Commentary

HYPOTHYROXINEMIA, HYPERTHYROTROPINEMIA, AND RADIOIODINE: PARTNERS IN CRIME AGAINST GRAVES ORBITOPATHY?

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Abbreviations:
GO = Graves orbitopathy; **rhTSH** = recombinant human thyroid-stimulating hormone; **TSH** = thyroid-stimulating hormone

Graves orbitopathy (GO) has a complex pathogenesis that is yet to be fully understood. Treatment can be difficult, and some patients require multiple therapies, including rehabilitative surgery; hence, the personal burden and societal costs are significant. GO usually consists of a single episode lasting 1 to 3 years, rather than recurrent exacerbations and remissions, as is the case for many other autoimmune diseases. This allows fewer opportunities to study precipitants. Nonetheless, risk factors for the development or worsening of GO have been identified, including radioiodine treatment for thyrotoxicosis and hypothyroidism. It is not uncommon for a patient with Graves disease treated with radioiodine for thyrotoxicosis to develop hypothyroidism within a few months of treatment, followed by new onset or exacerbation of GO. Usually, the GO is mild, and with restoration of euthyroidism, the eyes settle. This familiar scenario highlights three potential partners in crime, radioiodine per se, hypothyroxinemia, and hyperthyrotropinemia. Trying to tease out the relative contribution of each is a difficult but worthy task. The role of radioiodine has been studied extensively. In 2 large randomized controlled trials, radioiodine was associated with a risk of GO independently of hypothyroidism (1,2). The guilty role of radioiodine therefore is established. An association between hypothyroidism and risk of GO has been shown by observational studies (3), so the evidence for hypothyroidism being a risk factor for exacerbation of GO is highly suggestive. Assuming that hypothyroidism stands guilty as charged, what is the mechanism by which it influences GO unfavorably? Is it the effect of thyroid hormone deficiency on orbital tissues or the raised circulating thyroid-stimulating hormone (TSH) levels that is the culprit?

In this issue of *AACE Clinical Case Reports*, Rocchi and colleagues (4) describe 2 patients with active, moderate to severe GO of relatively recent onset who had a total thyroidectomy. Because of a diagnosis of thyroid cancer, they underwent thyroid hormone withdrawal in preparation for radioiodine ablation. Prior to radioiodine ablation and following a brief period of hypothyroidism, both patients developed dysthyroid optic neuropathy (DON).

The 2 cases reported by Rocchi and colleagues (4) are notable for several reasons:

1. Exacerbation of GO occurred within a few weeks of inducing hypothyroidism, before radioiodine ablation. The time course of the exacerbation of GO and its rapid onset are therefore highly suggestive of a causal relationship and lend support to the hypothesis that hypothyroidism may be detrimental to the course of GO.
2. The duration of hypothyroidism, albeit brief, was sufficient to trigger GO. Given that the connective tissue changes associated with hypothyroxinemia take time to develop, one may be allowed to speculate that hyperthyrotropinemia could have played a role.
3. The severity of the GO following thyroid hormone withdrawal was extreme, highlighting that on some rare occasions, even the briefest episodes of hypothyroidism may have devastating effects on the course of GO.

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Dissecting out the relative contributions of hypothyroxinemia from hyperthyrotropinemia is no easy task. As the authors discuss, the evidence is based on a few isolated case reports showing that exacerbation of GO can occur after recombinant human (rh)TSH and radioiodine administration while euthyroxinemia was maintained. In one case, rhTSH was not followed by radioiodine, yet GO deteriorated (5).

What can we learn from the observations by Rocchi and colleagues (4)? For patients who have significant GO and require radioiodine ablation for thyroid cancer, it would seem prudent to recommend detailed ophthalmologic assessment in order to determine the severity and activity of GO before treating them. The presence of active disease, motility disturbance, and heavy smoking are associated with a risk of DON, and such patients should be monitored carefully for deterioration of GO during thyroxine withdrawal. Whether rhTSH is a less toxic alternative than thyroxine withdrawal for the eyes is unclear, though there may be other reasons why it is preferable. A short course of oral steroids can prevent deterioration of the eyes following radioiodine for thyrotoxicosis (1,6), and the same protocol should be used for patients with active GO undergoing radioiodine ablation for thyroid cancer. It is worth emphasizing that the risk of exacerbating GO after radioiodine (and possibly other insults, such as hypothyroidism) is probably time dependent and declines considerably when the patient has entered the inactive phase of GO, so that the above precautions are not necessary in patients with burnt out GO (6).

From the scientific perspective, the most interesting questions raised by Rocchi and colleagues (4) relate to the role of the TSH receptor in GO. Is hyperthyrotropinemia relevant; is the presence of TSH receptor antibodies obligatory; is stimulation of the TSH receptor necessary; what is the role of a source of thyroid antigen? Tools are already available or emerging (rhTSH, monoclonal antibodies to the TSH receptor, small molecules that modulate TSH receptor function, animal models) to address these important questions, and one can only hope that some eagerly awaited answers will be forthcoming in the near future.

DISCLOSURE

The author has no multiplicity of interest to disclose.

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