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.[1–3] 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.[4,5]

We describe a 72-year-old woman with an adverse reaction to levothyroxine. She was taking enalapril-hydrochlorothiazide 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,[2] 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.[2,6,7] 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.[7,8] In these cases, there are 2 main

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Table 1. Desensitization Dosing With Levothyroxine

Dose, μg	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.[1] They describe a positive lymphocyte proliferation test result, but neither skin tests nor specific in vitro IgE levels were evaluated.[1] A slow-increasing dosing program that enabled continuation of therapy was applied. Nugent et al[2] 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,[7] we considered this as a plausible option. The dosing protocol was adapted from Nugent et al.[2] The final dose was 50 μg, 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-a-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.