EDITORIAL

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Management of thyroid ophthalmopathy: the approach and challenges

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Thyroid ophthalmopathy, or Graves' ophthalmopathy, is the most common cause of exophthalmos in adults. Graves first described thyroid disease with associated ophthalmopathy in 1835.[1] To date, the pathogenesis of thyroid ophthalmopathy remains speculative, as reflected by the numerous names by which it is described such as dysthyroid ophthalmopathy or thyroid eye disease, thyroid orbitopathy, euthyroid ophthalmopathy, euthyroid Graves' disease, thyrotoxic exophthalmos, infiltrative ophthalmopathy, or malignant exophthalmos. It is considered to be an organ-specific autoimmune disease, strongly associated with Graves' hyperthyroidism. For some patients, thyroid function may remain normal or subnormal for part or all of the course of the disease. Some evidence indicates that radioiodine ablation, surgical thyroidectomy, or hypothyroidism after medical treatment can initiate or exacerbate thyroid eye disease. Smoking has also been shown to be a risk factor for developing more severe ophthalmopathy.[2]

Although the evidence for the autoimmune nature of the disease is circumstantial, it is compelling. Alterations in cellular immunity are thought to initiate the orbital changes associated with thyroid ophthalmopathy. Some evidence suggests that the thyroid and orbit share a common antigen — thyroid-stimulating hormone receptor protein. This antigen, together with some humoral factors present in the serum of patients with Graves' disease, forms the basis for the immunologic attack seen in thyroid ophthalmopathy. It is thought that activated CD8 T lymphocytes may contribute to the orbitopathy by binding to orbital fibroblasts that express thyroid-type receptors and antigens. The subsequent release of cytokines could promote the synthesis of glycosaminoglycans and collagen by surviving orbital fibroblasts with resulting edema and fibrosis. Loss of T-suppressor cell activity may also contribute to the inflammatory process by allowing greater proliferation of plasma cells and the production of autoantibodies against extraocular tissues.[1,2]

Clinically, enlargement of the extraocular muscles is the most striking abnormality of Graves' ophthalmopathy. Graves' ophthalmopathy is clinically apparent in 25 to 50% of patients with Graves' hyperthyroidism, but ultrasonography and computed tomography reveal evidence of thyroid ophthalmopathy in more than 90% of these patients.[3] In a study in Hong Kong, 16% of patients receiving radioiodine therapy had evidence of exophthalmos.[4] Orbital congestion, chemosis, diplopia, and proptosis occur secondarily to the extraocular muscle and orbital soft-tissue inflammation. Orbital fibrosis is a late sequela for a subset of patients. Proptosis, which can be regarded as 'natural decompression', together with lid retraction leads to a staring look, foreign body sensation, pain, lacrimation, and photophobia. The most significant complications are compressive optic neuropathy and corneal exposure with ulceration, which, although relatively uncommon, requires immediate and aggressive intervention.

The natural course of thyroid ophthalmopathy is characterized by an acute phase, with exacerbations and remissions evolving into a static phase over months to years. For individual patients, however, the course is unpredictable, making evaluation of treatment regimens difficult. For the majority of patients with thyroid eye disease, signs and symptoms are transient and respond to observation or conservative therapy. Perros at al noted that 64% of patients with thyroid eye disease improved without treatment, 22% had no change, and only 14% worsen.[5] However, for some patients, the disease expresses itself in a most disfiguring and severe form that profoundly impairs the visual function and quality of life of the affected patients.[6]

Treatment of the associated thyroid abnormality is the first logical step for managing these patients; however, the ophthalmopathy also has an important impact for patients, and must be addressed promptly. The goal in the treatment of thyroid ophthalmopathy is to reduce orbital inflammation and orbital tissue congestion in the acute phase, followed by treatment of late sequelae of orbital inflammation such as strabismus, lid retraction, corneal exposure, or secondary glaucoma.[7] Corticosteroids have been useful for treating active thyroid ophthalmopathy through oral, retrobulbar, subconjunctival, and intravenous routes.[8,9] It is not known exactly how steroids alter the inflammatory and immune response of this disorder — they may modify the function of T and B lymphocytes, reduce the infiltration of inflammatory cells, inhibit the release of mediators, including cytokines, and decrease glycosaminoglycan synthesis and secretion by orbital fibroblasts. Corticosteroids are especially useful when the orbital inflammation is severe and active. Approximately 50 to 60% of patients with compressive optic neuropathy and moderate to severe orbital inflammation respond to corticosteroids to some extent.[8,9] Many studies have documented a high effectiveness of high-dose oral or intravenous steroids on soft-tissue changes and optic neuropathy, whereas the decrease in proptosis and the improvement in ocular motility have not always been impressive. Recurrence of ophthalmopathy is common during or after withdrawal of the steroids.[2,8,9] Since the drug has to be taken for several months, its numerous possible side effects and complications are a major drawback.

External radiation has been employed for this disorder for more than 60 years because of its non-specific anti-inflammatory effects and the radiosensitivity of lymphocytes, which are suppressed by low doses of radiation. Radiation therapy may also reduce glycosaminoglycan production by orbital fibroblasts and alter helper/suppressor T lymphocyte function.[10,11] At present, the most commonly delivered dose is 20 gy per eye, divided into 10 daily doses over 2 weeks to reduce the cataractogenic effect of irradiation. Other side effects include transient exacerbation of eye inflammation, dry eye, radiation retinopathy (especially in patients with diabetes), and a theoretical risk of carcinogenesis. The procedure is usually well tolerated and has an overall success rate of approximately 60%, especially for patients with active eye disease and recent progression. Similar to systemic corticosteroids, radiation is felt to be more effective on soft tissue inflammatory changes and recent extraocular muscle involvement and, to a lesser extent, optic neuropathy. The effect on proptosis is again less obvious. Also, the effects of orbital radiation may take several days or weeks to become manifest and, when given alone, may not be ideal for patients with severe or progressing optic nerve compression. A recent study from the Mayo Clinic has challenged the effectiveness of orbital radiotherapy for Graves ophthalmopathy.[12]

Orbital decompression, classically performed by removing part of the bony orbit, provides an increased space for the increased orbital soft-tissue content.[13-15] Although it does not act on the pathogenic mechanisms of the ophthalmopathy, it is very effective on proptosis and on the other ocular manifestations caused by venous and soft tissue congestion, including optic nerve compression. It can also markedly improve the cosmetic appearance and corneal exposure problems of the patients. Several techniques aiming to remove portions of 1 to 4 walls of the orbit have been used.[15,16] Removal of the floor and medial wall can be accomplished by an anterior approach through a transconjunctival, transcaruncular, or a translid incision. This can be combined with a lateral approach to decompress the lateral wall. Traditional lateral wall decompression, which only includes removal of the more anterior aspect of the lateral wall, has been considered to be of limited effectiveness. More recently, Goldberg et al[17] and Meyer[18] have described improved decompression by a more aggressive deep lateral orbital wall decompression. The inferior (transantral) approach is also popular and typically includes removal of the medial wall and floor of the orbit. This technique is effective for optic nerve compression, because it is easier to remove the posterior part of the ethmoid near the orbital apex, but carries with it a higher incidence of postoperative diplopia. The transcranial approach may also be effective but is associated with greater risk and morbidity.

Three-wall decompression can be achieved by a bicoronal approach. The main advantage of the coronal approach cited by most authors is that the incisions can be hidden; however, the lateral orbit can be approached by an inconspicuous upper eyelid or subcanthal incision and, as already mentioned, the floor and medial wall can be approached transconjunctivally.[18] In recent years, an endoscopic approach to decompress the orbit has been gaining popularity and will continue to be evaluated. Another significant advance in orbital decompression in the past decade has been the concept of orbital fat excision. Orbital fat excision can be done alone or in combination with bony decompression. Orbital fat excision alone seems to be particularly well suited to patients without optic nerve compression who predominantly have an increase in orbital fat volume as the cause of their proptosis.[18,19]

Although corticosteroids, radiation therapy, and surgical decompression can all be effective for treating patients with

thyroid ophthalmopathy, the choice and sequence of treatment is controversial. Both oral corticosteroids and orbital radiotherapy remain attractive owing to the simplicity of administration, their non-invasive nature, and their ability to modulate the inflammatory processes of this disease. However, it is not always possible to predict which patients will or will not benefit from steroids or radiotherapy. Apart from short disease history, rapid progression, or younger age, no specific factors related to a favorable response to these treatment modalities have been determined.[6] Radiotherapy can sometimes be useful for patients who do not respond to steroids. Some studies suggest that combined radiation and steroid therapy is more effective than systemic steroids alone.[9]

In contrast to medical or radiation therapies, surgical decompression produces rapid relief of proptosis and can quickly restore vision to a normal level. However, surgical decompression acts on the mechanical effects of the orbitopathy and does not act on the etiology and the swelling of the extraocular muscles near the apex. This approach carries some risk of damage to the nerves inside the orbit, including the optic nerve, as well as a chance of various degrees of orbital asymmetry with postoperative diplopia and squint. Owing to its invasive nature, orbital decompression is considered by some to be the treatment of last resort for Graves' optic neuropathy. However, others favor early decompression because it has the potential to restore vision immediately to those whose vision is threatened or compromised. Surgical decompression for cosmetic improvement can also be performed and most patients are grateful for the results. In practice, some ophthalmologists suggest initial treatment with steroids, followed by radiation therapy and, if this approach is not successful, surgical decompression may be used as a last resort. Some centers prefer radiotherapy alone or combined with steroid therapy as the initial treatment while others favor early decompression surgery. The choice, of course, depends on the local availability of experienced orbital surgeons or radiotherapists, as well as contraindications or intolerance to systemic steroids and the presence of sight-threatening complications.

In Hong Kong, severe thyroid ophthalmopathy does not appear to be a common problem and corticosteroids appear to be the most commonly used treatment modality. In this issue, Dr Liang and colleagues report a study on the outcome of radiation therapy for patients with thyroid ophthalmopathy.[20] In many aspects, the results are similar to those of previous studies in other centers. Some of the patients received combined steroid and radiation therapy, while others had had a poor response to medical therapy prior to radiation therapy. The treatment response to radiation therapy is frequently only partial. In Liang et al's report, only 1 patient underwent subsequent surgical decompression.[20] With the improved standard of medical care in Hong Kong and the development of subspecialty interest, more experienced orbital surgeons are now available to perform decompression surgery. The surgical complications of decompression surgery are generally acceptable in the hands of experienced surgeons and recovery can be rapid.[13-16] From the results observed in our patients and of those reported in the literature, it appears that surgery can be offered selectively to some patients while new forms of medical treatment continue to be evaluated. The question of how to select patients who may benefit from medical treatment versus early surgery remains difficult to answer from an evidence basis. Patients with Graves' ophthalmopathy should be informed of the potential benefits, risks, and limitations of the various treatment options.

A vast amount of research on hyperthyroidism and associated ophthalmopathy has been performed but the ideal treatment for this disease still awaits further clarification. Because of the variable manifestations of the disease, it is not easy to stage or classify different severities for evaluating the various treatment modalities or studying natural history. Different ophthalmopathy indexes, clinical scoring systems, and indicators of the activity of the disease have been proposed.[21] The value of these indicators, including glycosaminoglycan level in plasma or urine, T2 relaxation time on magnetic resonance imaging, internal muscle reflectivity on ultrasound, or octreotide receptor-mediated scintigraphy remains to be confirmed. The lack of coordination among different disciplines involved in the research and treatment of these patients also make comparison of different parameters less straightforward.

Our knowledge and understanding of thyroid ophthalmopathy have certainly improved during the past 10 to 20 years, as has our experience in the different forms of treatment of this disease. The quality of life of patients is often markedly affected by this disease. Recent studies show that patients with thyroid ophthalmopathy scored lower quality of life indices than patients with diabetes mellitus, pulmonary emphysema, or heart failure.[21,22] To further improve the management of these patients, a multi-disciplinary approach will be required to coordinate study of the pathogenesis, epidemiology, classification, risk factors for development or progression of ophthalmopathy, therapeutic outcomes, and possible new treatments for this potentially debilitating and challenging disease.

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