Mini Review

Graves' orbitopathy: Management of difficult cases

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ABSTRACT

Management of Graves' ophthalmopathy (GO) is based on three pillars: to stop smoking, to restore and maintain euthyroidism, and to treat the eye changes according to severity and activity of GO. Difficulties are frequently encountered in each of these three management issues. The advice to discontinue smoking is straightforward, but just a small minority of smokers is able to quit smoking. Detailed information on how smoking adversely affects the outcome of Graves' disease may convince patients they have to stop smoking right away. Controversy exists on the most appropriate treatment of Graves' hyperthyroidism in the presence of GO. 131I therapy is associated with a risk of about 15% for worsening of GO; a preventive course of steroids is indicated in the presence of risk factors (smoking, biochemically severe hyperthyroidism, high level of TSH receptor antibodies, active GO). Alternatives are thyroidectomy or long-term treatment with antithyroid drugs, which apparently are rather neutral with respect to the course of GO. Mild GO is not always perceived as being mild by the patients themselves. Selenium improves mild GO. Moderate-to-severe GO is preferably treated with intravenous methylprednisolone pulses, but serious side effects and relapsing GO do occur. After steroid failure combination therapy with low-dose oral prednisone with either cyclosporine or retrobulbar irradiation can be effective. Dysthyroid optic neuropathy is best treated with IV pulses, followed by orbital decompression if visual functions do not improve. In resistant cases, rituximab might be considered, although failures of this drug are also described.

Key words: Decompression, Graves' Orbitopathy, hyperthyroidism, immunosuppression, management, smoking, unilateral eye disease

Introduction

Management of Graves' Orbitopathy (GO) is based on three pillars: 1/discontinuation of smoking, 2/restoration and maintenance of euthyroidism, 3/specific eye treatment according to disease severity and activity. Smoking is a well-known risk factor for GO, but even in established GO continuation of smoking is associated with worse outcomes. With regard to hyperthyroidism, it matters for the eyes how the patient is rendered euthyroid, as 131I therapy is associated with a risk of about 15% for worsening or developing GO. Lastly, the most appropriate treatment of GO itself depends not only on the severity of eye changes (mild GO qualifying for a "wait-and-see" policy, but very severe GO like dysthyroid optic neuropathy requiring immediate intervention) but also on the activity of GO: patients with active GO are more likely to respond to steroids and/or retrobulbar irradiation than patients with inactive GO, and rehabilitative surgery should be postponed until GO has become inactive. A nice treatment algorithm has been published by the EUGOGO group.[1] Close cooperation between internists/endocrinologists and ophthalmologists/orbital surgeons in combined thyroid-eye clinics is likely to improve the quality of care. In this review, we will focus on difficult cases of GO in order to provide some recommendations which may be helpful in obtaining better outcomes.

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Smoking Behavior

The standard advice to smokers is to stop smoking. The advice is simple and straightforward, but its efficacy is very

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low as most people continue to smoke. Methods to help people to quit smoking are in general not very successful: success rates are 1% for written self-help leaflets, 2% for proactive telephone counselling, 2% for brief opportunistic advice from a doctor, 7% for intensive behavioral support from a specialist, 9% for bupropion and 5-12 % for nicotine replacement. It could well be that patients with GO are more inclined to follow the advice to stop smoking, as many of them are really concerned about their changed appearance. The treating physician should use this window of opportunity to stress repeatedly the importance of quitting smoking. Chances to convince the patient can be enhanced by providing the following information: 1/in case Graves' hyperthyroidism is treated with antithyroid drugs, the risk of recurrent hyperthyroidism after withdrawal of antithyroid drugs is always higher in smokers than in non-smokers, irrespective of the level of TSH receptor antibodies;[2] 2/in case Graves' hyperthyroidism is treated with radioactive iodine, the risk of progression of GO is four times higher in smokers than in non-smokers, and improvement of GO by adding prednisone is four times lower in smokers than in non-smokers;[3] 3/the outcome of immunosuppression in GO is less favorable in smokers than in non-smokers.[4]

Restoration and Maintenance of Euthyroidism

Selection of the optimal treatment of Graves' hyperthyroidism in the presence of GO remains controversial.[5] Antithyroid drugs and thyroidectomy appear to be neutral with respect to the course of GO, but 131I therapy may have a negative effect. The adverse effect of radioiodine on GO is likely related to the post-radioiodine surge in serum TSH receptor antibodies, and can be prevented to some extent by prednisone. There is, however, wide variation in clinical practice on the applied dose and duration of prednisone.[6] In order to avoid unnecessary exposure of all patients to steroids, one may select patients for a preventive course of steroids according to risk factors (smoking, biochemically severe hyperthyroidism, high TBII, active GO).[5] To avoid the risk associated with radioiodine, one may opt for antithyroid drugs or thyroidectomy. Long-term treatment with antithyroid drugs (on average for 3.5 year until GO did not require further therapy) is a feasible option: any recurrent Graves' hyperthyroidism after withdrawal of anti-thyroid drugs could be managed satisfactorily by 131I therapy without preventive steroids. Flare-up of GO was not observed, obviously because GO had become inactive.[7] Thyroidectomy is an attractive option, although the advantage of total over subtotal thyroidectomy or the addition of an ablative 131I dose after surgery for the course of GO has not been convincingly demonstrated.[8]

Medical and Surgical Treatment of Graves' Ophthalmopathy

Mild graves' orbitopathy

One frequently encountered problem in patients with mild GO is that patient do not always agreed with the label "mild". Some patients report significant interference of their mild eye changes (rated as mild by their physician) with daily activities and well-being, which can be assessed quantitatively by a GO-specific quality-of-life questionnaire, the so-called GO-QOL.[9] Despite reassurance that spontaneous improvement of mild GO will occur in about 30%,[10] such patients may demand active intervention. Under these circumstances one may consider retrobulbar irradiation (10×2 Gy) which improves soft tissue involvement and eye muscle motility.[10] Alternatively, one may prefer treatment with 100 μg sodium selenite twice daily for 6 months, which in a recent RCT has shown to be superior to placebo in mild GO and also prevents progression to more severe GO.[11] Another problem is presentation as unilateral GO, occurring in 5-10% of all GO patients. Unilateral GO patients are older, more often euthyroid and have less severe eye changes in comparison to bilateral GO. Orbital imaging and measurement of TSH receptor antibodies is recommended in unilateral cases and in euthyroid patients to exclude an alternative diagnosis and confirm GO. Immunosuppression is effective, but treatment results can be lost upon progression of unilateral into bilateral GO (50%) or of euthyroidism into hyperthyroidism (25%).[12] It thus seems prudent to postpone rehabilitative surgery to a rather late point in time in the course of the disease.

Moderate-to-severe graves' orbitopathy

Short duration of GO (<1 year) and high clinical activity score (CAS ≥4) increase the likelihood of a favorable response to immunosuppression, but their predictive value for a successful outcome is not higher than about 80%. There is little doubt that intravenous methylprednisolone pulses are more effective than oral prednisone (success rate 74% vs. 51%) and better tolerated (adverse effects (56% vs. 81%).[13] A recent RCT on the optimal dose of pulse therapy observed that a cumulative dose of 7.5 g was more effective than lower cumulative doses of 2.25 and 5.0 g, but also associated with more major adverse events.[14] Disturbingly, about one-third of patients in each group experienced relapsing GO after discontinuation of pulses at 12 weeks. I am inclined to recommend the middle cumulative dose of 4.5 g intravenous methylprednisolone: 500 mg IV once weekly for 6 weeks, followed by 250 mg IV once weekly for another 6 weeks. Addition of low-dose oral prednisone during pulse intervals and after discontinuation of pulse therapy might reduce relapse rate of GO, but remains unproven. With regard to side effects, these can be

serious with a few reported fatal cases due to liver failure and cardiovascular events. Contraindications for pulse therapy are recent hepatitis, liver dysfunction (5-fold increased liver enzymes), cardiovascular morbidity, severe hypertension, inadequately managed diabetes mellitus, and glaucoma.[15] One should avoid cumulative doses >8 g and administration on consecutive days. Monthly monitoring of blood pressure, glucose and liver chemistry is warranted. An all too common problem is what to do when steroids fail. If the disease is still active, one may consider a low-dose of oral prednisone (20 mg/d) plus cyclosporine for another 3 months: about 50% of patients will still respond.[16] Alternatively, one may administer a low-dose of oral prednisone (20 mg/d) plus retrobulbar irradiation (10 × 2 Gy): the combination therapy is more effective than oral prednisone alone.[17] In resistant cases, one may try rituximab (2 × 1000 mg in 2 weeks), although this still should be considered as experimental therapy.

Very severe graves' orbitopathy (dysthyroid optic neuropathy, DON)

There is limited evidence from a RCT with small sample size that the preferred initial treatment is with steroids and not decompressive surgery.[18] One schedule is 1 g methylprednisolone IV on each of three consecutive days in week 1, to be repeated in week 2. If visual functions have improved at the end of the second week, continue with oral prednisone; if not, an urgent orbital decompression is required. Usually DON responds very well to treatment, although, less so in diabetic patients. Difficulties arise when after initial recovery of visual functions, signs and symptoms of DON reappear. One should order then an orbital CT scan to check if previous decompressive surgery was effective in creating more space for the retrobulbar tissues; if not, re-operation is necessary. We have encountered several patients with recurrent DON despite adequate IV pulses and decompression. Under these circumstances long-term combination treatment with low-dose oral prednisone + cyclosporine + radiotherapy might still be effective, but it may take 6-18 months before GO eventually will become inactive allowing rehabilitative surgery. Rituximab in these rare cases has sometimes been valuable, but has also resulted in deterioration of GO.[19]

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