Woźniak Magdalena, Tywanek Ewa, Rudzki Grzegorz, Świrska Joanna, Zwolak Agnieszka, Łuczyk Robert Jan. Treatment of ophthalmopathy in the course of Graves' disease. Journal of Education, Health and Sport. 2019;9(9):912-920. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3460670
http://ojs.ukw.edu.pl/index.php/johs/article/view/7507

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.08.2019. Revised: 31.08.2019. Accepted: 22.09.2019.

Treatment of ophthalmopathy in the course of Graves' disease

Magdalena Woźniak[1], Ewa Tywanek[2], Grzegorz Rudzki[1], Joanna Świrska[2], Agnieszka Zwolak[2], Robert Jan Łuczyk[2]

[1]Chair and Department of Endocrinology, Medical University of Lublin, Jaczewskiego 8, 20-954 Lublin, Poland

[2]Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Chodźki 7, 20-093 Lublin, Poland

ABSTRACT:

Introduction: Graves' disease is an autoimmune disease in which the TSH receptor (TSHR) is an autoantigen. Its stimulation by antibodies inhibiting thyrotropin binding causes increased secretion of free thyroid hormones and consequently symptoms of thyrotoxicosis. Due to the presence of the same antigen also on orbital and skin fibroblasts, after activating the cell response mechanisms, non-thyroid symptoms of the disease appear, i.e. ophthalmopathy. In most patients, ophthalmopathy is mild and resolves spontaneously. However, in about 10% of patients the disease develops severe to moderate form and requires intensive therapy.

Purpose: The aim of this paper is to present the treatment options for ophthalmopathy, which is the most common manifestation of non-thyroid symptoms of Graves' disease, as well as to draw attention to the fact that treatment may be difficult and requires an interdisciplinary approach, and the treatment plan should be individually adapted to each patient.[1,2,3]

State of knowledge: The first-line treatment according to the guidelines published in 2016 by the European Group on Graves Orbitopathy (EUGOGO) are high doses of glucocorticosteroids administered intravenously. The second-line treatment is repeated use of intravenous steroid cycle, oral therapy with glucocorticoids, then combined with orbital or cyclosporine radiation therapy, rituximab or expectant management approach. Rehabilitation treatment is necessary in most patients after the disease has been inactive and maintained for at least 6 months with vision impairment and/or reduced quality of life.[1,2,3,7,9]

Summary: Ophthalmopathy is the most common non-thyroid manifestation of Graves' disease. This is a relatively rare disorder, but it has a significant negative impact on the quality of life of people affected by this disease. Therefore, it is very important, both among physicians and patients, to increase the awareness of this disease, apply effective preventive measures and inhibit its progress. Early diagnosis and appropriate treatment are of crucial importance.[2,16,17]

Keywords: thyroid; Graves's disease; ophthalmopathy; EUGOGO

Introduction

Graves' disease is an autoimmune disease in which the TSH receptor (TSHR) is an autoantigen. Its stimulation by antibodies inhibiting thyrotropin binding causes increased secretion of free thyroid hormones and consequently symptoms of thyrotoxicosis. In addition, it stimulates the growth of thyroid gland volume and vascularization (thyroid goitre). Due to the presence of the same antigen also on orbital and skin fibroblasts, after activating the cell response mechanisms, non-thyroid symptoms appear, i.e. ophthalmopathy, pretibial myxedema or acropachy.[9]

The most frequent manifestation of non-thyroid symptoms of Graves' disease is a set of ophthalmic symptoms caused by immune inflammation of muscles, as well as adipose and connective tissue of orbits, the so-called ophthalmopathy. It develops in 10-30% of sick patients and is mild in most cases. Initially, there is only edema, which in later stages of the disease may be accompanied by fibrosis and steatosis of the above mentioned structures. Straight muscles – lower and/or upper muscles – are most often affected by this disease. The lesions usually occur on both sides, and only 5% of patients have only one orbit affected by

disease process. Ophthalmopathy in 75% of cases is accompanied by manifest hyperthyroidism, in 20% it precedes it, and in 5% of cases it occurs without clinical symptoms of hyperthyroidism. The main symptoms of the disease are: pain or pressure in eyes, pain when looking in different directions, redness of eyelids, conjunctival hyperaemia, lacrimal caruncle edema, conjunctiva and eyelid edema.[7]

Treatment may be difficult and requires an interdisciplinary approach. The treatment plan should be individually adapted to patients and their preferences. The choice of thyrostatic treatment, the severity and activity of the disease, the age of patient, risk factors and possible complications of the therapy should be taken into account.[1]

In most patients, ophthalmopathy is mild and often resolves spontaneously. However, a six-month selenium supplementation cycle effectively alleviates the severity of this disease and prevents the transition to severe form. In addition, the symptoms should be alleviated with the use of supportive methods, i.e. sunglasses, thus reducing photophobia and ailments related to dryness of the wind. Application of preparations containing artificial tears to the conjunctival sac, thus alleviating symptoms of exposure to cornea and faulty tear film. In patients with lagofthalmos, adhesion of closed eyelids is useful in preventing night-time drying of the cornea. Prisms should be used to correct double vision, although there are cases of intolerance to this method by patients. Injection of a botulinum toxin into the eyeball area may reduce the reversal of upper eyelid, while the elimination from everyday life of risk factors such as smoking may reduce the progression of disease and cause symptoms to disappear more quickly. However, despite these methods, in about 10% of patients the disease develops severe to moderate forms and requires intensified therapy.[1,2]

The first-line treatment according to the guidelines published in 2016 by the European Group on Graves Orbitopathy (EUGOGO) are high doses of glucocorticosteroids, administered preferably intravenously. The second-line treatment is repeated use of intravenous steroid cycle, oral therapy with glucocorticoids, then combined with orbital or cyclosporine radiation therapy, rituximab or expectant management approach. However, rehabilitation treatment (orbital decompression surgery, strabismus surgery or eyelid surgery) is necessary in most patients after the disease has been inactive and maintained for at least 6 months with vision impairment and/or reduced quality of life.[1,2,3]

State of knowledge:

<u>Steroid therapy is the first-line treatment for moderate to severe ophthalmopathy in the course of Graves' disease</u>

The choice of appropriate treatment for individual patients depends on the disease activity assessed on the scale of clinical activity (CAS) – ≥ 3/7 indicates active form of disease (Table 1) and the severity of eye lesions referred to as mild, moderate/severe and risk of vision loss (Table 2).[2,3,4]

It should be noted that it is the activity and intensity of this disease, and not its duration, that is the main determinant of therapeutic effect.[4]

Table 1: Evaluation of Graves' ophthalmopathy activity according to CAS (Clinical Activity Score) – 7-point scale, where ≥ 3 suggests active inflammatory process

1. rest orbital pain
2. eye movement pain
3. eyelid hyperaemia
4. conjunctival hyperaemia
5. eyelid edema
6. conjunctiva edema
7. lacrimal caruncle edema

Table 2: Severity of ophthalmopathy according to EUGOGO

Parameter	Mild	Moderate/Severe	Risk of vision loss
eyelid retraction (mm)	< 2	≥ 2	
exophthalmos above normal (mm)	< 3	≥ 3	
affected soft tissues	mild	moderate/severe	
doubling	not present, transient	not regular, regular	
corneal damage	not present	mild	severe
optic nerve neuropathy			reduced visual acuity, disc edema n. II, visual impairment, keratoconus obstruction
eye subluxation			yes

In most cases, in patients with active disease and moderate to severe forms, the recommended steroid therapy regimen according to European Group on Graves Orbitopathy 2016 (EUGOGO 2016) is a cumulative dose of 4.5 g administered initially 0.5 g once a week for 6 weeks and then 0.25 g once a week for the next 6 weeks. High-dose regimens, i.e. an initial dose of 0.75 g once a week for 6 weeks and then 0.5 g once a week for the following 6 weeks (cumulative dose of 7.5 g) should be reserved for the most severe cases.[2]

Before the treatment, it is recommended to evaluate liver enzymes, hepatitis viral markers, fasting glucose levels in blood serum and to perform liver ultrasound. Contraindications for therapy include recent viral hepatitis, significant hepatic impairment, severe cardiovascular disease, uncontrolled hypertension, mental disorders and unbalanced diabetes. Hepatic enzymes, glucose levels and blood pressure are best monitored monthly throughout the treatment period. In addition, the use of proton pump inhibitors to prevent digestive ulcers is recommended and particular attention should be paid to patients with osteoporosis risk factors.[2,5,6]

Alternative treatment in case of lack of therapeutic effect after a single cycle of steroid therapy according to European Group on Graves Orbitopathy 2016 (EUGOGO 2016)

As has been shown by the scientific research conducted so far, as well as the observation of clinicians and their patients, in about 20% of patients after the use of a single cycle of steroid therapy according to the regimen of European Group on Graves Orbitopathy 2016 (EUGOGO 2016), symptoms of activity and intensity of ophthalmopathy do not disappear completely. An alternative to the expectant management approach, which is also recommended in some cases, is the administration of a second intravenous cycle of steroids, oral therapy with glucocorticoids, in combination with orbital or cyclosporine radiation therapy, or rituximab therapy.[2,8]

The second cycle of steroid therapy should be administered only if the patient has tolerated the previous treatment well and no life-threatening and/or health-threatening side effects occurred during the therapy. In addition, it is important that the cumulative dose of glucocorticosteroid administered to the patient during the first cycle does not exceed 8 g. If this happens, the second cycle is contraindicated.[2]

Another therapeutic option for ophthalmopathy as second-line treatment is the combination of orbital radiation therapy with oral glucocorticosteroids. Orbital radiation therapy synergistically increases the effect of oral glucocorticosteroids, hence this combination seems to be beneficial in the light of scientific reports. Ideal candidates for this type of treatment are patients in the early, active phase of ophthalmopathy with moderate to severe form of disease or rapidly progressing disease, including patients with significant mobility deficit and compressive visual neuropathy, who have not completely overcome their ailments after first-line therapy. Patients with progressive strabismus will also benefit. A cumulative dose of 20 Gy on the orbital cavity is commonly used, divided into 10 doses per day, administered over a period of 2 weeks. It should be noted that smaller doses may be considered in e.g. younger patients. An alternative 1 Gy per week for 20 weeks is equally effective and additionally better tolerated by patients. The rationale for radiation therapy is based on sensitivity to low doses of radiation from T lymphocytes and fibroblasts, which are mainly responsible for edema and fibrosis of the eyeball muscles respectively. The rate of improvement or stabilization of symptoms of ophthalmopathy in combination with radio- and oral steroid therapy ranges from 94% to 97%.[2,9,10]

Oral glucocorticosteroid therapy combined with cyclosporine also showed synergistic effects. Previous studies of patients with moderate to severe ophthalmopathy undergoing oral steroid

therapy combined with cyclosporine showed that this drug combination is associated with a much better therapeutic effect in the form of elimination of eye ailments, improvement of patient's comfort of life and a lower percentage of recurrence of orbitopathy than in the case of monotherapy.[2,11,12]

Some scientific reports suggest that in some patients with ophthalmopathy in the course of Graves' disease, the treatment with rituximab – a monoclonal antibody against B-cell receptor concentration of the differential receptor (CD) 20 lymphocytes – was a significant therapeutic success. However, in order to determine whether it can be considered an alternative to high doses of steroids, it still requires further multi-centre research.[2,13,14.15]

Inactive form of disease and persistent visual impairment and/or reduced QoL

Rehabilitation treatment, i.e. orbital decompression surgery, strabismus surgery and/or eyelid surgery, is often necessary in patients after the disease has been inactive for at least 6 months. Patients with impaired vision and/or reduced quality of life (QoL) despite inactivity of this disease should be qualified for such therapy. However, if more than one surgical procedure is required, orbital decompression should precede the strabismus surgery and be followed by eyelid surgery.[2]

Concludes

Ophthalmopathy is the most common non-thyroid manifestation of Graves' disease. This is a relatively rare disorder, but it has a significant negative impact on the quality of life of people affected by this disease. Therefore, it is very important, both among physicians and patients, to increase the awareness of this disease, apply effective preventive measures and inhibit its progress. Early diagnosis and appropriate treatment are of crucial importance. Thanks to the guidelines developed by the European Group on Graves Orbitopathy 2016 (EUGOGO 2016) in 2016, this task was slightly facilitated. However, it should be remembered that the decision on the choice of therapy should be adapted not only to the severity and level of disease activity. Each case should be considered individually. The potential side effects of a given therapy, coexisting diseases, the influence of disease on the quality of life and, above all, the patient's own preferences should be taken into account.[2,16,17]

References:

1. Marcocci, C., Smith, T. J., (2017). Graves' Ophthalmopathy. *Thyroid Diseases pp 1-39* https://link.springer.com/referenceworkentry/10.1007/978-3-319-29195-6_16-1#Sec33

2. Bartalena L., Baldeschi L., Boboridis K., Eckstein A., Kahaly G. J., Marcocci C., Perros P., Salvi M., Wiersinga W. M., and European Group on Graves' Orbitopathy (EUGOGO)., (2016). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J. 2016 Mar; 5(1): 9–26.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4836120/

3. Jastrzębska H., (2016). Graves' Orbitopathy 2016. *Post N Med 2016; XXIX(12): 864-867* http://www.pnmedycznych.pl/wp-content/uploads/2017/01/pnm_2016_12_864-867.pdf

4. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 1997;47:9–14. https://www.ncbi.nlm.nih.gov/pubmed/9302365

5. Zang S, Ponto KA, Kahaly GJ. Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab. 2011;96:320–332. https://www.ncbi.nlm.nih.gov/pubmed/21239515

6. Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, Bartalena L. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. Eur J Endocrinol. 2012;166:247–253. https://www.ncbi.nlm.nih.gov/pubmed/22058081

7. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits MP, Perros P, Boboridis K, Boschi A, Curro N, Daumerie C, Kahaly GJ, Krassas GE, Lane CM, Lazarus JH, Marino M, Nardi M, Neoh C, Orgiazzi J, Pearce S, Pinchera A, Pitz S, Salvi M, Sivelli P, Stahl M, von Arx G, Wiersinga WM, European Group on Graves' Orbitopathy (EUGOGO) Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158:273–285. https://www.ncbi.nlm.nih.gov/pubmed/1829945972

8. Zang S, Ponto KA, Pitz S, Kahaly GJ. Dose of intravenous steroids and therapy outcome in Graves' orbitopathy. J Endocrinol Invest. 2011;34:876–880. https://www.ncbi.nlm.nih.gov/pubmed/22322535

9. Nicosia L., Reverberi C., Agolli L., Marinelli L., De Sanctis V., Minniti G., Valeriani M., Osti M. F. 2019. Orbital Radiotherapy Plus Concomitant Steroids in Moderate-to-Severe Graves' Ophthalmopathy: Good Results After Long-Term Follow-Up. Int J Endocrinol Metab.

2019 Jan 27;17(1):e84427. doi: 10.5812/ijem.84427. eCollection 2019 Jan. https://www.ncbi.nlm.nih.gov/pubmed/30881470

10. Godfrey K.J., Kazim M., Radiotherapy for Active Thyroid Eye Disease. 2018. Ophthalmic Plast Reconstr Surg. 2018 Jul/Aug;34(4S Suppl 1):S98-S104. https://www.ncbi.nlm.nih.gov/pubmed/29771752

11. Kahaly G, Schrezenmeir J, Krause U, Schweikert B, Meuer S, Muller W, Dennebaum R, Beyer J. Ciclosporin and prednisone v. prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. Eur J Clin Invest. 1986;16:415–422. https://www.ncbi.nlm.nih.gov/pubmed/3100309

12. Prummel M.F., Mourits M.P., Berghout A., Krenning E.P., van der Gaag R., Koornneef L., Wiersinga W.M., 1989. N Engl J Med. 1989 Nov 16;321(20):1353-9. https://www.ncbi.nlm.nih.gov/pubmed/2519530

13. Karasek D., Cibickova I., Karhanova M., Kalitova J., Sphere J., Frysak Z., Clinical and immunological changes in patients with active moderate-to-severe Graves' orbitopathy treated with very low-dose rituximab. 2017. Endokrynol Pol. 2017; 68 (5): 498–504. https://www.ncbi.nlm.nih.gov/pubmed/28660988

14. Eid L., Coste-Verdier V., Longueville E., Ribeiro E., Nicolescu-Catargi B., Korobelnik J.F. The effects of Rituximab on Graves'orbitopathy: A retrospective study of 14 patients. 2019. Eur J Ophthalmol. 2019 Apr 26:1120672119845224. https://www.ncbi.nlm.nih.gov/pubmed/31025590

15. Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, Simonetta S, Guastella C, Pignataro L, Avignone S, Beck-Peccoz P. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015;100:422–431. https://www.ncbi.nlm.nih.gov/pubmed/25494967

16. Ponto KA, Hommel G, Pitz S, Elflein H, Pfeiffer N, Kahaly GJ. Quality of life in a German Graves' orbitopathy population. Am J Ophthalmol. 2011;152:483.e1–490.e1 https://www.ncbi.nlm.nih.gov/pubmed/21676374

17. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid. 1997;7:885–889. https://www.ncbi.nlm.nih.gov/pubmed/9459632