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Preventing Graves' Ophthalmopathy

Graves' ophthalmopathy and Graves' hyperthyroidism are closely linked, but the precise relation between these different expressions of the same disease is poorly understood. One much-debated issue is whether ophthalmopathy develops or becomes more severe as a result of the treatment of hyperthyroidism with antithyroid drugs, thyroidectomy, or radioiodine. The question must be considered in the context of the natural history of Graves' ophthalmopathy. In patients with Graves' hyperthyroidism, eye disease appears before the onset of hyperthyroidism in about 20 percent, at the same time as hyperthyroidism in about 40 percent, and after hyperthyroidism in about 40 percent. Furthermore, this eye disease often improves spontaneously. In a recent study of 59 patients with ophthalmopathy who were followed for one year, the condition improved substantially in 22 percent and slightly in 42 percent; 22 percent had no change, and 14 percent had worsening.¹

What factors underlie the development of Graves' ophthalmopathy? Enlarged extraocular eye muscles are seen on computed tomographic scans of the orbit in almost all patients with Graves' hyperthyroidism, yet ophthalmopathy is clinically apparent in only about half. In those who have ophthalmopathy, the changes are mild (e.g., swollen eyelids and slight proptosis) in about 60 percent and more severe (with diplopia and visual loss) in 40 percent. These differences could be due to genetic or environmental factors. A search for genetic markers specifically linked to susceptibility to Graves' ophthalmopathy has so far been unsuccessful.² More progress has been made in delineating environmental factors. In a case– control study, more patients with Graves' hyperthyroidism but without ophthalmopathy were smokers than was the case among normal subjects (odds ratio for Graves' hyperthyroidism among smokers as compared with nonsmokers, 1.9), and the association was much stronger for patients who had both Graves' hyperthyroidism and ophthalmopathy (odds ratio, 7.7).³ The smokers also had more severe ophthalmopathy than the nonsmokers. Smoking thus increases the risk of Graves' ophthalmopathy.

The biologic explanation for this association is unknown, but recent studies provide some interesting clues. First, orbital fibroblasts synthesize more glycosaminoglycans when cultured under hypoxic conditions.⁴ Glycosaminoglycans attract water, and excessive production of glycosaminoglycans contributes to the characteristic swelling of the eye muscles in Graves' ophthalmopathy. Second, serum concentrations of soluble interleukin-1 receptor antagonist are lower in smokers than in nonsmokers with Graves' ophthalmopathy, and low concentrations are associated with a poor response to orbital radiotherapy.⁵ The inference is that in smokers the proinflammatory and fibrogenic effects of interleukin-1 are less inhibited. Finally, in normal subjects smoking is associated with antibodies to heat shock protein 72, a protein involved in autoimmune reactions that is also expressed on orbital fibroblasts.⁶

The study by Bartalena and coworkers⁷ in this issue of the *Journal* suggests that radioiodine is another nongenetic factor promoting ophthalmopathy in patients with Graves' hyperthyroidism. These investigators randomly assigned patients with Graves' hyperthyroidism who had slight ophthalmopathy or none to treatment with radioiodine, radioiodine plus prednisone, or methimazole. Ophthalmopathy developed or worsened in 15 percent of the patients treated with radioiodine, in none of those treated with radioiodine and prednisone, and in 3 percent of those treated with methimazole. The good results obtained with radioiodine plus prednisone indicate only that prednisone is effective in patients with Graves' ophthalmopathy. To evaluate which treatment for Graves' hyperthyroidism entails the lowest risk of the development or progression of eye disease, the proper comparison is between the radioiodine and methimazole groups. The finding that ophthalmopathy developed or worsened in patients treated with radioiodine more often than in patients treated with methimazole confirms the results of a previous randomized trial.⁸ That study, however, has been criticized because all the radioiodine-treated patients became hypothyroid and thyroxine therapy was slightly delayed. Subsequent studies have demonstrated that high serum thyrotropin concentrations after radioiodine therapy are associated with the development of ophthalmopathy.^{9,10} In the study by Bartalena et al., the patients were closely monitored for both hyperthyroidism and hypothyroidism and either was quickly corrected. As a result, there was no relation between thyroid status and the incidence of ophthalmopathy.

This study does not prove that the higher frequency of new or worsened ophthalmopathy in the radioiodine group was caused by the radioiodine therapy. It could still reflect the natural history of ophthalmopathy, but in that case one has to assume that methimazole has a beneficial effect on ophthalmopathy. I favor the view that radioiodine is causally involved, because a plausible biologic explanation exists. Destruction of the thyroid by radioiodine is associated with an increase in thyrotropin-receptor antibody and other thyroid antibodies in serum, presumably because of the release of thyroid antigens and the activation of T and B lymphocytes. In the orbit, activated T lymphocytes may bind to orbital fibroblasts that express thyrotropin receptors or other antigens shared with thyroid tissue. The resulting release of cytokines could stimulate the production of glycosaminoglycans and collagen by orbital fibroblasts, resulting in edema and fibrosis.

How should the finding that ophthalmopathy develops or worsens more often after radioiodine therapy than after methimazole therapy be applied to clinical practice? Should all patients with Graves' hyperthyroidism receive prednisone for several months after radioiodine treatment? I don't think so, for several reasons. First, the changes in the eye after radioiodine therapy were often mild and transient. Second, exposing many patients to the side effects of prednisone in order to prevent eye changes in no more than 15 percent is inappropriate. The results should, however, lead to a more thorough assessment of the risk that ophthalmopathy will develop or worsen after radioiodine therapy in a particular patient. In other words, what factors determine whether ophthalmopathy will appear or become more severe after radioiodine therapy? Several can be mentioned: preexisting active ophthalmopathy, smoking, high serum triiodothyronine concentrations before treatment, and high serum concentrations of thyrotropin-receptor antibodies and thyrotropin after treatment. The patients in whom ophthalmopathy worsened after radioiodine therapy were more often smokers than those without worsening, and they had slightly more active ophthalmopathy. In the study by Tallstedt et al.,⁸ a pretreatment serum triiodothyronine concentration of at least 325 ng per deciliter (5 nmol per liter) was a risk factor for ophthalmopathy, but a high concentration of thyrotropin-receptor antibodies was not. Finally, it should be recognized that the study by Bartalena et al. dealt with patients who had little or no ophthalmopathy before radioiodine treatment. In patients with more severe ophthalmopathy and especially those with active eye

disease, it seems prudent to treat hyperthyroidism with an antithyroid drug or to administer prednisone if radioiodine is given.

In my opinion, the study by Bartalena et al. provides conclusive evidence that radioiodine treatment of Graves' hyperthyroidism carries a small but definite risk of the development or worsening of ophthalmopathy, whereas antithyroid-drug treatment does not. Even though the changes in patients' eyes after radioiodine therapy are usually mild and transient, I prefer to use antithyroid-drug therapy in high-risk patients.

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