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Thyroid associated orbithopathy

Orbitopatia tarczycowa

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S u m m a r y

Graves' orbithopathy, frequently termed thyroid-associated orbitopathy an autoimmune disorder characterized by orbital inflammation involving both extra-ocular muscles and adipose tissue. Inappropriate immune reactions averse to the orbital antigens and damage of immune tolerance are probably involved in its pathogenesis. It is characterized by a wide open orbit appearance, caused by exophthalmus and upper eyelid retraction, occurs far more often in women than in men and is most prevalent between 30 and 60 years of age, however severe cases occur more often in men than in women. The ocular manifestations of thyroid-associated orbitopathy include also chemosis, proptosis, periorbital edema, as well as altered ocular motility with significant functional cosmetic or social consequences. The clinical manifestation may vary – from mild disease when it may be overlooked and misdiagnosed to severe irreversible sight-threatening complications. Although most cases of Graves' orbithopathy do not result in visual loss, this disease can cause vision-threatening exposure keratopathy, troublesome diplopia or even compressive optic neuropathy. The present article summarize pathogenesis, clinical manifestations, and treatment of this so far poorly understood disorder, which is a problematic challenge to the ophthalmologist.

Key words: Graves' ophthalmopathy, Graves' disease, recognition, treatment

S t r e s z c z e n i e

Oftalmopatia tarczycowa (w przeszłości choroba była nazywana także oftalmopatią Gravesa-Basedowa) jest chorobą autoimmunologiczną, w przebiegu której dochodzi do immunologicznego zapalenia mięśni, tkanki tłuszczowej i łącznej wypełniającej oczodół. Etiologia zmian ocznych w przebiegu choroby nie jest do końca poznana. Podkreśla się jej autoimmunologiczny charakter, występowanie wspólnego antygenu w komórkach nabłonka pęcherzykowego tarczycy i fibroblastach oczodołów. Choroba występuje częściej u kobiet, a szczyt zachorowań przypada między 30. a 60. rokiem życia, należy jednak pamiętać, że cięższe przypadki zachorowań występują z większą częstością u mężczyzn. Objawy oczne pojawiające się w przebiegu tego schorzenia to m.in. wytrzeszcz, obrzęk spojówek, obrzęk mięska łzowego zaczerwienienie powiek, obrzęk wokół oczu, zmniejszona ruchomość gałek ocznych, czy pogorszenie ostrości widzenia. Objawy oczne mogą być różnorodne, od zmian o charakterze łagodnym, które często zostają przeoczone i mają tendencję do samoistnego ustępowania, aż po zmiany o charakterze ciężkiej naciekowej oftalmopatii. Celem pracy jest przedstawienie i analiza aktualnej wiedzy na temat tej jednostki chorobowej – stanowiącej współcześnie diagnostyczne i terapeutyczne wyzwanie, z uwzględnieniem patogenezy, objawów klinicznych i metod leczenia.

Słowa kluczowe: oftalmopatia tarczycowa, choroba Gravesa-Basedowa, rozpoznanie, leczenie

INTRODUCTION

Graves' orbithopathy (GO, thyroid ophthalmopathy, thyroid eye disease, thyroid-related ophthalmopathy, orbitopathy) is an autoimmune, chronic, debilitating infiltrative eye disorder, which affects the orbit and eyelids. It is often connected with thyroid pathology. Generally it appears in patients with active or treated Graves' disease or uncommonly with Hashimoto's thyroiditis (HT) or even among euthyroid patients. Grave's ophthalmopathy could be disfiguring and potentially severely disabling because of ocular suffering, as well as its influence on vision and appearance. GO influences orbital tissues in 25-50% of patients with Graves' disease (1-3). On the other hand about 5% of patients with autoimmune thyroiditis or without clinically evident thyroid disease will develop Graves' ophthalmopathy (4-6). It is diagnosed most commonly in women with female-to-male ratio of 5:1 and with peak occurrence of onset between the ages of 30 and 60 years, much less common in children than in adults (7). GO patients

are older than patients with Graves' hyperthyroidism without orbitopathy. The annual incidence of TAO in the general population is 16.0 per 100 000 population for women and 3 per 100 000 population for men with severe forms accounting for no more than 3-5% of the cases. Although GO is unquestionably more common in women, statistically, severe cases are slightly more common in men. The female to male ratio was 9.3:1 in patients with mild Graves' orbithopathy, 3.2:1 in those with moderate orbitopathy, and 1.4:1 with severe cases. The severity and incidence of GO depends not only on the gender but it also appears to be significantly higher among smokers compared with nonsmokers (8, 9). Furthermore, cigarette smoking is one of the strongest modifiable risk factor for developing GO. It not only increases the risk of developing Graves' ophthalmopathy, but also increases its severity and progression with a less beneficial response to therapy. Recently studies reported higher risk for prevalence of GO in patients with hyperthyroidism in Europeans compared to Asians (10). Bartalena at al. and some others researchers investigated relation between the therapy of hyperthyroidism due to Graves' disease and the course of Graves' orbitopathy. They showed that that radioiodine therapy for Grave's disease was followed by the development or more often, the evolution of ophthalmopathy. Otherwise, the patients treated with thionamides or with radioiodine and prednisone had no progression of eye disease. The development of ophthalmopathy after radioiodine therapy could be related with liberate of thyroid antigens as an effect of radiation injury leading to stimulation of autoimmune reactions directed to antigens shared by the thyroid and the orbit. In addition, the post-treatment hypothyroidism is crucial in the development of ophtalmopathy (3, 11).

ETIOPATHOGENESIS

Although the pathogenic mechanism of Graves' ophthalmopathy (GO) is still unknown, there is significant evidence for autoimmune reactions directed to orbital antigens, in particular to extraocular muscles, orbital fat, interstitial tissues or lacrymal glands which increase the volume of the orbital contents. Probably Graves' orbitopathy is induced by an autoimmune reaction against antigens shared by orbital and thyroid fibrous and adipose tissues. The orbital autoantigen has not been conclusively identified but the most popular candidate antigen is the TSH receptor (TRAb) since GO is frequently connected with Graves' disease and anti-TSH-receptor autoantibodies are founded in nearly 100% of patients with Graves' orbitopathy. TRAb transcripts were presented by northern blot in orbital adipose tissue from a patient with GO, whereas transcripts in normal adipose tissue being at the limit of the detection (12-16). Recently many researchers and clinicians accepted that TRAb titers and prevalence correlate with the severity and activity of GO (14). It is known that orbital fibroblasts, which present the TSH receptor, are major participants in the pathogenesis of Graves' ophthalmopathy. Firstly, T lymphocytes are activated by unknown mechanisms and then transit to the thyroid gland, orbit and eyelids. Subsequently, activated T lymphocytes produce cytokines to affect inflammation, local fibroblast activation and expansion of adipose tissue via cellular metaplasia. Activated orbital fibroblasts produce chemokines that recruit T lymphocytes into the orbit. These lymphocytes then cooperate with fibroblasts, probably activating each other. There is increasing evidence that orbital fibroblasts alone and interacting with lymphocytes can release excessive amounts of the of glycosaminoglycans, hyaluronic acid, chondroitin sulfate and finally collagen upon stimulation with various cytokines. In this scenario throglobulin, the TSH receptor, insulin-like growth factor-1 receptor (IGF-1R) or B cells have all been implicated. Inflammation targeted at the extraocular muscles as well as periocular tissues consists of lymphocytes, mast cells, and plasma cells. The histological changes are due to the accumulation of hydrophilic glycosaminoglycans, predominantly hyaluronan, and an increase in orbital adipose and connective tissue. Graves' ophthalmopathy begins as an active phase (inflammatory phase) followed by partial regression of symptoms which eventually leads to spontaneously remission (inactive phase, static stage) (4, 5). The different clinical signs of active GO are induced by inflammatory processes of retroocular adipose/connective tissue with infiltration of type 1 helper T (Th1) cells but also plasma cells, B cells, mast cells or macrophages. The demonstrate of primarily Th1 cells and connected cytokines (Interferon-gamma [IFN-γ], tumour necrosis factor [TNF], interleukin-2) in early disease indicates that cell-mediated immunity predominates in initial disease. On the other hand in later phases of Graves' ophthalmopathy predominate Th2 cells and cytokines (interleukin-5, interleukin-4, interleukin-10 and interleukin-13) which stimulating B-cells to produce autoantibodies. Accelerated production of glycosaminoglycans induces an edematous expansion of orbital connective tissue that effects in dysfunction of changed muscles like disturbances in ocular motility, increased orbital pressure and even displacement of the eye (proptosis) (6-8).

CLINICAL MANIFESTATIONS

The histological changes explain the clinical manifestations of Graves' orbitopathy which can be variable: exophthalmos, lagophthalmos (inability to close the eye), eyelid retraction, corneal exposure, periorbital and lid edema, edema of the bulbar conjunctivae, palpebral and conjunctival redness, chemosis, epiphora, photophobia, inflamed caruncle, visual changes (visual field defects, reduced visual acuity, reduced color sensitivity), orbital pain, diplopia (most commonly on up-gaze) or strabismus. They may also include loss of eyelashes and eyebrows, dermatochalazia or conjunctival injection. Superior limbic keratoconjunctivitis is known as a prognostic marker for severe disorder (9).

In very severe cases, visual loss due to compressive optic neuropathy occurs. It is connected with crowding of the orbit apex by increased extraocular muscles (4, 8, 9, 17, 18). This potentially blinding complication occurs in approximately 5% of GO. The diagnosis may be lost in patients without obvious proptosis. A European Group on Graves' Orbitopathy in 2007 proposed optic disc swelling, impaired colour vision and radiological evidence of apical optic nerve compression as often present when a suspicion of optic neuropathy was made (17).

Eyelid retraction is one of the common findings in GO. According to various sources, the value ranges from 91-98%. It is frequently mistaken for exophthalmus. In early stages it is caused by increased sympathetic tone, in the later stages, it may be associated with concentration of fibroblasts around the levator palpabrae muscle and with fibrosis of lid tissues. It can be recognized by watching the upper eye lid during downward gaze: when eyelid retraction existing the upper eyelid follows the eyeball with some delay (Von Graefe's sign) (5, 10).

Exophthalmus is created when oedema and fibrosis lead to increased intraorbital volume. Exophthalmos is usually bilateral, although it may be asymmetric or unilateral. Measurement of the degree of exophthalmos is performed using an exophthalmometer, for instance a Hertel exophthalmometer. Exophthalmos can cause the eyelids to fail to close leading to corneal dryness and damage. Another possible complication could be a form of redness or injury called superior limbic keratoconjunctivitis, where the area above the cornea becomes inflamed as a result of increased friction when blinking (5, 6).

INVESTIGATIONS

It is known that approximately 77-80% of cases of GO occur in association with hyperthyroidism, 3% with hypothyroid, and 20% is euthyroid (9, 10). This is the reason why the systemic thyroid status should be evaluated especially the signs like: weight loss, anxiety, intolerance to heat, hair loss, muscle aches, weakness, fatigue, hyperactivity, palpitations and arrhythmias.

It is important to define the phase of the disease because it have implications for treatment. Graves' ophthalmopathy is assessed on the basis of its activity and severity. A Clinical Activity Score (CAS) is often used to qualify whether GO is in its active phase. There are 10 symptoms suggested inflammation. Each sign is assigned by one point and a score of 3 points or more presents active phase of disease. This ten-point scoring system can be easily used by the clinicians to helps direct appropriate treatment. The second severity classification is NOSPECS it contains lid retraction, proptosis, soft tissue inflammation, corneal defects, size difference, extraocular muscle involvement, and optic nerve compression (6, 10, 19). NOSPECS is less popular among internists or endocrinologists than the former because of its strictly ophthalmological character. The third alternative score which consists aspects of NOSPECS and CAS is VISA. It is includes Vision, Inflammation, Strabismus, and Appearance (5). As we mention before in each case of GO the systemic thyroid status should be examinated. Measuring the level of thyroid-stimulating hormone (TSH) is typically the initial test for suspected hyperthyroidism. TSH produced by the pituitary will be decreased in hyperthyroidism. Thus, the diagnosis of hyperthyroidism is nearly always associated with a low TSH level. In this cases thyroid hormones themselves (T3, T4) will be increased. In some cases further testing should be performed. TRAb measurements are useful to diagnose GO in euthyroid patients. The diagnosis of GO is frequently made clinically. Eye examinations performed by an ophthalmologist in many cases can detect symptoms of Graves' ophthalmopathy. A visual field test is one of an eye examination that can detect dysfunction in central and peripheral vision. It is an essential part in evaluation in patients with GO. Ideally, the eye examination consists of an external examination, followed by specific tests for visual acuity, pupil function, visual fields, extraocular muscle motility, intraocular pressure (IOP) and ophthalmoscopy through a dilated pupil. External examination of eyes consists of inspection of the eyelids, surrounding tissues and palpebral fissure. Ocular motility should always be tested, especially when patients complain of double vision or physicians suspect thyroid disease (5, 6).

In the face of fact that access to orbit, especially its extra-equatorial regions, in physical examination is difficult, very important role in monitoring of pathological process play imaging methods such as USG, CT and MR. Ultrasonography is useful, inexpensive, easy accessible, noninvasive eyeball and orbit imaging method. It helps demonstrates enlargement of extraocular muscles. The restriction of this method is estimation of the orbits apex bone structures and superficial changes were use of invasive techniques is required. Orbital CT is more sensitive than MR in discovering enlarged muscles. It can imagines extraocular muscles, retrobulbar fat accumulation as well as the orbital apex. Furthermore, CT should be performed in any suspition of optic neuropathy, before orbital decompression likewise in patients with atypical proptosis or motility disturbances (5, 8-10).

TREATMENT

The management Graves' ophthalmopathy continues to be challenging not only for clinicians but also for patients. Although the great number of cases have mild course and require minimal intervention, in its severe forms the treatment can be very difficult (20, 21). Generally, treatment of this orbital disorder is challenging and there is no agreement among the clinicians which treatment type should be preferred. Patients with GO should be treated in multidisciplinary clinics with input from ophthalmologists and endocrinologists (22).

First of all type of therapy is based on the phase of the disease. During inflammatory phase, GO can be cured with corticosteroids, immunosuppression, or local radiation therapies. The aim of therapy during active phase is to reduce the inflammation by interfering with cytokine release, infiltration by lymphocytes, fibroblast activation, and glycosaminoglycan synthesis. The constant stage results in permanent changes like hypertrophy and fibrosis of the extraocular muscles, likewise orbital fat, and subcutaneous eyelid alterations. In this stage efficacy of immunosuppressive therapy is very poor and glucocorticoids are generally not given. Treatment options at any stage of disease include: treatment of the thyroid gland abnormality, artificial tears and ointment, smoking cessation and supportive measures such as dark glasses. In mild Graves' orbitopathy clinicians usually used "wait and see" policy. In this cases selenium (an antioxidant agent) can indicates the beneficial effects on quality of life, this effect remains to be investigated (23). In moderate to severe cases many treatment strategies can be used.

Corticosteroids are the basis of therapy for GO. Almost all experts in the field recommend steroid therapy as the first-choice treatment of active and moderate to severe Graves' ophthalmopathy. They can be used alone as well as in combination with other drugs, radiation, or surgery. Steroids work by decreasing inflammation and reducing the activity of the immune system and production of inflammatory chemicals in order to minimize tissue damage. They can have a wide range of side effects, for example stomach irritation or even gastrointestinal ulcer disease, high blood pressure, acne, mood changes, further weight gain, osteoporosis, glaucoma or cataracts. In this cases proton pump inhibitors, bisphosphonates and other medicians should be considered. High-dose of corticosteroids are useful for cases with compressive optic neuropathy, for patients with continue disorder progression in spite of surgical or radiation treatment, and for patients having orbital decompression to restrict the inflammatory and finally allow surgery, if require, to be performed during the cicatricial phase. Steroids can be supply by oral and intravenous pathways, or as retrobulbar injections. The second one is suggested because of its better results compared with high-dose oral treatment. Moreover, intravenous therapy is attached to less side effects and is better tolerated (24, 25). **Retrobulbar injections are useful when the disorder is not responsive to primary treatments or systemic treatment is forbidden.** Another immunosuppressive medications for example cyclosporine may be used as an alternative therapy. It impacts cell-mediated as well as humoral immune reactions. It should be given especially in combination with prednisone when steroids alone fail because the result of cyclosporine given as monotherapy generally is less effective (26). Simillary, anti-CD20 monoclonal antibody rituximab can potentially modify the inflammatory phase of GO. It can be useful in patients with active disease (27). Ebner and colleagues showed that triamcinolone administered as a periocular injection can be useful therapeutic tool in reducing diplopia and size of extended muscles. Moreover, such kind of therapy is not connected with systemic or ocular side effects (28).

Radiation therapy works only on the active phase of GO, especially in mild ophthalmopathy. It influences to suppress both orbital radiosensitive lymphocyte and fibroblast activity. Radiotherapy especially improves muscles motility and decreases the severity of diplopia (29-31).

Surgical treatment is usually performed in stabile stage. In active phase it can be done in vision-threatening conditions like: dysthyroid optic neuropathy, corneal ulcer or orbital decompression. The clinical features of Graves' orbitopathy could be variable and patients may demand surgery for cosmetic problems, severe proptosis or optic neuropathy. Several surgical approaches have been adopted, including the removal one or more orbital walls, retro-orbital fat, or both together. The choice one of the surgical techniques depends mostly on the local surgeon experience. Preoperative proptosis is usually bilateral, although it may be asymmetric or unilateral. It is known that achieve a good decompression in the eye with a higher preoperative proptosis is more difficult than in the second one. Consequently, in cases where the preoperative difference in exophthalmos between the two eyes is larger than 2 mm, firstly the surgeon should fixed the worst eye (32). If various surgical strategies are needed, first should be done orbital decompression, followed by muscles surgery, and in the end eyelid adjustments (33-35).

CONCLUSIONS

Thyroid-associated orbitopathy is a comparatively rare disease with unclear mechanisms that are still being analyzed. It occurs most frequently in the middle--aged women, especially with active or treated Graves' disease. The diagnosis of GO is frequently made clinically. Imaging of the orbits by USG or CT is recommended when the diagnosis is unclear. We conclude that the diagnosis of thyroid ophthalmopathy ought to be suspected in any patients with hyperthyroidism. In addition it is significant to consider that absence of endocrine disease does not exclude the presence of Graves' orbitopathy.

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