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REVIEW ARTICLE

Graves' orbitopathy

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Summary

Graves' orbitopathy (GO) represents eye changes that most often occur in patients with autoimmune hyperthyroidism- Graves' disease (GD), although they can also occur much less frequently in euthyroid and hypothyroid patients. About 30% of patients with Graves' disease have GO, while less than 10% develop a more severe form that requires treatment. The choice of treatment should be based on the assessment of clinical activity and severity of GO. Activity represents the degree of inflammation while severity of GO reflects the degree of functional and cosmetic changes. Patients with mild orbitopathy usually recover spontaneously, so therapy is not always necessary. General measures to control risk factors and local treatments are usually sufficient. Treatment of active moderate-to-severe forms of GO still relies in most cases on high-dose systemic-intravenous glucocorticoids as monotherapy or in combination with mycophenolate. Second-line treatments for moderate-to-severe and active GO include the second course of i.v. methylprednisolone; oral prednisone combined with either cyclosporine or azathioprine; orbital radiotherapy combined with i.v. glucocorticoids; teprotumumab; rituximab and tocilizumab. Sight-threatening GO is treated with several high single doses of i.v. methylprednisolone per week and, if unresponsive, with urgent orbital decompression. Rehabilitative surgery (orbital decompression, squint, and eyelid surgery) is indicated for inactive residual GO manifestations.

Keywords: Graves' orbitopathy, Graves' disease, glucocorticoids, mycophenolate, orbital decompression

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INTRODUCTION

Graves' orbitopathy (GO) represents eye changes that most often occur in patients with autoimmune hyperthyroidism – Graves' disease (GD), although they can also occur much less frequently in euthyroid and hypothyroid patients (1). Considering that it limits the performance of usual daily activities, orbitopathy has a significant impact on the patients' quality of life. In order to start the treatment, it is necessary to perform an adequate assessment of the disease. Moderate-to-severe forms GO are a major therapeutic challenge because there is still no safe and highly effective therapy. European Group on GO (EUGOGO) was founded in 1999. with the idea of improving treatment of GO. To date, two EUGOGO guidelines for the management of GO have been published, the first in 2016, and in updated version in 2021.

PATHOGENESIS, EPIDEMIOLOGY, CLINICAL MANIFESTATIONS AND DIAGNOSIS OF GRAVES' ORBITOPATHY

The pathogenesis of Graves' ophthalmopathy (GO) is rooted in an autoimmune process occurring in the retrobulbar tissue (1). Autoimmune reactions ongoing in the orbit are probably initiated by autoreactive T lymphocytes which trigger a cascade of events including secretion of cytokines, proliferation of orbital fibroblastas, differentiation of preadypocytes into adipocytes, infiltration of extraocular muscles and secretion of glycosaminoglycans by the orbital fibroblasts (1,2).

As a consequence of the above, the intraorbital mass increases, which leads to the development of the typical clinical picture of GO (3). The most typical clinical sign is the retraction of the eyelids, which is present in over 90% of patients, then eyelid edema and exophthalmos, both bilateral or unilateral. Also, lagophthalmos may be present, as well as conjunctival redness, limited extraorbital muscle motility, double vision and compressive optic neuropathy. At the beginning of the disease, almost half of the patients have symptoms of irritation, complain of increased tearing, dry eyes, light sensitivity and feeling of discomfort (4). The clinical picture can sometimes be atypical with dominance of any of the listed clinical signs (5). It is believed that the clinical picture of GO became milder over time due to rapid diagnosis and initiation of treatment (6).

GO is a rare disease (estimated incidence: 0.54–0.9 cases/100 000/year in men, 2.67–3.3 cases/100 000/year in women) with more commonly mild and no progressive cases. Moderate-to-severe forms accounting for 5–6% of cases only (7). Some factors may influence the course of GO. Risk factors for the occurrence and progression of GO include smoking, thyroid dysfunction, radioiodine treatment for hyperthyroidism, and high TSHR antibody levels.

The diagnosis of GO is usually made clinically (8). Sometimes that is not easy, especially in unilateral or unusual cases. In these cases, orbital visualization plays a major role in diagnosis and differential diagnosis.

Both CT and MR imaging are in use and have their advantages. MR examinations play a significant role in the assessment of soft tissues and disease activity, while CT is superior in the evaluation of bones and has a special role in planning the surgical treatment of GO. Although generally occurring in hyperthyroid patients with Graves' disease, GO is occasionally seen in patients with autoimmune hypothyroidism and patients without thyroid dysfunction (9) which can make diagnosis even more difficult. Besides thyroid function test it is useful to determine thyroid autoantibodies. TSH receptor autoantibody are indispensable biomarker in the laboratory assessment of GO, especially TSAb measured using most sensitive cell-based bioassay (10).

ASSESSMENT AND CLASSIFICATION OF GRAVES' ORBITOPATHY

A significant proportion of patients with GO improve spontaneously. In patients receiving no specific treatment typical course of disease is described: GO undergoes an initial phase of florid inflammation (active disease) followed by a phase of stabilization (plateau phase) and a final phase of remission (burned-out or inactive disease) (11).

In order to decide on the treatment of GO, it is necessary to perform an adequate examination. The examination includes an assessment of the activity and severity. Disease activity represents the degree of inflammation, i.e. the presence of redness and swelling on the eyelids, conjunctiva and plica and the presence of retrobulbar pain.

The concept of severity relates to the features that result from the chronic changes in the extraocular muscles and soft tissues. Assessment of severity is based on various parameters, including soft tissue changes, exophthalmos, extraocular muscle dysfunction and diplopia, corneal involvement, and optic nerve involvement (13). Based on the performed examination, the severity of the disease is divided into mild, moderate to severe and sight threating GO. exophthalmos **(Table 1)**.

MANAGEMENT OF GO

Although management depends on severity and activity of GO, there are general measures that apply to all patients. They include control of risk factors and local treatment.

Control of risk factors. Both hyperthyroidism and hypothyroidism have a negative effect on orbitopathy. Disorders of thyroid function, hyperthyroidism and hypothyroidism adversely affect orbitopathy (14,15). For this

Table 1. Classification of severity of Graves' orbitopathy (GO)

Classification	Clinical features
Mild GO	• exophthalmos <3 mm above normal for gender and race • minor lid retraction <2 mm • mild soft-tissue involvement • no double vision or intermittent
Moderate to severe GO	• exophthalmos ≥3 mm above normal for gender and race • lid retraction ≥2 mm • moderate to severe soft-tissue involvement • inconstant or constant double vision
Sight-threatening (very severe) GO	• involvement and damage to the cornea and/or optic nerve

reason, it is extremely important to maintain thyroid hormones in normal values with adequate treatment.

The association between GO and smoking is well known: smoking increases the risk of GO in patients with GD, smokers have more severe GO, smokers have worse or delayed outcome of immunosuppressive treatments, development or progression of GO after radioactive iodine (RAI) treatment is more frequent in smokers (16). All patients with GO and GD should be urged to quit smoking.

Considering that RAI treatment carries a risk of aggravation and de novo occurrence of GO, oral prednisone prophylaxis should be given to radioactive iodine (RAI)-treated patients with risk factors (smokers, severe or unstable hyperthyroidism, high serum TSHR-Ab) (17).

Local treatment. GO patients often have dry eyes as a consequence of several factors such as exophthalmos, lagophthalmos, increased width of the palpebral fissure, blinking rate, lid lag and altered tear film osmolality. Therefore, patients are advised to use artificial tears during the day and ophthalmic gels with a possible taping of the lids or using swimming goggles at nighttime when severe lagophthalmos is present (18).

Management of mild GO

Patients with mild orbitopathy usually recover spontaneously, so therapy is not always necessary. General measures to control risk factors and local treatments are usually sufficient (18). So far, one randomized study has been published that showed a beneficial effect of selenium on current eye changes as well as the degree of progression. Based on that, according to the latest EUGOGO guidelines (19) selenium is recommended for patients with mild orbitopathy. Occasional patients with mild and active GO may require intervention with glucocorticoids if their quality of life is severely impaired by the disease (19) **(Figure 1)**.

Management of moderate-to-severe and active GO

Due to their anti-inflammatory and immunosuppressive effects, *glucocorticoids* have been the **first line of**

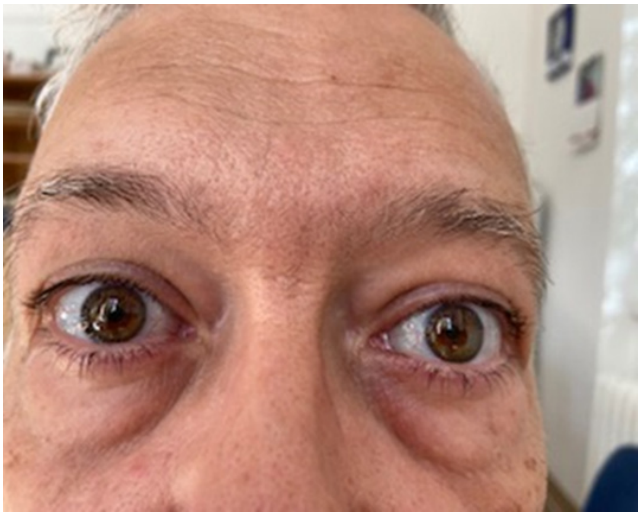

Figure1. Mild GO

treatment for moderately severe active orbitopathies for decades (19). In recent years, they have been combined with mycophenolate. According to current official recommendations, glucocorticoids are administered intravenously at weekly intervals for 12 weeks: six infusions of 0.5 g, followed by six infusions of 0.25 g. This protocol is well tolerated, it is effective in most patients and in the Clinic for Endocrinology of the University Clinical Center of Serbia it represents the first line of treatment.In more severe clinical cases a protocol with higher doses of corticosteroids is applied, with the starting dose of 0,75g for 6 weeks, followed by 0,5g for the next 6 weeks. Previous studies have shown that intravenous administration is more effective than oral administration and is better tolerated (21,22). Clinical and biochemical evaluation of patients is necessary before starting therapy because some conditions like viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, or psychiatric disorders represent absolute contraindications to i.v. glucocorticoid treatment (20, 23), while diabetes and hypertension should be well controlled before starting treatment (24).

In addition to the i.v. protocol, oral route is still used in many countries (25). In the Clinic for endocrinology in previous years we used Combined GC protocol which included 500mg of methylprednisolone in 500ml of saline solution for two alternative days. After that, the patients would continue to receive oral prednisone in decreasing doses for 4 weeks. In total, this therapy lasted for 6 months (26) and was successful in 65% of patients. Side effects were mostly mild, with weight gain, alterations in lipid profile, hirsutismus and myalgia that occurred most frequently (27) **(Figure 2)**.

Although it is known that intravenous glucocorticoids are better tolerated and have fewer side effects than oral (21-23) very serious complications have also been described during intravenous therapy (28-30).

Glucocorticoids can also be applied locally, as peribulbar, retrobulbar or subconjunctival injections in case of contraindications for systemic administration (31).

Figure 2. Moderate to severe GO

Immunosuppression with nonsteroidal agents has been studied either alone or as way to enhance the efficacy of GC. Mycophenolate mofetil (MMF) specifically targets activated T and B lymphocytes (32). In a randomized clinical trial MMF specifically comparing MMF in addition to IVGC vs IVGC alone, MMF showed benefit (33).

Second-line treatments for moderate-to-severe and active GO include the second course of i.v. methylprednisolone; oral prednisone combined with either cyclosporine or azathioprine and orbital radiotherapy combined with i.v. glucocorticoids particularly in the presence of diplopia and/or restriction of extraocular motility (19).

A number of immune cells and cytokines are thought to be involved in the pathogenesis of GO (34,35). Several monoclonal antibodies able to interfere with cytokine signaling are available for treatment of moderate-to-severe GO. Novel agents, such as rituximab. tocilizumab or teprotomumab or other biologicals, might represent a new way of approaching moderate-to-severe GO. However, they are not widely available and affordable. For the time being, evidence is missing regarding their effectiveness and safety.

Management of sight threatening GO

Sight threating GO (optic neuropathy) should be treated as soon as possible with high single doses of i.v. methylprednisolone (0.5–1 g of methylprednisolone daily for either three consecutive days or more preferably on every second day), and urgent orbital decompression should be performed if response is absent or poor within 1–2 weeks (19).

Management of inactive GO

Once GO has been inactivated by medical treatment, many patients require rehabilitative surgery for residual ocular manifestations (exophthalmos, lid retractions, eyelid, and periorbital puffiness, strabismus, and correlated symptoms such eye grittiness, retro/ periocular tension, and diplopia). They can be treated by a combination of decompression, ophthalmic plastic, and strabismus surgery (36).

CONCLUSION

Based on all the relevant clinical trials so far, intravenous glucocorticoids represent the most effective and safest method of treatment. Treatment should be carried out in combined thyroid-eye clinics or specialized centers providing both endocrine and ophthalmic expertise. Clinicians should monitor each individual patient receiving glucocorticoid therapy for response to treatment and adverse events. When drug-induced side effects outweigh benefits, clinicians should consider withdrawing glucocorticoid treatment in favor of another modality,

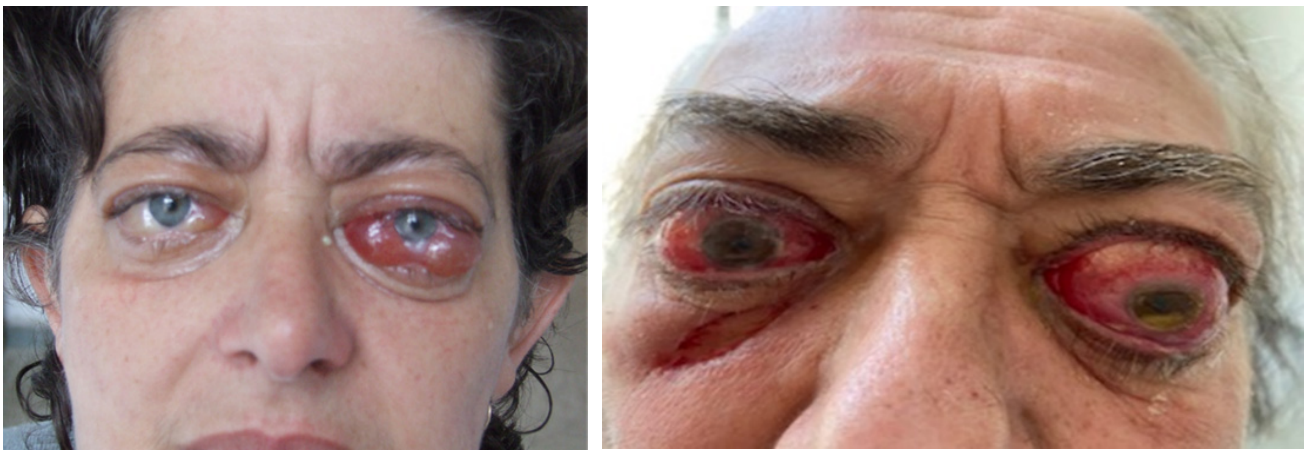

Figure 3. Sight threatening GO

or watchful monitoring. For second line treatment, biologicals, teprotumumab, tocilizumab or rituximab, hold great promise in the future management of GO and can be useful if patients are intolerant or resistant to standard immunosuppressive treatment.

In the University Clinical Center of Serbia, the treatment of GO is carried out in specialized endocrine-ophthalmic center in accordance with the current recommendations of the European Group of Graves Orbitopathy.

Author Contributions

Biljana Nedeljković Beleslin conceived and wrote the paper.

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GREJVSOVA ORBITOPATIJA

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Sažetak

Grejvsova orbitopatija (GO) je autoimino oboljenje orbite i glavna ekstratiroidna manifestacija Grejvsove bolesti. Oko 30% pacijenata sa Grejvsovom bolešću ima GO, dok manje od 10% razvije težu formu koja zahteva lečenje. Lečenje GO je multidisciplinarno. Izbor terapije se zasniva na proceni aktivnosti i težine bolesti Aktivnost predstavlja stepen inflamacije. Težina predstavlja stepen kozmetičkih i funkcionalnih poremećaja. Za blage i aktivne GO savetuje se kontrola faktora rizika, lokalna oftalmološka terapija i selen (posebno u oblastima deficitarnim selenom). Lečenje aktivnih srednje-do-teških formi GO u većini slučajeva se zasniva na primeni visokih doza intravenski primenjenih glukokortikoida kao monoterapijja ili u kombinaciji sa mikofenolatom. Druga linija lečenja obuhvata ponovljeni ciklus glukokortikoida intravenski, oralne glukokortikoide u kombinaciji sa ciklosporinom ili azatioprinom, radioterapiju u kombinaciji sa intravenskim glukokortikoidima, teprotumumab, rituksimab ili tocilizumab. U slučaju veoma teških, po vid ugrožavajućih GO se primenjuje više visokih, pojedinačnih doza metilprednizolona tokom nedelju dana. U slučaju da ne postoji povoljan odgovor na terapiju sprovodi se hitna hirurška dekompresija. Rekonstruktivna hirurgija (dekompresija, strabološka operacija ili operacija kapaka) je indikovana za neaktivne, posle medikamentne terapije zaostale, manifestacije GO.

Ključne reči: Grejvsova orbitopatija, Grejvsova bolest, glukokortikoidi, mofetil, orbitalna dekompresija

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