin, apamin, and mast cell degradation peptide 401 (MCD peptide 401) are the major substances, and their amino acid sequences are known, including that of tertiapin, a minor venom peptide. Activation by bacterial or viral superantigens that trigger T cells bearing a particular T-cell receptor (TCR) V β segment and activation by bacterial or viral peptides that have sufficient sequence similarity with an immunodominant self-peptide are the important mechanisms accounting for the activation and clonal expansion of autoreactive T cells in the periphery.³ Two recent studies showed that almost one third of patients initially given a diagnosis of ADEM will

progress to multiple sclerosis (MS) on long-term follow-up.⁴ It is conceivable that the underlying pathogenic molecular mechanisms of relapsing-remitting MS and the recurrent symptoms occurring in some patients with ADEM are similar; this is referred to as epitope spreading. There is no evidence regarding the pathogenic immunodominant MBP peptide in ADEM or whether this peptide is the same as that of MS. Two regions of human MBP, residues 84 to 102 and 143 to 168, were found to be immunodominant in MS.⁵⁻⁸ HLA-DR2b (DRA, DRB1*1501) was found to be the restriction element of MBP84-102 peptide-specific T-cell clones, and structural characterization of the MBP85-99 peptide identified residues critical for MHC class II binding and for TCR recognition.⁷ Hydrophobic residues (Val-89 and Phe-92) in the MBP88-93 peptide were identified as anchor residues for HLA-DR2b binding, whereas His-90, Phe-91, and Lys-93 were the primary TCR contact residues.⁷ In the present report the MHC class II and TCR contact residues of the immunodominant MBP88-93 peptide were subjected to analysis to define the set of amino acids permitted at each critical position. The structural criteria were then used to search a protein sequence database of melittin, apamin, MCD peptide 401, and tertiapin of a honeybee (*Apis mellifera*), and the structural similarity between these venom peptides and the immunodominant MBP88-93 peptide was analyzed to support the hypothesis of molecular mimicry and their potential role for induction of autoimmunity.

SWISS-PROT release 40.20 protein database was searched for 4 *A. mellifera* venom peptides: 26-amino-acid melittin (accession no. P01503), 18-amino-acid apamin (accession no. P01500), 22-amino-acid MCD peptide 401 (accession no. P01499), and 21-amino-acid tertiapin (accession no. P56587). T-Coffee (Tree-based Consistency Objective Function for alignment Evaluation, version 1.40) was used to investigate global sequence similarity between the 15-amino-acid immunodominant human MBP residues 85 to 99 and residues of *A. mellifera* melittin, apamin, MCD peptide 401, and tertiapin.

For structural similarity analysis, on the basis of the knowledge of properties of amino acid side chains, including hydrophobic or hydrophilic character, polar or nonpolar nature, and presence or absence of ionizable groups, the immunodominant MBP residues 88 to 93 (VVHFFK), which bound with high affinity to the HLA-DR2b molecule, with 2 hydrophobic residues serving as the primary anchors (Val-89 and Phe-92), and which had primary TCR contact residues at His-90, Phe-91, and Lys-93,^{7,8} was used as the structural motif to identify, by means of the local alignment program (SIM) in combination with manual adjustment, *A. mellifera* peptides that structurally fit the MBP88-93 peptide. For the MHC anchor residues, aliphatic amino acids were allowed at the first residue (Val-89), and aliphatic and aromatic residues were permitted at the second residue (Phe-92). For the TCR contact residues, Phe-91 could be substituted with some aromatic or aliphatic amino acids, Lys-93 could only be substituted with arginine, and several structurally related amino acids were per-