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Ocular manifestations in Hashimoto's thyroiditis and Graves' disease

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HIGHLIGHTS

Ocular manifestations in Graves' disease and Hashimoto's thyroiditis often overlap, complicating diagnosis. Comprehensive ophthalmologic assessment is essential to provide tailored treatment based on disease activity and severity. Early diagnosis and appropriate management are crucial to preventing vision-threatening complications and improve patient outcomes.

ABSTRACT

Introduction: Autoimmune thyroid diseases such as Hashimoto's thyroiditis (HT) and Graves' disease (GD) can present with ocular manifestations. While these are well documented in GD, less is known about their prevalence and characteristics in HT.

Methods: This narrative review summarizes current knowledge on the epidemiology, pathophysiology, clinical features, diagnostics, and treatment of ophthalmic symptoms in HT and GD. Special focus is placed on dry eye syndrome, thyroid-associated ophthalmopathy (TAO), and diagnostic approaches including imaging and tear biomarker analysis.

Results: HT most frequently presents with dry eye syndrome, eyelid edema, and rare manifestations like diplopia or vision loss. TAO, typically associated with GD, is also observed in a small percentage of HT cases. GD-related orbitopathy affects up to 50% of patients and may lead to severe complications, including optic neuropathy. Several immunological markers, including TSHR and IGF-1R, play a key role in the pathogenesis of Graves' orbitopathy (GO).

Conclusion: Ocular symptoms in HT and GD are diverse and can significantly impact patients' quality of life. Although GO is more characteristic of GD, its presence in HT should not be underestimated. Comprehensive ophthalmologic evaluation is essential for timely diagnosis and treatment.

Key words: Hashimoto's thyroiditis, thyroid autoimmunity, Graves' disease, Graves' ophthalmopathy, ophthalmic symptoms

HASHIMOTO'S THYROIDITIS AND GRAVES' DISEASE: OVERVIEW, PATHOGENESIS, AND EPIDEMIOLOGY

Hashimoto's thyroiditis (HT) is an autoimmune disease affecting thyroid gland. Dysregulation of the immune system plays a critical role in the pathogenesis of the disease, leading to the gradual destruction of the thyroid gland.

It is estimated that genetic factors account for 80% of Hashimoto's disease cases, with environmental influences contributing to the remaining 20% [1, 2]. The disease affects approximately 2% of the general population, making it one of the most common health concerns [3]. In iodine-sufficient regions, hypothyroidism affects 1–2% of the population [4]. In Europe, the prevalence of Hashimoto's disease ranges from 0.2% to 5.3% [5].

The mechanisms underlying the development of chronic lymphocytic thyroiditis involve complex interactions between genetic factors, such as class II MHC genes: *HLA--DR3, HLA-DR4, HLA-DR5*, polymorphisms in genes regulating the immune system (e.g., *CTLA-4, PTPN22*), and environmental factors such as iodine deficiency, infections, medications, and toxins, as well as autoimmune processes. Helper T lymphocytes recognize thyroid antigens and release cytokines that stimulate an inflammatory response, activating cytotoxic T lymphocytes responsible for destroying thyroid gland cells. Activated B lymphocytes produce antibodies characteristic for this disease (anti-TPO, anti-TG), which exacerbate organ damage. As a result, infiltration of lymphocytes and macrophages into the thyroid gland occurs, leading to destruction, with consequent fibrosis, and the loss of hormonal function, culminating in hypothyroidism [6].

Graves' disease (GD) is a form of hyperthyroidism that can be diagnosed when TSH (thyroid-stimulating hormone) levels are low, and triiodothyronine (T_3) and/or prohormone thyroxine (T_4) levels are elevated. There is also a subclinical form, in which TSH levels are decreased, but T_3 and/or T_4 remain within the normal range.

In countries with sufficient iodine levels, such as the United Kingdom, Sweden, Germany, and the United States, the incidence of hyperthyroidism hovers around 0.2–2.5% [7].

The most common ophthalmic complication of GD is orbitopathy, with approximately 50% of GD patients developing exophthalmos [8]. A 15-year study conducted in Minnesota estimated the prevalence of Graves' orbitopathy (GO) at 16 per 100,000 women and 2.9 per 100,000 men [9]. Based on these findings, the rate of ophthalmic complications was determined to be 6 times higher in women than in men. The age groups with the highest risk of developing orbitopathy are 40–44 and 60–64 years for women, and 45–49 and 65–69 years for men.

In a large Swedish study involving 3.5 million residents of Swedish cities, GD was diagnosed in 2,200 individuals, of whom 20% developed GO [10]. This corresponds to a prevalence of 3.3 per 100,000 women and 0.9 per 100,000 men.

In a prospective study involving 8.9 million residents of Denmark, the annual incidence of GO was estimated at 2.67 per 100,000 women and 0.54 per 100,000 men [11]. These figures are lower than previously reported; however, it is important to note that this study included only cases with moderate or severe disease. Mild cases make up as much as two-thirds of all cases, so the reported data may underestimate the true incidence [12].

The trend in disease severity has also shifted, with an increased frequency of milder cases due to earlier detection, more effective treatment, and improved preventive measures. An example of effective prevention is the significant reduction in smoking rates. Comparing data from 1990 and 2020, the number of smokers decreased by 27.2% among men and 37.9% among women [13].

The involvement of fibroblasts is fundamental to the pathogenesis of orbitopathy. Mesenchymal stem cells can undergo adipogenesis – a key factor in GO, as well as chondrogenesis and myogenesis. Moreover, it has been shown that osteogenesis and neurogenesis are induced in orbital fibroblasts and orbital mesenchymal stem cells in patients with GO [14].

Orbital fibroblasts are largely positive for CD90 and negative for CD45, which serve as positive and negative markers of mesenchymal stem cells, respectively. Additionally, it has been shown that orbital fibroblasts are more sensitive to inflammation compared to fibroblasts from other areas of the body. One possible cause is the overexpression of CD40, which makes them a target for T lymphocytes.

T lymphocytes play a significant role in the pathomechanism of GO. They exhibit overexpression of TSH receptor (TSHR), which can be activated by anti-TSHR antibodies, leading to the stimulation of adipogenesis in orbital fibroblasts and promoting orbital fat tissue expansion [14].

In addition to orbital fibroblasts, fibrocytes progenitor from bone marrow, which migrate to sites of inflammation and damage, have been identified in the orbit of patients with GO. These fibrocytes have been shown to present 2 main thyroid autoantigens: TSHR and thyroglobulin. Studies have proven that circulating TSHR-Ab levels correlate with GO activity. Furthermore, the concentration of TSHR-Ab may serve as a predictive factor for disease progression and a marker of treatment efficacy [15].

A significant role in the pathogenesis of GO is attributed to the TSHR and insulin-like growth factor 1 (IGF-1) receptors, which are expressed in orbital tissues, with their expression levels markedly elevated in patients with GO. The activation of TSHR likely modulates adipogenesis.

TSHR activation in orbital fibroblasts, mediated through the cAMP–protein kinase A (PKA) signaling pathway and the cAMP response element-binding protein binding sites in the promoters of *HAS1* and *HAS2*, enhances hyaluronan

synthesis. The processes of hyaluronan production and adipogenesis are interrelated in the orbital adipose tissue. During adipogenesis, there is an increase in hyaluronan accumulation, which is not observed in adipose tissue from other anatomical regions [16].

IGF-1 and its receptor (IGF-1R) are critical mediators in the development of orbitopathy. Lymphocytes B and T in patients with GD demonstrate overexpression of IGF-1R, which results in the upregulation of hyaluronan synthesis by ocular fibroblasts. Furthermore, this activation promotes fibroblast proliferation and cytokine secretion. It is hypothesized that IGF-1R activation may be driven by crosstalk between TSHR and IGF-1R. This hypothesis is supported by a study demonstrating a reduction of exophthalmos in patients treated with teprotumumab, suggesting that IGF-1R plays a pivotal role in the pathogenesis of orbitopathy. [17]. The key cytokines and chemokines involved in the development of GD are summarized in the table 1 [17].

TABLE 1

The key cytokines and chemokines involved in the development of GD.

Cytokines and chemokines	Function and role
Th-1	Induces chemotaxis of immune cells. In the early stages of the disease, it leads to inflammation and the recruitment of Th1 cells.
IL-21	Higher levels in patients with GD and HT. Likely plays a key role in the pathogenesis of autoimmune thyroid diseases. Causes an exaggerated immune response.
IL-37	The role in reducing local and systemic inflammation in GD is still unclear. IL-37 levels are closely associated with TSH, FT_3, and IL-17. Patients with GD have significantly higher levels of IL-37 compared to patients in the inactive phase. Research indicates that IL-37 protects against inflammation in GD by reducing the production of pro-inflammatory cytokines.
IL-23	Elevated IL-23 levels have been observed in patients with GD compared to the control group. Studies on IL-23 gene polymorphisms have shown that individuals with a specific IL-23A gene variant have a higher risk of developing GD, making this a potential genetic risk marker.
TNF-α	Assessment of polymorphisms rs1800629 and rs361525 in the TNF-α gene has shown that the homozygous and recessive models are associated with the occurrence of GD.
IL-6	The IL-174 G/C polymorphism is associated with the risk of GD in dominant, recessive, and homozygous models. It has been shown that patients with severe GD had lower levels of methylation at CpG sites 664 and 666 compared to patients in remission, suggesting a relationship between IL-6 gene methylation and treatment resistance.

GD – Graves' disease; FT_3 – free triiodothyronine; HT – Hashimoto's thyroiditis; IL – interleukin; TNF-α – tumor necrosis factor α; TSH – thyroid-stimulating hormone.

GENERAL AND OCULAR SYMPTOMS OF HASHIMOTO'S DISEASE AND GRAVES' DISEASE

The symptoms of Hashimoto's disease are varied and can affect multiple systems. The most common clinical symptoms include fatigue, drowsiness, cold intolerance, constipation, and weight gain. A characteristic feature is myxedema, along with dry, brittle hair and cold, dry skin. Additionally, women may experience menstrual disturbances and infertility, while men may report reduced libido and erectile dysfunction [18].

Ophthalmic symptoms in the course of HT are less typical but they constitute an important aspect of the clinical picture. Their occurrence can be associated both with hypothyroidism and other autoimmune mechanisms accompanying the disease. Thyroid-associated ophthalmopathy (TAO) is one of the main ocular syndromes caused by autoimmune inflammation of the soft tissues of the orbit. 90% of cases are associated with GD, 5% with Hashimoto's disease, and the remaining 5% are found in cases without clinical symptoms of thyroid disease [18].

In HT, one of the most frequent clinical symptoms is dry eye syndrome, which can lead to a burning sensation, itching, or redness of the eyes. Dry eye syndrome and ocular discomfort are significantly more common in patients with HT, even in the absence of TAO [19].

Chronic lymphocytic thyroiditis may be manifested with eyelid edema. The inflammatory process associated with immune system activation may involve orbital tissues, causing localized swelling and fluid retention, which, by affecting the body's metabolism, may lead to fluid retention and edema in the eyelids [18].

There are rare cases of HT presenting with double vision and vision loss [20]. Inflammation of the extraocular muscles can lead to diplopia and other disturbances in ocular motility. Reported symptoms also included eyelid retraction, proptosis, and extraocular involvement [21]. Scientific literature confirms that among atypical ocular symptoms associated with HT, the following are distinguished: TAO, ptosis, reduced color vision, upper eyelid retraction, chemosis, conjunctival prolapse, proptosis (exophthalmos), and lid lag. Typical ophthalmic symptoms include dry keratoconjunctivitis, keratitis, photophobia, and the aforementioned double vision [22].

Thyroid hormones have a broad impact on the body, which makes the symptoms of GD very diverse. Typical symptoms include tremors, heat intolerance, a feeling of warmth, anxiety and irritability, goiter, menstrual cycle disturbances,

erectile dysfunction, decreased libido, fatigue, frequent bowel movements, and palpitations [23].

Ophthalmic symptoms depend on the course of the disease. In the early stages, with mild disease, they are easily overlooked or misdiagnosed. Patients report a foreign body sensation, photophobia, and lacrimation. These symptoms are nonspecific, often leading to confusion with other conditions. Upon examination, moderate periorbital swelling, mild exophthalmos, eyelid retraction, and conjunctival infections may be observed.

In moderate cases, symptoms are more evident. Exophthalmos may be present due to orbital inflammation. There could be conjunctival swelling and hyperemia, corneal diseases, including those related to lid lag, pain induced by eye movements, diplopia, proptosis, and restricted eye mobility [24].

In severe cases, patients may develop optic neuropathy and corneal damage. Increasing orbital tissue swelling can compress the optic nerve, potentially leading to vision loss. Alarm signs that warrant urgent ophthalmologic evaluation include blurred vision or a sudden decline in visual acuity, the presence of scotomas, and deficits in color vision [24].

The disease course can also be divided into the active (inflammatory) phase and the chronic (fibrotic) phase [25]. In the active phase, the dominant symptoms are eye pain, redness, and swelling. The onset of symptoms is acute. Typical clinical features include exophthalmos, periorbital swelling, and eyelid redness.

A common symptom of thyroid eye disease (TED) is dry eye syndrome. This is caused by incomplete blinking and loss of Meibomian glands. Initially, symptoms result from inflammation, but over time, symptoms are mainly due to exposure of the eyeball to the external environment due to eyelid dysfunction [26].

Diplopia in patients with GD results from inflammation and fibrosis of the extraocular muscles. It leads to restricted eye movements. As the inflammatory phase subsides, fibrosis and tissue remodeling intensify. Proptosis becomes permanent, eyelid lag worsens, and keratopathy develops over time.

Patients with GD require regular ophthalmic monitoring, as 40% of them will experience TED. These symptoms should not be overlooked. Changes in the appearance of the patient's face lead to deteriorating mental health and result in a higher suicide rate among patients with TED [26].

Currently, the standard for assessing the activity of GO is the Clinical Activity Score (CAS). This scale evaluates the presence of 7 specific symptoms, assigning one point for each:

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

If a patient scores fewer than 3 points, then is considered to be in the inactive phase, whereas a score of 3 or more points indicates the active phase of GO. The European Group on Graves' Orbitopathy (EUGOGO) is responsible for developing guidelines on grading, severity assessment, prevention, and treatment of GO. It is an interdisciplinary organization dedicated to improving the quality of care and quality of life for patients with GO [27].

DIAGNOSTICS IN THE COURSE OF THE DISEASE (OPHTHALMIC EXAMINATIONS)

Laboratory tests are decisive in diagnosis of Hashimoto's disease. An increased level of anti-TPO antibodies is typically observed. Thyroid hormones (TSH, FT_3, FT_4) are also of significance. It is important to remember that the basis of any diagnosis is a thorough medical history and physical examination, with particular attention to the patient's symptoms. Imaging tests, such as ultrasound, are useful as they help assess the gland's structure and detect inflammatory changes [18].

Although the primary diagnostics focus on evaluating thyroid function, a number of ophthalmic examinations can be valuable in the diagnosis and monitoring of patients, especially when ocular symptoms are present. The medical history and reported symptoms may indirectly indicate chronic lymphocytic thyroiditis.

Ophthalmic examination is crucial, particularly for evaluating TAO: it includes assessment of proptosis using the Hertel exophthalmometer, evaluation of ocular motility, or B-mode ultrasound to assess soft tissue edema within the orbit. In the case of dry eye syndrome, diagnostic tests such as the Schirmer test, tear break-up time (TBUT), and fluorescein or Bengal rose staining are essential to detect epithelial and conjunctival damage.

Vision-related tests, including visual acuity, color vision assessment, and perimetry, are useful as they may reveal visual field defects, decreased visual quality, or possible thyroid neuropathy.

Examination of the anterior segment of the eye, such as slit-lamp biomicroscopy, enables the evaluation of the cornea, conjunctiva and iris for autoimmune changes. Tonometry (intraocular pressure measurement) is an important test for patients with thyroid ophthalmopathy who are at risk of glaucoma.

A fundus examination will allow for the detailed assessment of the retinal vessels and the optic disc, which may show changes due to optic neuropathy.

Although Hashimoto's disease is primarily an endocrine disorder, it may effects multiple systems and organs. Ophthalmic examinations, such as evaluating thyroid ophthalmopathy, assessing visual function, or diagnosing dry eye syndrome, are essential for the systematic monitoring of patients and the implementation of appropriate treatment, which may significantly improve their quality of life.

Tear diagnostics

Tears play a significant role as biomarkers in the diagnosis of GO. A significant advantage of tear diagnostics is the easy accessibility of the material, and that the sampling itself is minimally invasive. In the Shi et al. study involving tear-derived exosomal biomarkers of Graves' ophthalmopathy, samples were collected using the Schirmer test [28]. The study involved patients with active and severe forms of GO, newly diagnosed patients, and a healthy control group. In patients with GO, higher levels of cytokines IL-1β, IL-8, and IL-13 were detected in the tears. IL-1 and IL-18 expression was also significantly higher, with elevated concentrations observed in the serum as well [28].

In the Kishazi et al. study, increased levels of cytokines IL-10, IL-12p70, IL-13, IL-6, and TNF-α (tumor necrosis factor α) were noted [29]. The study also observed varying levels of cytokines depending on the cause of the disease. Regardless of the cause, there was a noticeable increase in IL-10, IL-12p70, and IL-8 cytokines, with significantly higher levels of IL-13, IL-6, and TNF-α in inflammatory TAO with a CAS of 3 or greater.

It was demonstrated that IL-7 plays a key role in the pathogenesis of GO [30]. Significantly higher expression of IL-7 was found in orbital tissue in patients with inactive GO. Unfortunately, IL-7 cannot be used as a marker, as its levels increase only 2 years after the clinical manifestation of the disease.

In the Ujhelyi et al. study, patients with GD and GO, GD without GO, and a healthy control group were compared [31]. Significantly higher levels of IL-1β, IL-6, IL-13, IL-17A, IL-18, TNF-α, and RANTES (regulated on activation, normal t-cell expressed and secreted) were found in GO patients compared to healthy controls. However, no cytokine was identified that could differentiate between patients with GD and GO and those with GD without GO.

Machine learning in diagnostics

DNA methylation allows for changes in gene expression without changing the DNA sequence itself. Modifications in methylation play a critical role in the pathomechanisms of many autoimmune diseases and cancers.

In a study using data from The Gene Expression Omnibus Database, 125 differentially methylated genes (DMGs) associated with GO were identified. The majority of these genes were linked to the differentiation of Th1 and Th2 cells, as well as the regulation of the innate immune response [32].

Biomarkers

The clinical presentation of GD and thyroid-associated orbitopathy is associated with the stimulation of antibodies against the TSHR. Therefore, measuring anti-TSHR antibodies is a valuable tool in the diagnosis and assessment of treatment efficacy in patients with GD/GO. Some studies even suggest that antibody levels may serve as a predictive factor for the onset of GO [8].

IgG4 is also considered as a potential biomarker for GO [33]. Patients with GD and elevated IgG4 levels tend to respond better to antithyroid medications; however, they also tend to experience earlier symptom onset and a more severe disease course. Elevated IgG4 levels are found in approximately 65.8% of patients with GO among all GD patients. It should be noted that elevated IgG4 levels are nonspecific for GD and are also present in allergic, rheumatologic, and oncological diseases.

Facial changes in Graves' orbitopathy

Through the analysis of magnetic resonance imaging (MRI) of the orbits in patients with GO, patients with exophthalmos unrelated to thyroid diseases, and healthy individuals, it was observed that patients with GO exhibit an increase in the volume of the eyebrow fat pad. Subsequent studies also identified an increase in the volume of fat and soft tissues in the temporal fossa. The enlargement of the eyebrow fat pad is noticeable to observers and has a significant impact on quality of life and mental health [34]. Furthermore, a study showed that alterations in facial appearance had a greater negative impact on patients' well-being than visual dysfunction [35].

TREATMENT OF GRAVES' OPHTHALMOPATHY AND HASHIMOTO'S THYROIDITIS

Treatment of Graves' ophthalmopathy among patients with GD according to EUGOGO guidelines is dependent on the activity and severity of the process.

Active and mild disease: antioxidant therapy with selenium (areas with selenium deficiency).

Active moderate-severe disease: high doses of steroids (intravenous administration preferably) as the first-line therapy, either alone or in conjunction with other immunomodulatory therapy such as rituximab, mycophenolate, teprotumumab etc.

Sight-threatening disease: high doses of intravenous steroids and in case of no response orbital decompression surgery performed urgently.

Inactive disease: moderate-severe rehabilitative surgery may be taken into consideration [27].

Quitting smoking and normalization of thyroid hormone levels are recommended. Clinical improvements in orbitopathy are reported after levothyroxine therapy initiation and thyroid hormones level stabilization [36]. Irrespective of disease activity local treatment such as injections of botulinum toxin A and ocular lubrication should be implemented when it is needed [27, 37].
Possible treatment modalities used in Graves' ophthalmopathy are specified below.

Selenium

In GO pathomechanism high oxidative stress plays an important role. Selenium is an antioxidant and immunoregulator [38–40]. It is reported that selenium supplementation leads to overall ocular improvement, better quality of life and prevents progression of the disease. Moreover it exhibits low toxicity [12, 41, 42].

Corticosteroids

Corticosteroids have immunomodulatory and anti-inflammatory effects. They function also in orbital fibroblasts by minimising activation of proinflammatory cytokines [43, 44]. The most frequently reported steroid used to treat GO is methylprednisolone. Unfortunately this therapy has some contraindications and many side-effects [42]. It should be remembered that intravenous therapy is more effective and has less adverse events in comparison to oral administration [45–47]. Results of local administration are appraised as poor [48].

Rituximab

Rituximab is a monoclonal antibody targeting CD20-positive B cells, which play a role in the pathomechanism of Graves' ophthalmopathy [42, 45, 49]. In Salvi et al. randomized study more rituximab patients noticed the improvement of their condition compared to patients using intravenous methylprednisolone, but in different trial no relevant benefit of rituximab compared to placebo was proven [50, 51]. In the majority of cases it is well tolerated [42].

Tocilizumab

Tocilizumab is a monoclonal anti-IL-6 antibody. IL-6 intensifies the inflammation in orbital fibroblasts [52, 53]. Tocilizumab in some small studies were described as effective in patients with glucocorticoid-resistant GO [54–57]. Efficiency of tocilizumab in diplopia and exophthalmos was poor, but it was quite well tolerated [57].

Teprotumumab

Teprotumumab is a monoclonal antibody targeting IGF-1R – receptor which expression is higher in orbital fibroblasts and some other cells, among people suffering from GD [25]. In a few studies there were beneficial effects in patients taking teprotumumab in comparison to placebo such as exophthalmos and clinical activity score diminution, improvement in diplopia score and better quality of life. Teprotumumab is the first medicament presenting such a correction of proptosis [58, 59]. In trials teprotumumab was reported as rather safe but there were also some disturbing side effects noted [42, 45, 59–64].

Orbital radiotherapy

Lymphocytes and fibroblasts in orbit are radiosensitive. Trials show that orbital radiotherapy gives similar results to glucocorticosteroids. What is more, the combination of these two therapies provides better response than using them separately [65–67]. Orbital radiotherapy is also effective in patients resistant to high doses of steroids [42, 45, 68].
The primary treatment for Hashimoto's disease involves thyroid hormone replacement. The main approach is the use of synthetic T_4 to restore euthyroidism. Regular monitoring of TSH and FT_4 levels is crucial to determine the appropriate medication dosage. Stabilizing thyroid function may have an impact on reducing the exacerbation of ophthalmic symptoms. Selenium supplementation may reduce symptoms of TAO.
Treatment of dry eye syndrome, which is a common symptom for patients with Hashimoto's disease, is divided into local and anti-inflammatory treatments. Local treatment focuses on alleviating symptoms through the use of artificial tears and moisturizing ointments to replace the missing tears. In contrast, anti-inflammatory treatment aims to reduce the inflammation of the lacrimal glands using anti-inflammatory eye drops. To reduce eyelid swelling or conjunctivitis, cold compresses, antihistamines, or nonsteroidal anti-inflammatory drugs (NSAIDs) are used.
Optic neuropathy, a rare complication, requires treatment based on the severity of the condition. Mild cases may be treated with lubricating eye drops, while more moderate to severe cases may require immunosuppressive therapy, orbital decompression, or orbital radiotherapy.
Ophthalmic symptoms in Hashimoto's disease are varied. Stabilizing thyroid function and applying appropriate pharmacological treatment are crucial. Ophthalmic evaluation should not be overlooked, as this disease can manifest with a range of ocular disorders.

Surgical treatment

In spite of many options of pharmacotherapy in Graves' ophthalmopathy some patients require surgical intervention using a variety of techniques [69]. According to the EUGOGO guidelines emergency decompensation of the orbit is needed in a vision-threatening condition if the results of corticosteroids therapy are unsatisfactory. Rehabilitative surgery is performed in patients with inactive,

stable disease. Its main focus is to achieve a state similar to normal [42].

Mycophenolate

Mycophenolate is an immunomodulator which suppresses proliferation of lymphocytes B and T as well as antibody production and expression of adhesion molecules. Its effectiveness in Graves' ophthalmopathy was reported both in monotherapy and in conjunction with corticosteroids and treatment is considered as well tolerated [45, 70, 71].

Cyclosporine

Cyclosporine is an immunosuppressant with beneficial treatment in GO if used in combination with oral prednisone, however less effective in monotherapy [45, 72, 73].

Prognosis

The prognosis for Graves' ophthalmopathy is dependent on many factors such as duration and amplitude of changes in the eye, its function and complications in the course of the disease [74].

CONCLUSIONS

Although ophthalmic symptoms, particularly ophthalmopathy associated with autoimmune thyroid diseases, are most commonly linked to GD and hyperthyroidism, they can also occur in patients with Hashimoto's disease and hypothyroidism. The significant similarity and low specificity of ocular manifestations present in both conditions may pose diagnostic challenges. Therefore, conducting thorough examination is crucial to establishing an accurate diagnosis and, consequently, implementing appropriate treatment.

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