GRAVES' ORBITOPATHY TREATED WITH IMMUNOSUPPRESSIVE THERAPY AND ORBITAL RADIOTHERAPY IN A TERTIARY CARE ENDOCRINE CENTRE: CASE SERIES

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ABSTRACT

Graves' Orbitopathy (GO) is a localized entity of Graves' disease, which is a challenging disease to treat. We describe 6 cases of moderate to severe GO who presented to our endocrine centre, with a mean age of 48.6 years and equal gender distribution. All of them were thyrotoxic before the presentation and were treated with antithyroid drugs. CT scans of orbits in 5 patients were consistent with GO. All of the patients were treated with intravenous methylprednisolone pulse therapy for a duration of 12 weeks and orbital radiotherapy for two weeks according to European Groups on Graves' Orbitopathy (EUGOGO) guideline. All six patients went into remission and remained so after one year of follow-up. Combination therapy seems to be effective in treating moderate to severe GO.

INTRODUCTION

Graves' disease (GD) is a common autoimmune disorder of the thyroid, affecting approximately 0.5% of the population (1). A reasonable percentage of GD patients have localized effects to the orbits, which is known as Graves' Orbitopathy (GO). It is clinically seen in approximately 30 to 50% of patients with GD. However, radiological evidence of GO is seen in more than 80% of cases (1). Periorbital tissue, conjunctiva, and retrobulbar structures are usually involved and it can either precede, can occur during or after the clinical symptoms of GD. Treatment of this condition is usually guided by the severity and the activity score of GO (2, 3). Mild disease is usually managed with supportive therapy and moderate to severe active GO usually warrants immunosuppressive therapy with or without orbital radiotherapy. However, sight-threatening Graves' eye disease may require urgent

surgical interventions. Although this is the usual consensus in managing these patients, there is limited data as to how to manage moderate to severe active GO. Here we describe six patients who were managed with methylprednisolone pulse therapy with orbital radiotherapy (OR) in our Endocrine Centre.

CASE SERIES

Six patients with GO, who presented within a period of two years (2013-2015) to a tertiary Endocrinology Centre are described here. Fifty percent (3 patients) were females and age ranged between 26 to 64 years and the mean age was 48.6 years. All

Table 1: Assessment of GO activity

GO activity assessment according to Clinical Activity Score (CAS)

1. Spontaneous retrobulbar pain
2. Pain on attempted upward or downward gaze
3. Redness of eyelids
4. Redness of conjunctiva
5. Swelling of caruncle or plica
6. Swelling of eyelids
7. Swelling of conjunctiva (chemosis)

Table 2: Assessment of GO severity

Severity	Features
Mild GO	Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually only have one or more of the following: minor lid retraction (<2mm), mild soft tissue involvement, exophthalmos <3mm above normal for race and gender, transient or no diplopia, corneal exposure
Moderate to severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate to severe GO usually have any one or more of the following: lid retraction 2mm, moderate or severe soft tissue involvement, exophthalmos 3mm above normal for race and gender, inconstant or constant diplopia.
Sight-threatening GO	Patients with dysthyroid optic neuropathy (DON) and or corneal breakdown. This category warrants immediate intervention responsive to lubricants

six patients were initially thyrotoxic and two were euthyroid with antithyroid drugs when they were referred to the endocrine centre for treatment. Mean duration to develop GO after the initial presentation of thyrotoxicosis was 14.1 months. Clinical activity score (CAS) was carried out according to the European Group on Graves' Orbitopathy (EUGOGO) guidelines (Table 1) and ranged between 3 to 4 in all patients and CAS of 3 or more was considered as an active disease (Table 3). Most commonly encountered clinical features according to the CAS were the spontaneous orbital pain and conjunctival redness. However, chemosis and inflammation of caruncle or plica were not seen in any of the patients (Table 4). Disease severity was rated according to the guideline (Table 2)

and it was moderate to severe in all six patients. However, none of the patients had the sight-threatening disease. Two of the patients had a history of smoking and passive smoking, where the other four did not have any smoking history.

Thyroid function tests of all the patients revealed that they were biochemically thyrotoxic at presentation. CT orbits were carried out in five out of six patients and it showed bilateral involvement in 4 patients and asymmetrical

Table 4: Clinical features in Clinical Activity Score (CAS)

Clinical activity in GO	Number of patients
Spontaneous orbital pain	5
Gaze-evoked orbital pain	1
Eyelid swelling	6
Eyelid erythema	4
Conjunctival redness	6
Chemosis	0
Inflammation of caruncle OR plica	0

Table 3: Demographic data and clinical status of the patients

Patient No	Gender	Age (years)	Clinical Thyroid status	Clinical Activity Score of GO	Disease severity of GO	Smoking history
1	F	56	Thyrotoxicosis	3	Severe	Passive smoking
2	M	44	Thyrotoxicosis	4	Moderate	Smoking
3	F	64	Thyrotoxicosis	4	Moderate	Non Smoker
4	M	26	Thyrotoxicosis	3	Moderate	Non Smoker
5	F	60	Thyrotoxicosis	4	Moderate	Non Smoker
6	M	42	Thyrotoxicosis	4	Moderate	Non Smoker

Table 5: Investigations of the patients

Patient No	TSH (0.4 -4.6 mIU/L)	Free T4 (nmol/L)	CT Orbit
1	0.85	1.7	Swelling of bilateral symmetrical medial and superior rectus muscles with sparing of the tendons-suggestive of Graves Ophthalmopathy
2	0.001	4.37	B/L proptosis seen. Extraocular muscles thickened with sparing of lateral rectus. The optic nerve is normal. Thickening of muscle body sparing the tendons.
3	< 0.004	2.2	Fusiform enlargement of medial and superior rectus. Thickening of muscle body sparing the tendons. The optic nerve is normal.
4	0.01	2.6	Thickening of muscle bodies of extraocular muscles of L/S sparing the tendons. The optic nerve is normal. Suggestive of graves orbitopathy.
5	0.004	2.0	B/L proptosis seen (L>R). Extraocular muscles- Superior rectus, Inferior rectus medial rectus thickened with sparing of tendons. The optic nerve is normal.
6	<0.05	1.71	Not imaged.

involvement of orbital muscles in one patient and one patient did not have CT of the orbits. However, none had involvement of muscle tendons, which is a characteristic feature of GO. Compressive optic neuropathy was not seen in any of the patients (Table 5).

MANAGEMENT

The two patients who had smoking exposure were advised regarding cessation of smoking. All the patients were initially treated with moderate to high doses of oral steroids without much clinical

improvement. Therefore, all the patients had a pulse therapy with intravenous methylprednisolone 500 mg weekly for 6 weeks and 250 mg weekly for 6 weeks. One patient had a recurrence of active disease after single steroid pulse therapy and was given a repeat pulse after one month of the first pulse. Patients were screened for liver dysfunction before high dose steroids and during the pulse therapy. Patients' blood pressure and fasting blood sugars were carried out during every visit before the pulse therapy. All the patients received orbital radiotherapy of 10 Gy given in 10 days over a period of 2 weeks and it was given

the steroid pulse therapy. CAS improved to 0 or 1 after treatment in all the patients and it was sustained in five patients at one-year follow-up and in one patient after 6 months follow-up (Table 6). Response to the treatment regimen is shown in figure 1, 2 and 3 for the patient No 1.

None of the patients had potential side effects from steroid therapy, including liver toxicity, diabetes mellitus or hypertension. At one year follow-up, there was no evidence of retinopathy or cataracts in any of the patients.

Table 6: Clinical activity before and after treatment

Patient No	CAS before treatment	Oral steroids	No. of IV Methyl prednisolone pulses	Time duration between Steroid pulses and orbital radiotherapy	CAS 3 months after treatment	CAS 1 year after treatment
1	3	Yes	2	4 months	1	1
2	4	Yes	1	4 months	1	1
3	4	Yes	1	4 months	1	0
4	3	Yes	1	4 months	1	0
5	4	Yes	1	3 months	0	0
6	4	Yes	1	2 months	1	0

(after 6 months)

Figure 1: Patient 1, before treatment

Figure 2: Patient 1, 6 months after treatment

Figure 3: Patient 1, 1 year after treatment

DISCUSSION

GO being the commonest extra-thyroidal entity of Graves's disease, treatment is still a challenge to the treating physician and diagnosis and management warrant a multidisciplinary team approach. Understanding the pathophysiology of this disease is important in order to rationalize the management of these patients. TSH receptor autoantibodies are the key to this pathological process and the sharing of the same TSH receptor antigen by the orbital fibroblasts, adipocytes, and the thyroid gland is the cause for this disease entity. This autoimmune reaction within the orbital cavity causes the swelling of the extraocular muscles, due to glycosaminoglycan deposition and fibrosis leading to symptoms of GO. The accumulation of orbital connective tissue and fat tissue is also responsible for the restrictive ophthalmoplegia and proptosis that is seen in GO (4).

GO has been documented to be a disease of middle age. The mean age of our patients was 48.6 years, which is almost similar to most of the other studies found in the literature (5, 6). Usually, females outnumber the men in GO to 2-5 to 1 (5). However, in our series equal gender distribution was seen. Although hyperthyroidism is associated in around 80% of cases of GO, it may not coincide with the onset of the hyperthyroid state and it may

present before the onset of thyroid dysfunction, during thyroid dysfunction, or when the patient is euthyroid following therapy. 5-10 % of GO patients do not develop hyperthyroidism and are called euthyroid GO and 10% of GO patients actually can have primary autoimmune hypothyroidism (4).

Among the clinical features of active eye disease, eyelid swelling and conjunctiva redness was the commonest in our patients. Around 3 to 5% of patients with GO have severe disease with intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy, although none of our patients were in this category. Ocular symptoms are commonly bilateral but asymmetrical involvement is also present in 15 % of GO patients as in one of our patients, in which case the other orbital pathologies such as pseudotumour, orbital inflammation and orbital lymphoma need to be excluded (7).

The clinical activity score (CAS) is a

validated scoring system for the identification of the activity level of GO (8). It's based on the assessment of inflammatory clinical features such as pain, eyelid and conjunctival erythema, chemosis, and eyelid oedema. CAS has shown high predictive value for the outcome of immunosuppressive treatment in GO patients, hence, it's widely used by clinicians in their patient management (8). European Groups on Graves' Orbitopathy (EUGOGO) has used this activity score and also disease severity to recommend treatment options (2, 3). CAS ≥ 3 is considered active disease and all our patients belonged to this category.

The severity of GO is determined by the level of lid retraction, the degree of soft tissue involvement, the degree of exophthalmos for that particular race and gender and presence of inconstant or constant diplopia (2, 3). Moderate to severe disease is considered when patients are without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppressive treatment and any one or more of the following features, lid retraction of 2mm, moderate or severe soft tissue involvement, exophthalmos 3mm above normal for race and gender, inconstant or constant diplopia (2, 3).

Investigations should include the Thyroid function tests (IFT), and the imaging to confirm the clinical diagnosis. Anti-TSH receptor antibodies are positive in 90 % patients with GD. Levels of anti-TSH receptor antibodies correlate positively with clinical features of GO and the prognosis (9). It was not carried out in our patients due to unavailability in the government hospital, which would have helped us to decide on their prognosis. Computed tomography (CT) is the most commonly utilized imaging technique for evaluating GO. CT is more sensitive than magnetic resonance imaging (MRI) in

identifying enlarged extra-ocular muscles. Enlargement of the muscle belly with sparing of the tendon insertion is typical of GO. An apparent increase in orbital fat volume and crowding of the optic nerve at the orbital apex are other characteristics. All our patients, except for one had CT orbits and all the scans correlated with the diagnosis of GO. MRI scan is better in differentiating soft tissue lesions compared to CT orbits and it can be useful when GO-related muscle involvement need to be differentiated from other orbital conditions (10).

Management of the patients with GO warrants a multidisciplinary approach, liaising with the ophthalmologist, radiologist and oncology specialties. General measures were instituted in all the patients. Active and passive smoking cessation have to be emphasized to the patients and their families. As uncontrolled hyperthyroidism is associated with severe GO, rendering the patient euthyroid is an important step in the management of GO (11). No particular antithyroid drug, antithyroid drug regimen or the type of thyroidectomy (subtotal or total) has demonstrated any advantages in terms of the outcome of GO. However, with radioiodine therapy, a definite proportion of patients (15%) have shown to develop new eye disease or experience progression of pre-existing GO within 6 months after therapy. However, treating them with a short course of steroids after the radiotherapy can ameliorate this problem (12).

Depending on the disease severity and activity of GO, treatment options can be tailored according to the EUGOGO guideline, which was revised in 2016 (3). For moderate to severe active disease, high dose steroids are recommended and IV steroids are preferred over to oral steroids, according to the recently revised EUGOGO guideline.

Glucocorticoids play an important role in reducing the inflammation and congestion of the orbital tissue and it is able to prevent the progression of the autoimmune disease.

Few studies including one randomized, a single-blinded study has shown that IV steroids are more effective than oral steroids (13). As all our patients were treated with a course of oral steroids once, IV steroids (methylprednisolone) was considered as the next treatment option. Contraindications to steroids include evidence of significant hepatic dysfunction, recent viral hepatitis, severe cardiovascular morbidity, uncontrolled hypertension, psychiatric disorders and inadequately controlled diabetes (3). Orbital radiotherapy is considered to hinder the inflammatory process, hence is another treatment option. Few study groups have studied the superiority of the combination of steroid therapy with orbital radiotherapy compared to either treatment alone. In a Canadian study with 245 patients where 144 patients (group 1) received only corticosteroids and 104 patients (group 2) received steroids with orbital radiotherapy, with an average of 3.2year follow-up, demonstrated that compressive optic neuropathy developed in 17% (25/144) in group 1 and 0% in group 2 ($P < .0001$) highlighting the superiority of the combination therapy (14). Results of another meta-analysis have also reassured the combination therapy (15). After looking at the risk of radiation-induced tumours, cataract, and retinopathy, a study done with 245 patients has demonstrated the safety of orbital radiotherapy for GO, except, possibly for patients who had diabetic retinopathy (16).

All six of our patients received IV Methylprednisolone 500 mg weekly for 6 weeks and 250 mg weekly for six weeks followed by the OR, 2 to 4 months after initiating steroid therapy, in a cumulative dose of 20 Gy per orbit fractionated in 10 doses over a 2-week period. None of our patients had side effects from either steroids or orbital radiotherapy at follow-up after one-year. Clinical activity score of GO was reduced to either 1 or 0 in all the patients at three months and it was sustained at one year as well. Therefore, IV steroids in combination with OR appear to be an effective and safe

therapy for active, moderate to severe GO patients.

CONCLUSION

GO remains a difficult condition to treat in some patients as recurrence is common, following treatment. According to our clinical experience, combination therapy with IV steroids and orbital radiotherapy is an effective treatment option that can be considered for active, moderate to severe Graves' eye disease.

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