

Influence of immediate hypersensitivity skin reactions on delayed reactions in patients with chronic fatigue syndrome

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It has been suggested that a false-negative delayed hypersensitivity skin reaction (DHR) to *Trichophyton quinckeanum* may result from an immediate hypersensitivity skin reaction (IHR) either by "washing" the antigen out of the skin or by "neutralization" of the antigen by the ingress of serum antibodies.¹ Other studies with tetanus antigen have not shown this effect.² In chronic fatigue syndrome (CFS), a variety of immunologic abnormalities have been reported including a high incidence of atopy³ and hypoergia or anergy.⁴ If an interaction exists between IHR and DHR, this could be important in the interpretation of hypoergia and anergy.

METHODS

Patients

Thirty patients with CFS, 18 years of age or older, were recruited from the registry of the Minnesota Regional CFS Research Program established at Hennepin County Medical Center, Minneapolis, Minn., in 1988.⁵ A diagnosis of CFS was established after thorough medical, psychometric, and psychiatric evaluations did not establish another explanation for chronic fatigue and after the other criteria for a case definition of CFS were met.⁶

Skin testing

All patients had not received antihistamines, tricyclic antidepressants, and corticosteroids for at least 30 days before testing.

DHR testing was done with five standardized antigens: tetanus (neat; Sclavo Labs, Wayne, N.J.), mumps (neat; Connaught, Swiftwater, Pa.), *Candida albicans*

Abbreviations used

CFS:	Chronic fatigue syndrome
DHR:	Delayed hypersensitivity skin reaction
IHR:	Immediate hypersensitivity skin reaction

(1:100; Miles Labs, West Haven, Conn.), *Trichophyton mentagrophytes* (1:1000, Greer Labs, Lenoir, N.C.), and tuberculin (5 tuberculin units; Connaught, Swiftwater, Pa.). Phosphate-buffered saline was used as a negative control. Intradermal tests were done by injecting 0.1 ml through a no. 27 tuberculin syringe. IHRs were read at 15 minutes. The wheal and erythema were outlined with a fine-tip pen. The longest diameters connecting the inner margins of the pen outlines were measured, and at the midpoint of each line, a perpendicular diameter (orthogonal diameter) was drawn. Results of IHR tests were considered positive if the net mean wheal or erythema diameter (mean wheal or erythema diameter = largest + midpoint orthogonal diameter ÷ 2) was 3 or more mm larger than that of the phosphate-buffered saline control. Intradermal tests were read at 48 hours, and results were considered positive if the net mean induration diameter (mean induration diameters ÷ 2 was ≥5 mm).

Statistical methods

A Student's *t* test was used to compare the overall skin reactions between the two groups.

RESULTS

Demographics

The demographic features of the 30 study participants showed that 23 of 30 (77%) were women. The 30 subjects ranged in age from 19 to 74 years (mean age, 36.2 years).

Delayed hypersensitivity

All patients had a positive delayed skin test response to at least one antigen. There was a mean of 2.3 positive skin test responses per patient (range, 1 to 4). The mean induration diameter was 11.7 mm. The percent positive for each antigen is shown in Table I.

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TABLE I. The effect of immediate reactivity on the mean 48-hour induration in 30 patients with CFS

	48-hr induration (% positive)	Negative immediate reaction			Positive immediate reaction		
		No.	Induration (mm)		No.	Induration (mm)	
			Mean	SD		Mean	SD
<i>C. albicans</i>	37	11	9.2	2.2	0	—	—
<i>T. mentagrophytes</i>	10	3	17.7	4.3	1	—	—
Mumps	83	12	9.1	4.3	11	8.1	2.3
Tuberculin	3	1	—	—	0	—	—
Tetanus	97	20	13.2	3.6	9	12.6	4.8
Totals*	100	47	11.5	4.2	21	11.8	7.5

* $p = 0.82$ ($t = 0.23$).

Immediate hypersensitivity

Of the 68 positive delayed reactions, 31% were preceded by immediate reactions to one of the five antigens: *C. albicans*, 0 of 11 (0%); *T. mentagrophytes*, 1 of 4 (25%); mumps, 11 of 23 (48%); tuberculin, 0 of 1 (0%); and tetanus toxoid, 9 of 29 (31%). There were 11 patients who had immediate reactions without delayed reactions: *C. albicans*, 5 of 30 (17%); *T. mentagrophytes*, 5 of 30 (17%); mumps, 12 of 30 (40%); tuberculin, 0 of 30 (0%); and tetanus, 9 of 30 (30%). No significant association was observed between the IHR skin test findings and the DHR skin test results ($p = 0.82$, $t = 0.23$) (Table I).

DISCUSSION

The results of our DHR tests have been reported.³ The induration measured at 48 hours in DHR appears to be due in large part to the deposition of extracellular fibrin, which clots and gels after cross-linking. The source of the fibrin appears to be extravasated plasma fibrinogen from increased microvascular permeability at the site. The formed fibrin mesh, which is essential to development of induration, also contains inflammatory cells and extravasated plasma and fibronectin.⁷

Several studies have suggested that IHR could influence DHR. Marcussen⁸ showed that a passively transferred IHR blocked or reduced the DHR in patients who had had only a DHR to *Trichophyton* spp. Hunziker and Brun¹ reported that five atopic patients with chronic dermatophytosis who had no DHR to *Trichophyton quinckeanum* after a strong IHR experienced a strong DHR after trichophyton was injected into the wheal 20 minutes after the first injection.

Our observations of 31% of delayed tetanus reactions preceded by IHR and lack of association

between IHR and DHR are in agreement with those of Fairshter et al.² who used tetanus toxoid and reported an IHR in 45% of subjects tested and that the size of the DHR did not differ in those with a preceding IHR.

Studies of skin responses to *Trichophyton* spp. in patients suggest that, in some, an IHR precedes the 24-hour DHR.⁹ In addition to vascular permeability changes resulting from gap formation between endothelial cells, these gaps may induce the expression of adhesion molecules facilitating migration into the site of CD4⁺ T cells, which promote the DHR.⁷ Even though extravasation of fluid caused by increased vascular permeability occurs in IHR, our results suggest that either the extravascular fluid removes an insignificant amount of antigen, or if a significant amount is removed, that upregulation of the DHR, as a consequence of the extravasation compensates for the loss.

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Losartan-induced bronchospasm

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Losartan is the first angiotensin II type 1 (AT₁) receptor antagonist to become available for the treatment of hypertension. Because the mechanism of action of the AT₁ receptor antagonists does not involve the inhibition of angiotensin-converting enzyme (ACE), side effects induced by ACE inhibitors are not expected to occur with these agents. Adverse effects of ACE inhibition include cough¹ and (rarely) bronchospasm² and angioedema,¹ probably caused by the protussive and bronchoconstricting agents bradykinin and substance P, which are normally degraded by ACE and therefore accumulate when the enzyme is inhibited. However, two reported cases of losartan-induced angioedema³ suggest that the AT₁ receptor antagonists may not be entirely free of ACE inhibitor-related side effects.

We herein describe the development of upper airway discomfort and bronchospasm in three hospital pharmacists who inadvertently inhaled losartan in the course of preparing capsules containing the drug.

CASE REPORTS

Three of four pharmacists at our hospital pharmacy experienced acute onset of respiratory symptoms including throat discomfort, nasal irritation, chest tightness, and cough while preparing capsules containing losartan for use in a blinded, placebo-controlled study. The pharmacists' task included pulverizing, with mortar and pestle, 50 tablets, each containing 50 mg of losartan (Cozaar; Merck & Co., West Point, Pa.), into a fine

Abbreviations used

ACE: Angiotensin-converting enzyme
AT₁: Angiotensin II type 1

powder and subsequently transferring 50 mg of powder into capsules.

Symptoms were noted almost immediately on initiation of crushing of the tablets and persisted for several hours. All episodes occurred during the subjects' initial exposure to the drug. Each of the pharmacists who experienced symptoms had previously engaged in similar projects involving other medications without having any reaction. All three individuals reported histories of mild asthma but were free of symptoms and had not required any medication for treatment of respiratory symptoms in the previous 4 to 10 months.

Study methods

To objectively evaluate the effect of losartan exposure, we performed a double-blind, placebo-controlled, crossover study, for which subjects granted informed consent. On two separate days, each pharmacist underwent spirometry (performed by a blinded pulmonologist) before and after exposure to losartan or placebo. While blindfolded, subjects pulverized 50 losartan tablets (50 mg each) or placebo for exactly 5 minutes in a manner identical to that of their initial exposure. For the placebo studies, we used a combination of ranitidine hydrochloride and sertraline hydrochloride tablets, which were indistinguishable from the study drug to the blinded participants and which contained the two types of dye (D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake) present in the film coating of the losartan tablets.

On a separate day, allergy skin testing was performed on two of the subjects. A 50 mg losartan tablet was dissolved in 5 ml of sterile albumin saline solution with phenol (Bayer, Spokane, Wash.) to produce a 10 mg/ml solution, which was used to perform a percutaneous skin

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