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Thyroid disease and associated ophthalmopathy

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Abstract

Thyroid-associated ophthalmopathy is a complex pathology most of the time accompanying Graves' disease, also present in other thyroid states, such as Hashimoto's hypothyroidism and euthyroid states. The term Grave's disease associated ophthalmopathy can be misleading as it does not include all thyroid states associated to this eye condition. Its pathophysiology includes complex autoimmune mechanisms associated with fibroblasts, T-lymphocytes, myocytes, thyroid cells, adipocytes, and pro-inflammatory molecules, leading to several changes in the orbital content, including limitation of space, functional impairment, and complications secondary to the initial process. Reviewing its diagnostic methods and treatments is necessary due to new insights into the pathophysiology. The complexity of its pathogenesis is accompanied by a practical assessment and classification that allows clinicians to obtain significant amount of success when treating it.

Keywords: *Thyroid. Ophthalmopathy. Orbitopathy. Hypothyroidism. Graves'. Cancer.*

Introduction

Thyroid disease is one of the most frequent conditions in endocrinology disturbances. Several alterations of the physiology of the thyroid can occur: infectious processes, autoimmune mechanisms, cancer, pituitary/hypothalamic alterations, and dietary deficiencies. In many cases, the thyroid affection leads to a myriad of multisystemic manifestations that will lead to the diagnosis, while in others, there is a subclinical alteration. One of these common manifestations is the thyroid-associated ophthalmopathy, described by some, only as Graves' disease associated ophthalmopathy or thyroid disease associated ophthalmopathy. The term Grave's disease associated ophthalmopathy can be misleading as it does not include other thyroid states such as hypothyroidism and subclinical thyroid conditions.

Not all pathogenesis mechanisms in thyroid disease associated ophthalmopathy have been understood. A series of inflammatory phenomenon, many times related to autoimmune mechanisms, lead to several changes in the orbital content, resulting in alterations that can be explained by limitation of space, functional impairment, and complications secondary to the initial process. These ophthalmic manifestations can result in a severe, life-changing impairment for the patient that not necessarily will correct or regress with initial treatment and thus require careful review by specialized and general practitioners.

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Etiology

Autoimmune mechanisms are the most frequent processes in thyroid diseases. Other etiologies, such as nutritional deficiencies, radiation exposure, and genetic factors, can also be present. In the specific scenario of thyroid-associated ophthalmopathy, it is mainly present in cases of Graves' disease, but can also be present in thyroid cancer, hypothyroid states such as Hashimoto's thyroiditis and subclinical hypothyroidism[1,2].

Graves' disease is an autoimmune disorder in which there is a failure in tolerance to autoantigens, especially to the thyroid-stimulating hormone (TSH) receptors in the thyroid gland. This leads to the formation of multiple auto-antibodies[3]. In Hashimoto's thyroiditis, there is also a failure of tolerance to autoantigens, with the formation of auto-antibodies against thyroglobulin and thyroid peroxidase. Both Hashimoto's thyroiditis and Graves' disease share common autoimmune backgrounds and their manifestations are strongly associated to genetic factors. Moreover, the development of thyroid-associated ophthalmopathy is also associated to autoimmune mechanisms[3]. These mechanisms are not absolutely understood and constitute an important field of study in ophthalmology and endocrinology, it is considered that the shared autoimmune mechanism is the main factor by which thyroid-associated ophthalmopathy develops.

Pathophysiology

The TSH receptor is mainly expressed in epithelial cells of follicles in the thyroid gland. An important issue is the presence of TSH receptor in both thyroid tissue and orbit tissue. It is known the TSH receptor and auto-antibodies against it, plays a role both in thyroid Graves' disease and Hashimoto's hypothyroidism. The expression of the TSH receptor in the orbit is present in connective tissue: fibroblasts and adipocytes, but can also be expressed in other cells and organs, such as lymphocytes, thymus, pituitary, testis, kidney, heart, and bone[4].

An increase of connective tissue in the orbit when thyroid-associated ophthalmopathy is present manifests clinically in proptosis and other symptoms[5]. It is considered that the main target of the autoimmune attack in the orbit is against the TSH receptor expressed by the fibroblasts[6]. When evaluating the increase of the orbital tissue with computed tomography scan, the majority of patients have an enlargement in both the orbital fat and the extraocular muscles, however in a lower subset, there is an increase in just one or the other[6].

There is increasing evidence that other antigenic targets are involved in the pathophysiology, mainly calsequestrin 1 (CASQ1), an orbital muscle calcium-binding protein; and collagen XIII, expressed by orbital fibroblasts[7]. It is considered that the TSH receptor might be the initial target and the autoimmune reaction against CASQ1 and collagen XIII a continuation of it. The sub-portion G2s of the transcription factor FOX-P1 and flavoproteins, both present in orbital muscle, are also considered targets to autoantibodies in the subsequent process of inflammation[7,8].

Failure of tolerance toward autoantigens in the orbital tissue leads to the activation of t-lymphocytes by antigen presenting cells. T-lymphocytes, production of pro-inflammatory substances (interleukin [IL]1-β, IL-6, IL-8, and PGE_2), migration of B-lymphocytes, and production of autoantibodies ultimately lead to production and deposition of glycosaminoglycans in the orbital tissue as well as adipocytes hyperplasia[9] that will generate the characteristic clinical signs in thyroid-associated ophthalmopathy. This inflammatory process will involve the orbit connective tissue as well as the extraocular muscles of the eye, with remodeling of the orbit[10].

Remodeling in the orbit will lead to a series of subsequent changes that will affect the functionality and image of the organ. These subsequent manifestations can easily be understood by the presence of the inflammatory process and the mechanical effect of the remodeling, and can include visual alterations due to changes in the cornea, eye pain, eyelid retraction, and restricted eye movement, among others (see clinical manifestations).

The association of reactive oxygen species in the development of the disease explains its association to factors such as smoking. It has been demonstrated that the presence of oxidative markers in tears and urine, including 8-hydroxy-2′-deoxyquanosine and malondialdehyde (urine only), is higher in patients with thyroid-associated ophthalmopathy and correlates to the clinical activity of the disease[11,12]. It is logical to conclude that the presence of this oxidative stress is to a great degree associated to the presence of the inflammatory process itself. The exact mechanism by which these reactive species enhance the disease activity has not yet been fully elucidated.

Epidemiology

The most frequent cause of thyroid alterations is iodine deficiency; when not associated to iodine

deficiency, autoimmune diseases of the thyroid are the second major cause of alterations. In the case of Graves' disease, it is the most frequent cause of thyrotoxicosis, more frequent in women than in men (0.4 cases/1000 vs. 0.1 cases/1000)[13], and its peak of incidence is greater between 20 and 50 years old[3,13]. Hashimoto's hypothyroidism is the most frequent cause of thyroid disease in places with sufficient iodine in diet. It is also more frequent in women than in men (10-20/1) and with a peak of cases between ages 45 and 65 years old[3,13].

Thyroid ophthalmopathy is more frequent in women than in men (5:1), it can be detected in even 50% of patients with diagnosed Graves' disease, even though it can be more severe in men[2,5,14]. The vast majority of cases are related to Graves' disease, a minor percentage of cases can also be associated to Hashimoto's hypothyroidism, subclinical hypothyroidism, euthyroid states, and even thyroid cancers.

It is difficult to describe the worldwide prevalence of thyroid-associated ophthalmopathy due to lack of research and publications in many regions. A systematic review of prevalence of thyroid function in patients already diagnosed with thyroid-associated ophthalmopathy found 86.2% prevalence with hyperthyroidism; 10.36% prevalence with hypothyroidism; and 7.9% with euthyroid states, (studies were mainly in Wales, the United States, Iran, Spain, Singapore, Ghana, Germany, Korea, and Japan)[15].

Smoking is a major risk factor for the development of thyroid-associated ophthalmopathy, evidence suggest that active smokers are at increased risk than former smokers, making it logical to recommend smoking cessation to patients[16], additionally, chronic smokers treated with radioiodine are at increased risk of developing thyroid ophthalmopathy[17]. The specific mechanism by which inflammatory substances such as IL-1, IL-6, and processes such as adipogenesis and hyaluronic acid production increase with exposure to cigarette smoking has not been fully described yet and constitutes an important field of research[17,18].

Clinical manifestations

Clinical manifestations in thyroid disease, as a systemic pathology, are broad. Thyroid ophthalmopathy can exist without systemic manifestations of thyroid disease or even, without overt thyroid dysfunction, thus a cautious analysis of each case is required. Even though rare, symptoms of thyroid ophthalmopathy, such as proptosis, diplopia, pain, and conjunctival erythema, can be the initial and only manifestations referred by the patient, even in pediatric cases[19,20]. Probably, the most striking symptoms in thyroid ophthalmopathy are eyelid retraction and proptosis with an enlargement of the palpebral cleft. Giving the face a typical appearance described in classic medical literature as a surprised face or scared face[21].

Signs and symptoms are usually insidious in appearance and include proptosis, diplopia, periocular and eyelid edema (more prominent in the morning), periocular hyperpigmentation, and increased size in lacrimal gland, which can possibly evolve to decline in its function. Other manifestations are corneal and conjunctival damage, in some cases with progression to corneal ulceration and subsequent blurred vision; sensation of a foreign body and increased tearing; and sensation of retroocular pressure and pain with eye movement, which is an indicator of disease activity. Optic nerve damage can be present, with manifestations varying from chromatic perception alterations to scotomas[5,22,23]. Due to similar symptoms observed in other eye diseases, the differential diagnosis includes allergic conjunctivitis, myasthenia gravis, orbital tumors, inflammatory orbitopathies related to autoimmune processes, and some myopathies[24].

Thyroid ophthalmopathy is often initiated by a clinically active phase followed by a non-active phase. The clinical activity of the disease is not always related to the severity or degree of its progression. At present, two systems are used for its classification to make adequate management decisions: the Vision, Inflammation, Strabismus, and Appearance (VISA) and European Group of Graves' Orbitopathy (EUGOGO) classifications. The VISA considers presence or absence of caruncular edema; conjunctival redness; lid redness; retrobulbar ache with rest and gaze; diurnal variation; and the level of chemosis and lid edema. Scores help deciding between conservative and aggressive treatment.

The EUGOGO classification assesses the activity and severity of the disease using 10 items, including: degree of eyelids swelling/erythema, degree of conjunctival redness/edema, degree of inflammation of caruncle or plica semilunaris; eyelid functionality measurements (palpebral retraction, upper/lower lid retraction, and the presence or absence of lagophthalmos or Bell's phenomenon); degree of proptosis; integrity of the cornea; ocular motility; and presence of optic neuropathy[19].

Treatment and prognosis

Treatment is based on activity and severity; severity means the level of functional impairment, which in the

moment of the evaluation, can be accompanied or not by clinically active disease. According to the EUGOGO classification, mild forms of the disease should be managed with follow-up and lubricants to relieve symptoms. Moderate-to-severe forms with clinical activity require added treatment with corticosteroids or other immunosuppressants and possibly, radiotherapy. Intravenous corticosteroids are the most common, first-line treatment, notable for better outcomes than oral route. Radiotherapy can be used to improve management. However, it is often times not used in relatively moderate cases mainly due to its possible side effects. If the disease is not active at time of evaluation, then surgery can be offered.

In sight-threatening category, the first line of treatment is intravenous corticosteroids or other immunosuppressant therapy as needed; with orbital decompression or corrective surgery being offered to patients with inadequate response to medication or inactive forms of the disease[25-27]. It is important to note that treatment with radioiodine implies a risk of progression of thyroid orbitopathy in patients with Graves' disease[17].

Novel treatments that are currently being explored include the use of selenium, small-molecule ligand antagonists for the TSH receptor stimulatory antibodies and the use of teprotumumab (an IGF-1 receptor blocker), tocilizumab (IL-6 receptor antagonist), and rituximab (Anti-CD20 monoclonal antibody), especially for corticosteroids resistant cases[28-30].

Teprotumumab has recently being compared against placebo in patients with active thyroid ophthalmopathy, showing better proptosis response, as well as better scores in secondary outcomes assessing disease activity and severity[31]. There is an increased likelihood that with better understanding of the pathophysiology more specific molecular targeted treatments will become available.

Adequate management should also address thyroid disease itself. As previously stated, ophthalmopathy can be present in different thyroid scenarios, therefore, the accompanying treatment will depend on the main stem disease. In hypothyroidism, treatment would include adequate levothyroxine supplementation. In hypothyroidism, treatment would include adequate levothyroxine supplementation; in hyperthyroid states treatment will include symptomatic management with beta-blockers, antithyroid medications (methimazole, propylthiouracil), radioactive ablation and surgery in certain cases.

In many cases, thyroid-associated ophthalmopathy is non-progressive and significantly improves with adequate treatment. Unfortunately, in the vast majority of cases, there is not a complete resolution of the case, with only very few patients being actually considered thyroid ophthalmopathy free after any kind of treatment[32].

Conclusion

Thyroid ophthalmopathy should be considered mainly as an autoimmune chronic process, associated to several different factors not yet well understood. Research in modifiable risk factors, specially smoking cessation, continues to be an important issue that will probably help us better comprehend this condition. In recent years, an increased understanding of its pathophysiology has allowed us to better assess it and significantly improve the life quality of patients. Even though complete regression of the symptoms is most of the time not achievable, novel immunomodulatory and non-immunomodulatory therapies are being explored.

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References

1. Szczapa-Jagustyn J, Gotz-Więckowska A, Kocięcki J. An update on thyroid-associated ophthalmopathy in children and adolescents. J Pediatr Endocrinol Metab. 2016;29:1115-22.
2. Şahlı E, Gündüz K. Thyroid-associated ophthalmopathy. Turk J Ophthalmol. 2017;47:94-105.
3. Maitra A. Endocrine System; On: Robbins and Cotran: Structural and functional pathology [Patología estructural y funcional]. Kumar V, Abbas A, Fausto N, Aster J, (Eds.) ElSevier 8th Edition, Barcelona, Spain, 2010, pp. 1097-1164.
4. Davies T, Marians R, Latif R. The TSH receptor reveals itself. J Clin Invest. 2002;110:161-4.
5. Fernández Hermida RV, Pinar S, Muruzábal N. Clinical manifestations of thyroid ophthalmopathy. An Sist Sanit Navar. 2008;31 Suppl 3:45-56.
6. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. Am J Ophthalmol. 2006;142:147-53.
7. Wall JR, Lahooti H. Pathogenesis of thyroid eye disease – Does autoimmunity against the TSH receptor explain all cases? Endokrynol Pol. 2010;61:222-7.
8. Lahooti H, Parmar KR, Wall JR. Pathogenesis of thyroid-associated ophthalmopathy: does autoimmunity against calsequestrin and collagen XIII play a role? Clin Ophthalmol. 2010;4:417-25.
9. Huang Y, Fang S, Li D, Zhou H, Li B, Fan X. The involvement of T cell pathogenesis in thyroid-associated ophthalmopathy. Eye (Lond). 2019;33:176-82.
10. Kamboj A, Lause M, Kumar P. Ophthalmic manifestations of endocrine disorders-endocrinology and the eye. Transl Pediatr. 2017;6:286-99.
11. Choi W, Li Y, Ji YS, Yoon KC. Oxidative stress markers in tears of patients with Graves' orbitopathy and their correlation with clinical activity score. BMC Ophthalmol. 2018;18:303.
12. Tsai CC, Cheng CY, Liu CY, Kao SC, Kau HC, Hsu WM, et al. Oxidative stress in patients with Graves' ophthalmopathy: relationship between oxidative DNA damage and clinical evolution. Eye (Lond). 2009;23:1725-30.
13. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39-51.
14. Smith TJ, Hegedüs L. Graves' disease. N Engl J Med. 2016;375:1552-65.
15. Muñoz-Ortiz J, Sierra-Cote MC, Zapata-Bravo E, Valenzuela-Vallejo L, Marin-Noriega MA, Uribe-Reina P, et al. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. Syst Rev. 2020;9:201.
16. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid. 2010;20:777-83.
17. Bartalena L, Piantanida E. Cigarette smoking: number one enemy for Graves ophthalmopathy. Pol Arch Med Wewn. 2016;126:725-6.
18. Cawood TJ, Moriarty P, O'Farrelly C, O'Shea D. Smoking and thyroid-associated ophthalmopathy: a novel explanation of the biological link. J Clin Endocrinol Metab. 2007;92:59-64.
19. Santos M, Martínez N. Thyroid ophthalmopathy as initial and sole clinical manifestation of Graves' disease in a patient of school age. Rev Esp Endocrinol Pediatr. 2013;4:87-92.
20. Pokhrel B, Bhusal K. Graves disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
21. Surós Forns J, Surós Batlló J, Surós A. Endocrine System; On: Medical semiology and exploratory technique [Semiología médica y técnica exploratoria]. Salvat. 6th Edition, Barcelona, Spain, 1978, pp. 707-748.
22. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. J Ophthalmol. 2015;2015:249125.
23. Maciques J, Cáceres M. Thyroid orbitopathy. Rev Cubana Endocrinol. 2012;23:225-33.
24. Perros P, Neoh C, Dickinson J. Thyroid eye disease. BMJ. 2009;338:b560.
25. San Miguel I, Arenas M, Carmona R, Rutllan J, Medina-Rivero F, Lara P. Review of the treatment of Graves' ophthalmopathy: the role of the new radiation techniques. Saudi J Ophthalmol. 2018;32:139-45.
26. Tu X, Dong Y, Zhang H, Su Q. Corticosteroids for Graves' ophthalmopathy: systematic review and meta-analysis. Biomed Res Int. 2018;2018:4845894.
27. Savku E, Gündüz K. Diagnosis, follow-up and treatment results in thyroid ophthalmopathy. Turk J Ophthalmol. 2015;45:156-63.
28. Topliss DJ. Clinical update in aspects of the management of autoimmune thyroid diseases. Endocrinol Metab (Seoul). 2016;31:493-9.
29. Perros P. A decade of thyroidology. Hormones (Athens). 2018;17:491-5.
30. Silkiss RZ, Paap MK, Roelofs KA, Agi J, Weis E. Treatment of corticosteroid-resistant thyroid eye disease with subcutaneous tocilizumab. Can J Ophthalmol. 2021;56:66-70.
31. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020;382:341-52.
32. Sabini E, Leo M, Mazzi B, Rocchi R, Latrofa F, Nardi M, et al. Does graves' orbitopathy ever disappear? Answers to an old question. Eur Thyroid J. 2017;6:263-70.