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Review Article

ROLE OF STEROID IN THYROID ASSOCIATED OPHTHALMOPATHY

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ABSTRACT

Thyroid-associated orbitopathy (TAO), frequently termed Graves ophthalmopathy, is part of an autoimmune process that can affect the orbital and periorbital tissue, the thyroid gland, and, rarely, the pretibial skin or digits (thyroid acropachy). The disease process is actually an orbitopathy in which the orbital and periocular soft tissues are primarily affected with secondary effects on the eye. The ocular manifestations of thyroid-associated orbitopathy include eyelid retraction, proptosis, chemosis, periorbital edema, and altered ocular motility with significant functional, social, and cosmetic consequences. Of those patients affected, 20% indicate the ocular morbidity of this condition is more troublesome than the systemic complications of dysthyroidism. The estimated incidence of GO in the general population is 16 females and 3 males per 100,000 person years, (Ameican journal of ophthalmopathy, 1995). Management of orbitopathy can be either medical and surgical. The medical therapy relies on the use of high dose systemic glucocorticoids or retro-orbital irradiation, either alone or in combination. Recent randomized clinical trials have confirmed that glucocorticoids are more effective in intravenous than oral use.

Key Words: Graves disease, literature review, ophthalmopathy, steroid

INTRODUCTION

Thyroid-associated ophthalmopathy is the most frequent extrathyroidal involvement of Graves' disease but it sometimes occurs in euthyroid or hypothyroid patients. Thyroid-associated ophthalmopathy is an autoimmune disorder, but its pathogenesis is not completely understood. Autoimmunity against putative antigens shared by the thyroid and the orbit plays a role in the pathogenesis of disease. There is an increased volume of extraocular muscles, orbital connective and adipose tissues. Clinical findings of thyroid-associated ophthalmopathy are soft tissue involvement, eyelid retraction, proptosis, compressive optic neuropathy, and restrictive myopathy [1]. Graves' orbitopathy (GO), thyroid dermopathy (also called pretibial myxedema) and acropachy are the extrathyroidal manifestations of Graves' disease. They occur in 25, 1.5, and 0.3 % of Graves' patients, respectively. Thus, GO is the main and most common extrathyroidal manifestation [10]. The epidemiologic data provided evidence that severe, infiltrative orbitopathy is present in 3-5% of patients, and the quality of life is impaired even in individuals with mild form of this disease. The anti-TSH receptor and anti-eye muscle autoantibodies have been proved to be involved into pathomechanism of orbitopathy [2]. While most authors believe that autoimmunity against the TSH receptor expressed in the orbital connective tissue cells is the main reaction that leads to the development of ophthalmopathy in patients with Graves' hyperthyroidism, an older hypothesis that deserves fresh consideration is based on the notion that thyroglobulin (Tg) in the thyroid gland passes in a retrograde fashion to the orbit where it is recognized by Tg autoantibodies, leading to inflammation [8]. Autoimmune thyroid diseases consist of two subgroups: autoimmune thyroiditis (AIT) and Graves' disease. The AIT is the most common human autoimmune disease. Infiltration of the thyroid gland with cytotoxic T cells can lead to an initial thyrotoxicosis und during the course to hypothyroidism due to destruction of the thyroid gland [3]. Oftentimes, the diagnosis of thyroid eye disease is straightforward, based upon history and physical examination. Eye-care practitioners play an important role in the multidisciplinary team by assessing functional vision while also managing ocular health [4]. Active inflammation can often be effectively treated by intravenous steroids/immunosuppression, however does not lead to full remission, since inflammation rather quickly results in irreversible fibrosis and increase of orbital fat. Very important is the control of risk factors (smoking cessation, good control of thyroid function, selenium supplementation) to prevent progression to severe stages [5]. The main symptoms of GO comprise soft tissue inflammation, proptosis, impairment of ocular motility and lid retraction. Inflammatory reactions of orbital fibroblasts are responsible for the symptoms [6]. Defects in inactive stable Graves' orbitopathy can be successfully treated by surgery and involve decompression for proptosis reduction, muscle recession to correct diplopia and (finally) lid surgery [7]. Diagnosis is based on the clinical presentation and findings. Imaging, mainly CT and MR imaging, are helpful to reveal the extent of disease and degree of muscle enlargement and to evaluate for complications, such as optic nerve compression [9] (Fig. 1 and Fig. 2).

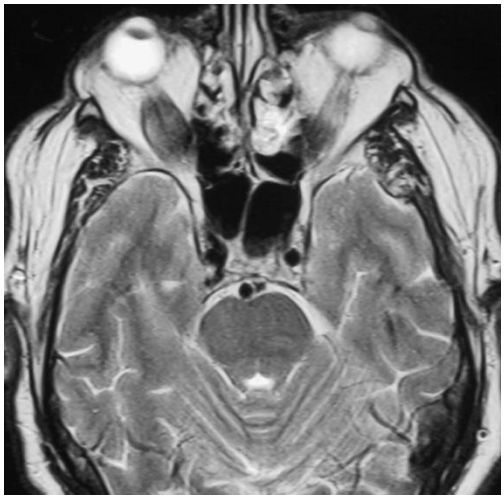

Figure 1: MRI axial section demonstrating enlarged inferior rectus muscles.

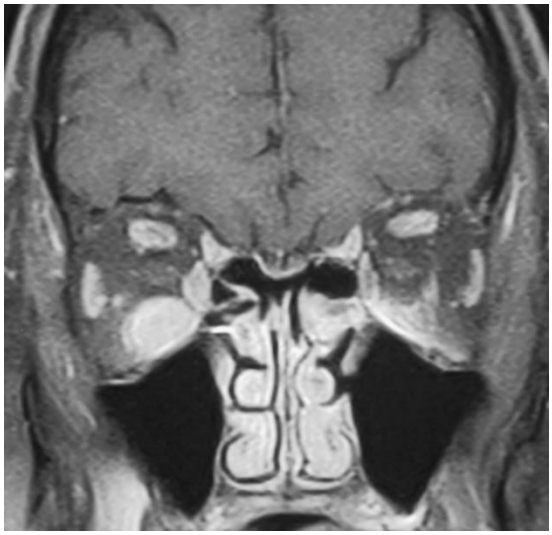

Figure 2: MRI coronal section demonstrating enlarged right inferior rectus muscle.

Role of Steroids:

Current evidence indicates that glucocorticoids (GCs) represent the only class of drug therapy which either in isolation or combined with other therapies has an unequivocal role in the routine clinical management of patients with GO [20]. Oral or intravenous corticosteroids are the first choice of clinicians in medical treatment of Graves' ophthalmopathy. Most clinicians use high-dose intravenous corticosteroid pulse therapy only in cases of severe ophthalmopathy [19]. Oral prednisolone prophylaxis, starting with a daily dose of 0.3 to 0.5 mg prednisone/kg body weight, be given in radioiodine treated patients as high risk of progression or denovo development of GO. Mild GO be treated with local treatments and general measures to control risk factors. A six month selenium supplementation be given to patients with mild GO of relatively short duratrion because it

improves eye manifestations and prevents GO progression to more severe form. First line treatment for moderate to severe and active GO, cumulative dose of intravenous GCs should not exceed 8.0 gm and that GO patients with evidence of recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity or psychiatric disorders should not be administered GCs; diabetes and hypertension should be well controlled before starting treatment(evidence grading very low quality).Intermediate dose schedule of methylprednisolone, i.e. a starting dose of intravenous methylprednisolone 0.5 gm once weekly for 6 weeks followed by 0.25 gm once weekly for 6 weeks(4.5 gm cumulative dose) in most cases of moderate to severe and active GO. High dose regimens, i.e. a starting dose of 0.75 gm once weekly for 6 weeks, followed by 0.5 gm once weekly for 6 weeks(7.5 g cumulative dose) should be reserved for the worst cases within the moderate to severe spectrum(evidence grading high quality)Sight threatening GO, Dysthyroid optic neuropathy(DON) be treated immediately with very high doses of intravenous GCs(500 to 1000 mg of methylprednisolone for 3 consecutive days or on alternate days during the 1st week),and urgent orbital decompression be performed if response is absent or poor within 2 weeks. If DON has resolved or improved after 2 weeks, pulses of weekly intravenous methylprednisole should be continued as per the management of moderate to severe and active GO [29]. Dexamethasone pulse therapy can be considered as an alternative to pulse methylprednisolone therapy. A prospective randomized control trial was carried out in 21 patients comparing pulse dexamethasone therapy versus pulse methyprednisolone therapy in Graves's ophthalmopathy. This study proved that pulse dexamethasone therapy is a cheaper and equally effective therapy for Graves's ophthalmopathy and the cost of therapy is reduced to at least 1/8(th) s. Furthermore, dexa had a better effect on reduction of exophthalmos. The dreaded complication of fulminant hepatic failure, associated with high dose of methylprednisolone, is not seen with dexa therapy [27]. The drug most widely used for the treatment of GO is methylprednisolone. However, in view of its easy availability and cost, dexamethasone has been often used in India for the above conditions [28].

Management of thyroid associated ophthalmopathy:

Graves' ophthalmopathy (GO) is a challenging disease that poses therapeutic dilemmas for endocrinologists and ophthalmologists. Numerous new treatments have been reported to have a beneficial effect. Management of Graves' ophthalmopathy is preferably done in a multidisciplinary setting. Smoking is associated with worse disease outcome. Iodine therapy for hyperthyroidism can also worsen ophthalmopathy, especially if administered during active disease or to patients who smoke or have severe hyperthyroidism, or those with high levels of TSH-receptor-binding inhibitory immunoglobulins [22]. Management of severe GO can be either medical or surgical (orbital decompression, eye muscle or lid surgery) [21]. Non-severe thyroid eye disease (TED) requires only supportive measures, such as eye ointments, sunglasses and prisms. By contrast, severe TED requires aggressive treatment, either medical (high-dose glucocorticoids, orbital radiotherapy) or surgical (orbital decompression) [26]. Most patients with Graves' orbitopathy have mild disease that requires no or minimal intervention. For the minority of patients with moderate or severe disease, multiple medical and

surgical treatments may be required at different stages [15]. Management of Graves' orbitopathy (GO) must be based on the correct assessment of activity and severity of the disease. Activity is usually assessed with the Clinical Activity Score, whereas severity is classified according to a European Group On Graves' Orbitopathy (EUGOGO) consensus statement as mild, moderate-to-severe, and sight-threatening. Myopathic and chronic congestive forms are uncommon clinical presentations of GO [11]. Corticosteroids continue to be the primary medical therapy for TED. Steroid-sparing medications, for example, rituximab and others are an area of active study. The use of balanced orbital decompression techniques have become popular, although the data regarding postoperative diplopia are mixed, and 'fat decompression' offers an alternative or an augmentation to bony decompression [12]. Intravenous pulsed corticosteroids, orbital radiotherapy, and orbital surgical techniques form the mainstay of current management of thyroid ophthalmopathy [19]. In most patients with TED, ocular and adnexal changes are mild and management involves controlling thyroid dysfunction, cessation of smoking, and addressing ocular surface inflammation and exposure [13]. The therapy of choice, after careful selection of patients, is pulse therapy with intravenous GC, with 79% of response [14]. Although surgical intervention may be required, a majority of TED patients can be managed with medical therapies. Of medical therapies, glucocorticoids remain the agent of choice in the control of TED activity [16]. Restoration of thyroid dysfunction, lubricant eye drops and smoking cessation is important. Clinical activity and disease severity determine specific treatment [17]. Systemic steroid therapy is the most commonly used treatment modality in the active phase. However, orbital decompression surgery is necessary in a small number of cases with sight-threatening ocular findings [23]. The presence of thyroid eye disease (TED) may influence the treatment of hyperthyroidism in patients with Graves' disease. Moreover, treatment of hyperthyroidism may affect the course of Graves' ophthalmopathy (GO) [24]. Radioiodine therapy is a significant risk factor for development or worsening of GO in GD. But GO progression can be prevented by prophylactic glucocorticoids in patients with preexisting GO [25]. Cushingoid features, glucose intolerance, gastritis, hypertension, hepatitis, and depression are major adverse effects of glucocorticoids. Fatal liver failure after high dose of pulse therapy (9-12g) was observed in 0.8%. Limiting the cumulative dose to 4.5-6g, assessment of liver virus markers and monitoring liver function before, during and after i.v. treatment are warranted [18].

CONCLUSION

Thyroid associated ophthalmopathy is the most frequent extrathyroidal manifestation of Graves' disease but this condition is also occurs in the absence of hyperthyroidism in 10% of patients. Most of these individuals have autoimmune hypothyroidism or thyroid antibodies. The earliest manifestations of ophthalmopathy are usually a sensation of grittiness, eye discomfort, and excess tearing. In most instances it is mild and non-progressive which requires only supportive measures but in 3 to 5% of cases it is severe which requires aggressive treatment, either medically by glucocorticoids, orbital radiotherapy or surgical by orbital decompression. Severity of TAO is classified according to EUGOGO consensus statement as mild, moderate to severe and severe sight threatening.

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