

Orbitopathy After Treatment of Graves' Disease

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Graeves' disease is currently understood to be an autoimmune process in which hyperthyroidism is caused by antibodies which bind to thyroid-stimulating hormone (TSH) receptors on thyroid follicular cells and stimulate production of excess thyroid hormone (1). Although less well understood, the specific eye disorder associated with Graves' disease is also thought to be autoimmune in nature. Current theory suggests that a cross-reacting orbital antigen, possibly related to the TSH receptor, leads to infiltration of the orbit with activated T-cells. Cytokines released by these T-cells stimulate secretion of glycosaminoglycans (GAGs) by orbital fibroblasts. As the GAGs accumulate, they bind water, causing edema and swelling. This process primarily involves the extraocular muscles but also affects retro-orbital fat. The resulting increase in volume of the orbital contents leads to congestion and forward displacement of the globe, while inflammation, edema and eventual fibrosis lead to extraocular muscle dysfunction (2). Symptoms include periorbital swelling, light sensitivity, gritty sensations, increased tearing, pain behind the eyes, pain on movement of the eyes, blurry vision and double vision. Infrequently there is a decrease in visual acuity due to compression of the optic nerve by the enlarged extraocular muscles. This process, known as ophthalmopathy, is more correctly described as orbitopathy, since it involves the retro-orbital muscle tissues and not the globe itself (3) and is specific to Graves' disease, as opposed to eye abnormalities that occur in hyperthyroidism of any etiology including stare, lid retraction and lid lag.

Sensitive imaging procedures such as ultrasound (4), CT (5) or MRI (6) show that the majority of patients with hyperthyroidism due to Graves' disease have some degree of orbitopathy. However, clinically detectable orbitopathy occurs in a much smaller proportion with the reported prevalence varying between 13% and 46% (7). In most patients orbitopathy is asymptomatic and no treatment is required. However, in 3%-5% of patients, orbitopathy is

severe enough to require specific treatment with high-dose corticosteroids, external irradiation of the retro-orbital muscles or orbital decompression (7).

Orbitopathy appears to be independent of thyroid status and can occur in patients with normal levels of circulating thyroid hormones (euthyroid orbitopathy), patients who have been successfully treated for hyperthyroidism many years previously and even patients with primary hypothyroidism. However, in 80% of patients, orbitopathy is diagnosed within 18 mo of the onset of clinical hyperthyroidism. Among patients with both conditions, orbitopathy is detected prior to the diagnosis of hyperthyroidism in 20%, at the same time as the hyperthyroidism in 39% and after the diagnosis of hyperthyroidism in 41% (7). Assuming that treatment of hyperthyroidism begins shortly after diagnosis, approximately 40% of patients with orbitopathy develop symptomatic eye disease following treatment.

Over the years, many investigations have been undertaken in an attempt to determine whether the risk of developing new orbitopathy or suffering an exacerbation of pre-existing orbitopathy is affected by the type of treatment used for hyperthyroidism. Most of these studies have been retrospective and have failed to document that any particular treatment is associated with an increased risk of orbitopathy (7). However, concern that radioiodine treatment might be causally related to orbitopathy has recently received special attention, in part because radioiodine treatment is often followed by an increase in circulating antibodies to thyroidal antigens while treatment with surgery or antithyroid drugs usually results in a decrease in antibody levels (8). Presumably, one or more of these antibodies or some as yet undetected antibody could bind to a cross-reacting antigen in the orbit and initiate or potentiate an autoimmune reaction. The recent discovery that orbital fibroblasts contain mRNA which encodes the extracellular domain of the TSH receptor (2) has provided support for this theory.

A recent prospective study by Tallstedt et al. (9) reported a significantly increased risk of new or worsening orbitopathy in patients treated with radioiodine as compared to those treated with surgery or antithyroid drugs. The study included 179 patients with hyperthyroidism due to Graves' disease treated at the Karolinska Institute between 1983 and 1990. Patients under age 35 were randomized to either antithyroid drug treatment or subtotal thyroidectomy, while older patients were randomized to

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antithyroid drugs, surgery or radioiodine. All patients in the study were examined prior to treatment and subsequently followed by the same ophthalmologist. Antithyroid drug treatment consisted of Tapazole (10 mg four times per day) plus levothyroxine (T4) to normalize TSH. Subtotal thyroidectomy was followed immediately by T4 to maintain euthyroidism. Patients treated with radioiodine were given an amount calculated to deliver 120 Gy (12,000 rad) to the thyroid. They were not placed on T4 until they developed biochemical hypothyroidism (not defined). Prior to treatment, 7% of younger patients and 16% of older patients had clinically apparent orbitopathy. Following treatment, orbitopathy developed or worsened in 13% of the patients treated with antithyroid drugs or surgery with no differences among the various groups. However, orbitopathy developed or worsened in 33% of patients treated with radioiodine yielding a risk ratio of 3.2 (1.1–8.8). Orbitopathy was mild in the majority but six patients (4% of the total) required treatment with prednisone or orbital irradiation. All of these were in the group of 39 patients treated with radioactive iodine. In the patients treated with antithyroid drugs or surgery, TSH receptor antibodies decreased gradually during the first year after treatment while in the radioiodine-treated group, TSH receptor antibodies increased during the first year after treatment with a mean peak approximately twice base line.

The major criticism of this study is that the patients treated with radioiodine were allowed to become hypothyroid before being placed on T4 while the patients treated with antithyroid drugs or surgery were routinely given T4 and never allowed to become hypothyroid. There is independent evidence that orbitopathy is more likely to occur or worsen in patients who have become hypothyroid following treatment (7). In a subsequent study begun in September 1988 (10), Tallstedt et al. routinely administered T4 to all patients treated with radioiodine starting with 50 µg daily 2 wk after treatment and increasing to 100 mcgs daily 4 wk after treatment. Two hundred and forty-four patients who were routinely given T4 were compared to 248 patients treated in the previous 2 yr who were given T4 only after they developed biochemical hypothyroidism. With a follow-up of 18 mo, 11% of patients given routine T4 and 18% of patients given T4 only after becoming hypothyroid had new or worse orbitopathy. Eleven patients in the routine T4 group and 26 patients in the group without routine T4 required specific treatment for their orbitopathy. These differences are significant, and suggest that hypothyroidism may have been primarily responsible for the increased risk of developing or worsening orbitopathy which was observed in the radioiodine-treated patients in the previous study.

Patients without clinically detectable orbitopathy are unlikely to develop orbitopathy after radioiodine treatment, with most series reporting a risk of 3%–5%. However, patients who have detectable orbitopathy prior to treatment have a 16%–33% risk of an exacerbation following radioiodine treatment (7). Bartalena et al. (11) have used

prednisone to prevent exacerbation of orbitopathy following treatment with radioiodine. Fifty-six patients with Graves' hyperthyroidism and slight or no orbitopathy were randomly assigned to treatment with either radioiodine alone or radioiodine combined with oral prednisone 0.3–0.4 mg/kg/day. One month after radioiodine treatment, prednisone taper was begun and prednisone was discontinued after an additional 3 mo. Orbitopathy did not develop in any patient in either group in whom orbitopathy was not detectable prior to treatment. In the patients with pre-existing orbitopathy who were treated with radioiodine alone, orbitopathy worsened in 56% and did not improve in any, while in the patients with pre-existing orbitopathy who were treated with radioiodine plus prednisone, orbitopathy improved in 50% and worsened in none. There was no difference between the two groups in the amount of radioiodine administered, the proportion of patients who became hypothyroid or the number who had an increase in antibodies to thyroglobulin or thyroid microsomal antigen. TSH receptor antibodies were not reported. Since there was no effect on antibody levels, it would appear that corticosteroids prevented exacerbation of orbitopathy via their anti-inflammatory effects.

Although Bartalena et al. found no significant side effects due to prednisone in their patients, serious side effects may occur when prednisone is given for prolonged periods of time. If it is postulated that orbitopathy may be initiated or exacerbated by an increase in TSH receptor antibodies, it might be possible to decrease the risk of orbitopathy by preventing the increase in antibodies which commonly occurs after radioiodine treatment. This can be achieved by treating patients with radioiodine while they continue to take antithyroid drugs. Due to Graves' disease, Gamstedt et al. (12) randomized 63 patients with hyperthyroidism to treatment with radioiodine alone, radioiodine plus methimazole or radioiodine plus betamethasone. The mean TSH receptor antibody level increased significantly after radioiodine treatment in both the radioiodine alone and radioiodine plus betamethasone groups but remained unchanged in the radioiodine plus methimazole group. No data regarding orbitopathy were given in this paper. The methimazole group required significantly more retreatment than the other two groups and the percentage of patients hypothyroid at 1 yr was significantly smaller.

Radioiodine is currently the preferred treatment for hyperthyroidism due to Graves' disease in the United States (13). Because of its effectiveness, simplicity and relatively low cost, it is likely to maintain this position until a more physiologic approach is devised. Since some patients will either develop new orbitopathy or suffer an exacerbation of pre-existing orbitopathy following radioiodine treatment, it is necessary to address this possibility when planning treatment and follow-up.

Either the referring or treating physician should evaluate patients with Graves' disease for the presence and extent of orbitopathy prior to radioiodine treatment and should inform them that orbitopathy may develop or worsen after

treatment. This should be documented in the record. The evaluation should include questions about changes in visual acuity, diplopia, retro-orbital pain, pain on eye motion, light sensitivity, gritty sensations, increased tearing and periorbital swelling. Soft-tissue changes are graded on a scale of 0–4, including edema of the upper and lower lids, injection of the conjunctiva and chemosis. Extraocular muscle function is evaluated by asking the patient to follow an object while holding their head still. The observer checks for any restriction of eye motion while asking the patient to report strain, blurring, or diplopia. These findings are evaluated in the primary field of view and at the extremes of up, down, right and left lateral, and right and left upward oblique gaze. Retro-orbital pressure is evaluated by pressing lightly on the globes (unless the patient is wearing contact lenses) and recording the resistance on a scale of 0–4. Proptosis is measured as the distance in millimeters between the orbital rim and the anterior corneal surface using a Hertel, Krahn or Luedde exophthalmometer. Patients with more than minimal orbitopathy should be referred to an ophthalmologist for evaluation of visual acuity, optic nerve function and exposure keratitis as well as quantitation of intra-ocular pressure and extraocular muscle function.

Follow-up arrangements should be clear to the patient and communicated to the referring physician. After therapy, thyroid function should be carefully monitored in all patients and T4 replacement started as soon as serum T4 falls into the normal range rather than waiting for clinical or biochemical hypothyroidism to develop. TSH may remain suppressed for weeks to months in patients who have become euthyroid or hypothyroid, and serum T4 is the most valid indicator of thyroid status in the 3 mo following radioiodine treatment. Replacement T4 can be decreased or discontinued if serum T4 becomes elevated or if TSH remains suppressed more than 3 mo after treatment.

Hyperthyroid patients with no or minimal orbitopathy require no special treatment, but should be asked to report the development of eye symptoms. Those with severe orbitopathy requiring treatment with prednisone, external radiation therapy and/or orbital decompression, are best treated with sufficient radioiodine to ablate the thyroid gland and ensure the development of hypothyroidism. This may lessen the progression of orbitopathy (14,2), and, at the least, prevents persistent hyperthyroidism which may be a factor in perpetuating orbitopathy (8). We treat such patients with 30,000 rad or approximately 400 μ Ci per gram, preferably while they are taking prednisone doses of at least 30 mg per day. Thyroid function is followed closely after treatment and replacement T4 is started as soon as

serum T4 begins to fall. Prednisone is tapered according to the response of the orbitopathy.

Patients with moderate orbitopathy present a more difficult problem. If the orbitopathy is symptomatic and/or progressive, treatment with both prednisone and sufficient radioiodine to ablate the thyroid usually stabilizes the situation. If the orbitopathy is stable and asymptomatic, radioiodine can be given alone with careful follow-up and addition of prednisone if there is significant deterioration. Another option for patients with moderate orbitopathy is treatment with an antithyroid drug until they are euthyroid and the orbitopathy has stabilized. The dose of antithyroid can then be decreased and radioiodine treatment given while they continue to take the lower dose (15).

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