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Graves' ophthalmopathy – thyroid eye disease

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ABSTRACT

Graves' disease (GD) is an autoimmune disorder that affects thyroid. It is caused by antibody, named thyroid-stimulating immunoglobulin (TIS) that acts like thyroid stimulating hormone (TSH), resulting in thyroid hormone overproduction – condition called hyperthyroidism. TSH receptors are located on thyroid cells, but also on ocular fibroblasts – that's why Graves' disease can result in ocular manifestations also known as Graves ophthalmopathy (GO). Typically patients with hyperthyroidism are affected by ophthalmopathy, but it can occur in hypothyroid or euthyroid patients as well. It is estimated that 20-35% of patients with Graves' disease develop thyroid eye disease. In most cases symptoms are mild and do not require specialist treatment. Decision about therapy should be made considering severity of the disease and it is influence on quality of life.

INTRODUCTION

Thyroid eye disease, also called Graves' ophthalmopathy or Graves' orbitopathy is the most frequent extrathyroidal manifestation of Graves' disease. It is an autoimmune inflammatory disorder associated with thyroid disease which affects orbital and ocular tissues. This condition results in oedema of lids, double vision, lacrimation and photophobia. Up to 35% patients with thyroid disorder develop thyroid orbitopathy. It can occur at any age.[1] Women are affected 7-10 times more often than men, especially in their third to fifth decade of life.[2] It usually occurs after age of 40 in people with hyperthyroidism (85-90% of cases), however sometimes may take place in patients without apparent thyroid abnormalities (Euthyroid Graves' Orbitopathy) or hypothyroid autoimmune thyroiditis.[3,4] Per year it is estimated that 16 women and 3 men per 100 000 population have an incidence of thyroid eye disease.[5–7]

PATHOPHISIOLOGY:

Thyroid hormones overproduction is called hyperthyroidism. It is caused by thyroid hypertrophy and stimulation – effect of anti-TSH-receptor antibodies (TRAb) reaction with the TSH (thyrotropin) receptor (TSHR) on thyroid follicular cells. Major pathogenesis factors of the disease are:

1. inflammation of the periorbital soft tissues,
2. overproduction of glycosaminoglycan's by orbital fibroblasts,
3. hyperplasia of adipose tissue[3].

In patients with Graves' hyperthyroidism, there is an over-expression of TSHR in the retrobulbar tissue, particularly in orbital fibroblasts, which are integral in the pathogenesis of thyroid eye disease.[8] After activation, orbital fibroblasts proliferate. They secrete pro-inflammatory cytokines and hydrophilic hyaluronian into the interstitial space. In result, extremely high osmotic pressure gradient in the orbit increases fluid volume between the muscle fibers. There is intense swelling of extraocular muscles. Main cause of periorbital oedema is compression of veins in orbital space. Orbital fibroblasts differentiate into mature adipocytes causing expansion of the orbital adipose tissue. Long-lasting oedema leads to atrophy, fibrosis and sclerosis of the extraocular muscles subsequently causing restrictive strabismus.[8–12]

DISEASE ACTIVITY

Clinical activity score (CAS) is a validated scoring system used to assess inflammation of the orbit in patients with GO. According to CAS one point is awarded for each of clinical parameters: pain on attempted upwards or downwards gaze, spontaneous retrobulbar pain, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, swelling of the caruncle or plica and swelling of the conjunctiva. Depending on CAS score GO can be classified as active (≥3 points) and inactive (<3 points). There is also extended CAS system used for consecutive evaluation, where additional points can be awarded for increasing proptosis, decreases in visual acuity and worsening diplopia. Subsequent CAS score ≥4 indicates active GO, and score <4 inactive.

Complications of GO can be severe, even endanger vision and require treatment. Various classifications assess clinical signs. EUGOGO (European Group Of Graves' Orbitopathy, http://www.eugogo.eu) is used in Europe, VISA (Vision, Inflammation, Strabismus, Appearance, http://www.thyroideyedisease.org) in the United States and Canada. Treatment depends on activity status and severity. Severity is graded as mild, moderate to severe or very severe.

The multifactorial autoimmune disease has a spectrum of signs and symptoms. Patients who are first diagnosed when they are over 50 years old and men have more severe

course of the disease.[6,13] Several risk factors have been identified. They include older age at diagnosis, cigarette smoking, prior radioactive iodine treatment, longer duration of Graves' hyperthyroidism and uncontrolled thyroid dysfunction.[6,14–19] Cigarette smoking slows immunosuppression effects. It is strongly linked to risk of development and progression of GO. Comparing to non-smokers with Graves disease, smoking patients are more likely to have severe ophthalmopathy.[20] Smoking cessation is an essential therapeutic step.

TREATMENT

Symptoms of dry eye such as itching, redness, light sensitivity may be more severe in Graves' ophthalmopathy. Artificial tears can be used in the treatment of dry eye, they can compensate lack of natural tears and dilute inflammatory factors. They should show no corneal toxicity and exclude preservative agents content. To prevent glaucoma, intraocular pressure should be assessed to start appropriate treatment. Hypertonia may be iatrogenic, caused by corticotherapy or mechanical, due muscle action on the eyeball. In photophobia sunglasses improve visual comfort. Elevation of the head at night can reduce morning periorbital congestive swelling. Many retrospective studies proved that botulinum toxin is more effective in the muscle inflammation stage than in the fibrosis stage.[21] It may lower the intraocular pressure, especially in upward gaze, when is injected in the inferior rectus muscle.[22] Also therapeutic ptosis can be performed in case of severe corneal ulceration. A multicenter randomized, placebo controlled trial had shown that selenium supplementation– an anti-inflammatory, immunomodulatory antioxidant can ameliorate the quality of life and clinical signs of GO.[23]

Thyroid function is important factor of GO treatment. Most of patients have elevated levels of thyroid hormones initially and it is associated with intensive GO progress. Normalization of hyperthyroidism is essential to alleviate GO. It can be accomplished using anti-thyroid drugs, but there are different types of treatment. In some cases surgery is preferred method, considering patient preferences. Another possibility is radioactive iodine use, which is reported to cause GO progress, more likely in smokers, and probably can be stopped by simultaneous steroids therapy.[24] Hypothyroidism is also GO progression factor – that is why thyroid function normalization have to be done with enough care and precision.

Glucocorticoids (GCs) exert on anti-inflammatory and immunosuppressive effect. They are the basic drugs in treatment of active moderate-severe GO, but they may cause side effects. GCs inhibit cytokines and antibody secretion, interfere with B and T lymphocytes functions, decrease the synthesis and secretion of glycosaminoglycan's by orbital fibroblasts, and decrease macrophages and neutrophils at the inflammation sites.[25] Many studies have shown that pulsed intravenous methylprednisolone is more effective than oral prednisone.[26–28] It also has a better safety profile. Oral therapy is more often associated with long term side effects as osteoporosis, Cushing's syndrome, glaucoma and hepatotoxicity.[27] Additionally after discontinuation or dose reduction causes relapse of symptoms.[26,29]

Retrobulbar irradiation can be beneficial adjuvant treatment, especially when eye movements are impaired.[30] This therapy is successful because lymphocytes are sensitive to radiation, and it reduces glycosaminoglycan's production by fibroblasts. There is evidence that irradiation relieve symptoms at 60% of patients, but it is less effective in patients with exophthalmos, eyelid retraction and soft tissue involvement.[31] Randomized trials shown, that combination treatment with irradiation and corticosteroids is more beneficial that each therapy alone.[32]

Approximately 5% of patients suffering from GO may require surgical treatment. Operative treatment is mainly multistage, including such procedures as:

1. orbital decompression surgery,

2. eye muscle surgery,
3. blepharoplasty.

New treatment modalities such as TSH-R antagonists, specific monoclonal antibodies, and other immunomodulatory agents show a promising outcome for Graves' orbitopathy patients.[33–35]

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