

# Letters

## ASSESSMENT OF A RHINITIS QUESTIONNAIRE IN A SEASONAL ALLERGIC RHINITIS POPULATION

Chronic rhinitis (CR) is a common disorder encountered by primary care physicians that affects approximately 25% of the general population.<sup>1</sup> Rhinitis is a very heterogeneous group of disorders that have diverse pathophysiologic mechanisms.<sup>1</sup> The general public typically associates CR conditions with an allergic "IgE-mediated" response. However, it is well established that nonallergic rhinitis (NAR) and mixed (allergic and nonallergic) rhinitis subtypes are also common diagnoses.<sup>2</sup> An accurate diagnosis of a rhinitis subtype is essential for making correct recommendations for treatment and preventing complications such as sinusitis and otitis media.<sup>2</sup> Previously, we developed a questionnaire survey designed to help physicians recognize differences between AR and NAR subtypes.<sup>3,4</sup> This study found that patients with symptom onset later in life (>35 years old), no family history of allergies, no seasonality or cat-induced symptoms but symptoms induced by perfumes and fragrances had more than 95% likelihood of having a physician diagnosis of NAR.<sup>4</sup> The presence of some but not all of these characteristics would indicate a nonallergic component. The results of this questionnaire study emphasize the complexity of diagnosing CR and the importance of referring these patients earlier to an allergist experienced in the treatment of AR and NAR. The purpose of this study was to use a modified version of this questionnaire to evaluate how it performed when administered to a larger, "well-phenotyped," seasonal AR (SAR) study population. Another objective was to determine whether therapeutic responses to different medications could be useful as diagnostic criteria for AR or NAR subtypes.

A modified version of the rhinitis questionnaire was distributed to 136 individuals during visit 1 of a multicenter mountain cedar SAR study.<sup>4</sup> The inclusion criteria for this study were a history of SAR for 2 years or more and a positive skin prick test reaction to Texas mountain cedar pollen that correlated with symptoms in the past year. Statistical analyses included factor analysis, hypothesis testing, and

univariate regression analyses.<sup>5</sup> Questionnaire responses were analyzed for "construct validity" using factor analysis to determine whether the questionnaire measured what it intended to measure and for internal consistency using Cronbach  $\alpha$  to determine whether responses were reliable.<sup>3,4</sup>

The population's median age was 39 years (range, 18–73 years), and median age at symptom onset was 19 years (range, 1–57 years). In the 136 patients, sneezing was reported in 127 (93%), stuffy nose in 130 (96%), runny nose in 125 (92%), postnasal drainage in 123 (90%), itchy eyes in 127 (93%), sinus pressure in 92 (68%); and ear plugging in 80 (59%). Symptoms were triggered in 45% (61/136) of patients by cats; 29% (39/136) by dogs; 21% (29/136) by furry pets; 85% (116/136) while outdoors during the spring, summer, or fall; 54% (74/136) by cigarette smoke; 72% (98/136) by weather changes; 49% (67/136) by perfumes; 35% (47/136) by incense, and 40% (54/136) by cleaning products. As previously demonstrated, factor analysis indicated that symptoms to cat, dog, and furry pets and to perfumes, incense, and cleaning products correlated, and the Cronbach  $\alpha$  for each factor was .78 and .7, respectively ( $\alpha \geq .7$  is reliable).<sup>4</sup>

Before study enrollment, 84% of patients had previously tried oral antihistamines, 67% nasal corticosteroid sprays, and 35% intranasal antihistamines (azelastine hydrochloride) (Astelin; MedPointe Pharmaceuticals, Somerset, New Jersey). There was no statistically significant difference in the satisfactory rate ([moderate + big effect patients]/total of treated patients) between these medications: 76% indicated that oral antihistamines had a moderate to big effect, 85% that nasal corticosteroids had a moderate to big effect, and 83% that intranasal antihistamines (Astelin) had a moderate to big effect ( $P = .2$ ). Patients exhibiting big effects in response to intranasal antihistamines (Astelin), indicating extreme satisfaction with this medication, were more likely to manifest symptoms induced by perennial allergens (furry pets, cats, and dogs) and nonallergic irritant triggers (Table 1).

In summary, many patients enrolled in this SAR study also experienced irritant-induced symptoms in response to perfumes, cleaning products, incense, and smoke, suggesting that they met the diagnostic criteria for mixed rhinitis.<sup>2,3</sup> These results indicate that the current criteria used to define the SAR phenotype may be inadequate. Incomplete characterization of patients with SAR

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Table 1. Percentages (No. of Positive Responses) of Patients With Symptoms Induced by Allergic and Nonallergic Triggers That Exhibited a "Big Effect" Indicating Extreme Satisfaction With Their Medication

| Drug     | Cat        | Dog        | Furry pets | Outdoor    | Weather change | Tobacco smoke | Perfume    | Incense    | Cleaning agents |
|----------|------------|------------|------------|------------|----------------|---------------|------------|------------|-----------------|
| AH       | 52 (15/29) | 41 (12/29) | 35 (10/29) | 69 (20/29) | 69 (20/29)     | 52 (15/29)    | 45 (13/29) | 35 (10/29) | 45 (13/29)      |
| Nasal CS | 44 (11/25) | 28 (7/25)  | 28 (7/25)  | 80 (20/25) | 56 (14/25)     | 52 (13/25)    | 44 (11/25) | 40 (10/25) | 48 (10/25)      |
| Astelin  | 83 (5/6)   | 67 (4/6)   | 67 (4/6)   | 83 (5/6)   | 100 (6/6)      | 67 (4/6)      | 83 (5/6)   | 67 (4/6)   | 100 (6/6)       |

Abbreviations: AH, H<sub>1</sub>-antagonists; CS, corticosteroids

could explain the large number of partial responders or nonresponders to medication and the requirement for large study population enrollment to demonstrate drug efficacy in clinical trials. These preliminary data warrant further investigation to determine whether response to medication may be a useful clinical criterion for distinguishing between CR subtypes. Finally, and probably most important, these findings support the need to establish improved consensus definitions of CR subtypes based on subjective and objective criteria to improve the clinical diagnosis and treatment of these disorders and our ability to better understand the underlying mechanism(s) of NAR phenotypes.

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## IMMEDIATE-TYPE HYPERSENSITIVITY REACTION TO LEVOTHYROXINE AND DESENSITIZATION

Although levothyroxine substitutive treatment is widely used, there are few reported cases of levothyroxine allergy.<sup>1–3</sup> Hypothyroidism prevalence is approximately 4:1,000 in females and 1:1,000 in males, and up to 10% of the population may have subclinical hypothyroidism.<sup>4,5</sup>

We describe a 72-year-old woman with an adverse reaction to levothyroxine. She was taking enalapril-hydrochlorothia-

zide for high blood pressure and zuclopenthixol for schizophrenia. She had been diagnosed as having hypothyroidism after radioiodine therapy for Graves-Basedow disease. She had been prescribed levothyroxine (Levothroid; Forest Pharmaceuticals Inc, St Louis, Missouri), 50 µg/d, and initially tolerated it without complications.

However, after several weeks, she reported generalized urticaria within 30 minutes of taking each dose. Symptoms resolved after discontinuing levothyroxine use. Her physician prescribed other brands of levothyroxine (Sanofi Aventis, Barcelona, Spain), Dexnon (Kern Pharma, S.L., Terrassa, Barcelona, Spain), and Eutirox (Merck Farm Q, Mollet del Vallès, Barcelona, Spain), and the patient reported the same urticarial reaction with both. The treatment was stopped under close analytical control of thyroid function. The patient was referred to us after 3 months without treatment owing to an abnormal elevation of thyrotropin, which required reinitiating treatment.

Results of a complete allergologic study, including skin prick tests with common inhalants and foodstuffs, were negative. Physical examination findings were normal. Blood count and biochemical variables were within the respective reference ranges, except thyrotropin (14.9 mU/L; reference range, <4 mU/L).

According to a published protocol,<sup>2</sup> liothyronine extract was prepared by crushing the tablet (25 µg) and mixing with 1 mL of 0.9% phosphate-buffered saline for 2 hours. The solution was passed through a 0.2-µm-pore filter. Levothyroxine solution for intravenous use was diluted to 50 µg/mL in phosphate-buffered saline.

Results of prick tests with liothyronine, 25 µg/mL, and levothyroxine, 50 µg/mL, were negative. Results of intradermal testing with 0.02 mL of the extracts in concentrations of 1:100,000, 1:10,000, 1:1,000, 1:100, and 1:10 were negative for liothyronine but positive for levothyroxine at 1:100 (6-mm wheal with negative saline control). Five individuals (3 atopic and 2 nonatopic) unexposed to exogenous levothyroxine were used as controls. Their skin test results were negative. Challenge with levothyroxine was not performed because the patient and her family refused.

In Spain, there are no commercially available alternatives to levothyroxine for hypothyroidism. Therefore, the patient was admitted to the hospital, and intravenous desensitization with levothyroxine was performed under strict clinical monitoring. The dosage was designed by adapting previously described protocols.<sup>2,6,7</sup> The procedure was started at an intravenous dose of 0.0002 µg. Every 15 minutes the dose was increased until a total dose of 50 µg was reached after 3 hours, without any adverse reactions (Table 1). The following day the patient received 50 µg of levothyroxine without complications. She currently tolerates 50 µg/d, with normalization of thyroid function (thyrotropin level, 2.3 mU/L).

It is unusual that biological substances induce allergic reactions when given exogenously. Nevertheless, insulin, heparin, and others have been reported to produce immediate or delayed hypersensitivity.<sup>7,8</sup> In these cases, there are 2 main

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Table 1. Desensitization Dosing With Levothyroxine

| Dose, $\mu\text{g}$ | Time       |
|---------------------|------------|
| 0.0002              | 0 min      |
| 0.0004              | 15 min     |
| 0.004               | 30 min     |
| 0.02                | 45 min     |
| 0.04                | 1 h        |
| 0.1                 | 1 h 15 min |
| 0.2                 | 1 h 30 min |
| 4                   | 1 h 45 min |
| 1                   | 2 h        |
| 5                   | 2 h 15 min |
| 15                  | 2 h 30 min |
| 30                  | 2 h 45 min |
| 50                  | 3 h        |

therapeutic options: to find a valid alternative treatment or to induce tolerance by means of desensitization.

Cases of possible levothyroxine allergy reported previously have not proved causality clearly. A case of fever, eosinophilia, and liver dysfunction in response to replacement doses of levothyroxine was reported by Shibata et al.<sup>1</sup> They describe a positive lymphocyte proliferation test result, but neither skin tests nor specific in vitro IgE levels were evaluated.<sup>1</sup> A slow-increasing dosing program that enabled continuation of therapy was applied. Nugent et al<sup>2</sup> reported a suspected anaphylactic reaction to levothyroxine, but results of skin testing and in vitro IgE determination to levothyroxine and liothyronine were negative, and the patient was finally diagnosed as having vocal cord dysfunction. Thus, to our knowledge, there are no previous reports of positive skin test results in patients with levothyroxine-induced allergic reactions.

Next we would have conducted an open drug challenge with levothyroxine because the allergic reaction was not severe. Nevertheless, the psychiatric disturbance of the patient precluded a prolonged stay in the hospital because she became progressively more agitated out of her usual surroundings. When consulted, the family refused a challenge test and accepted desensitization as the only possible therapeutic measure.

Because desensitization has been used successfully in other hormone allergies, such as insulin allergy,<sup>7</sup> we considered

this as a plausible option. The dosing protocol was adapted from Nugent et al.<sup>2</sup> The final dose was 50  $\mu\text{g}$ , following the endocrinologist's advice. If the patient would need an increase in this dose, she would be admitted to the hospital to monitor any possible allergic reactions.

We report the first case of levothyroxine allergy confirmed by positive immediate intradermal test results. Furthermore, we also report success in using a levothyroxine desensitization protocol.

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## Errata

In the January 2008 supplement article by Anthony J. Castaldo (Castaldo AJ. Hereditary angioedema: a current state-of-the-art review, IX: the US Hereditary Angioedema Association: a message from the president. *Ann Allergy Asthma Immunol*. 2008;100(Suppl 2):S47–S48), there is an incorrect statement in the opening paragraph. The correct statement should read “17- $\alpha$ -Alkylated **anabolic** steroids are useful for HAE prophylaxis in certain adults, but data from an unpublished survey conducted by the US Hereditary Angioedema Association (HAEA) revealed that many patients continue to experience periodic acute attacks notwithstanding ongoing therapy.”

In the practice parameter “Allergy Diagnostic Testing: An Updated Practice Parameter” (*Ann Allergy Asthma Immunol*. 2008;100(Suppl 3):S1–S148), David A. Khan, MD, Christopher C. Randolph, MD, and Sheldon L. Spector, MD, were omitted on the cover as Associate Editors.