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Review

EXTRINSIC EYE MUSCLE IMPAIRMENT IN BASEDOW'S DISEASE: A BRIEF REVIEW ON MOLECULAR MECHANISMS

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ABSTRACT

The thyroid gland is the main target of Basedow's disease or Graves' disease (GD), an autoimmune condition. It is the most typical cause of hyperthyroidism and affects people of all ages, notably fertile women. A brief review has been conducted to consider the impairment of eye muscles in Basedow's disease. A search operation was performed using PubMed, Science Direct and Research Gate databases. Some relevant articles were also collected from Google Scholars as well. Although thyroid-associated ophthalmopathy is an autoimmune disorder, the exact cause of the condition is unknown. GD links genetic variables with immune system dysregulation and the interplay between genetic and environmental factors. The pathophysiology of the disease involves autoimmune responses to suspected thyroid and orbital antigens. As a result, extraocular muscles, orbital connective tissues, and fat tissues have larger volumes.

KEYWORDS: *Basedow's disease, eye muscle, hyperthyroidism, exophthalmos, immune system dysregulation*

INTRODUCTION

One of the most frequent causes of exophthalmos is that caused by Graves' disease, an autoimmune condition that frequently affects the thyroid, skin, and eyes. The thyroid is a neck gland, a member of the endocrine system, a group of glands that release hormones able to control the body's metabolic processes and functions, along with blood pressure, core temperature, and heart rate. Goiter, an "abnormal enlargement of the thyroid", and excessive thyroid hormone production are symptoms of Graves' disease (1, 2).

Grave's disease is the most typical cause of hyperthyroidism and affects people of all ages, notably fertile women. In honour of Karl von Basedow, who first characterised an exophthalmic goitre in 1840, it is also referred to as "Basedow's

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disease" in German- and French-speaking nations. In English-speaking nations, it is referred to as "Graves' disease" in honour of Dubliner Robert Graves, who first described it in 1834 (3).

Thyroid eye disease can eventually manifest in certain Basedow's disease patients. People with or without an overactive thyroid (hyperthyroidism) less frequently develop thyroid eye disease. However, it can also happen to persons with hypothyroidism, including those who suffer from Hashimoto's thyroiditis. Long-standing mystery mechanisms are now acknowledged and linked to the emergence of auto-antibodies that stimulate thyroid proliferation and secretion. Its characterisation is not entirely clear, though (4).

Epidemiology

Men are more likely to experience severe ophthalmopathy, while women are 2.5–6 times more likely to have thyroid-associated ophthalmopathy (TAO). The disease often manifests at around 30 and 50 years of age, followed by a more severe course. According to reports, ophthalmopathy affects 25%–50% of Basedow's disease sufferers and 2% of "Hashimoto's thyroiditis" patients. These patients' rates of severe ophthalmopathy range from 3 to 5%. After 18 months of receiving a Basedow's disease diagnosis, most individuals experience ophthalmopathy. Nevertheless, development of ophthalmopathy can occur up to 10 years before and up to 20 years after the commencement of the thyroid disorder (5).

Pathogenesis

TAO is considered an autoimmune condition, although the pathophysiology is not fully understood. It is known that antigens shared by the thyroid gland and the orbit cause autoimmunity. Some researchers concur that the TSH receptor is a universal pathogenetic antigen. However, researchers discovered a 64-kDa protein shared by the orbit and the thyroid gland (5). According to recent investigations, the "cardiac calsequestrin gene" has been upregulated in TAO patients. They have hypothesised that autoimmunity to calsequestrin could be a pathogenic trigger for ophthalmopathy (6). Given a strong association between ophthalmopathy and TSH receptor antibodies, autoantibodies against the "orbital fibroblast membrane antigen collagen XIII" were also discovered.

The orbit and "extraocular muscle perimysium" are invaded by reactive T lymphocytes identifying thyroid-orbit common antigens. Circulating as well as local adhesion molecules that are activated by cytokines boost interaction. T-cell receptors on CD4+ T lymphocytes identify the common antigen succeeding T helper (Th) lymphocyte infiltration of the orbit. The immune response is strengthened by the cytokines that Th lymphocytes make, which stimulate CD8+ lymphocytes and B cells that produce antibodies (7). These cytokines encourage fibroblasts to produce and secrete glycosaminoglycans (GAGs) (8). GAGs cause swelling of the extraocular muscles, proptosis, and periorbital oedema due to their ability to collect water. The enlargement of the orbital contents is also aided by cytokine-induced fibroblast proliferation (9). Preadipocytes are found in orbital fibroblasts and are stimulated by hormones to become adipocytes. It has been established that these cells help to enhance the amount of retroorbital fat tissue (10).

Recent research has shown that immune system genetics and thyroid autoantibodies play a significant part in determining the beginning of ophthalmopathy and defining its severity after it has occurred. In cases of ophthalmopathy, frequencies of anti-Thrombopoietin (TPO) antibody and anti-Tyreoglobulin (TG) positive of 90% and 50%, correspondingly, have been recorded (11).

Genetic and environmental elements are reported to have a role in the etiopathogenesis of thyroid ophthalmopathy in combination with autoimmunity.

Genetic factors

Numerous research has looked into how genetics may play a part in the onset of ophthalmopathy (12). In research analysing the ocular and palpebral results of first and second-degree relatives of individuals diagnosed with TAO, Basedow's disease, and Hashimoto's thyroiditis, 33% of euthyroid relatives had TAO symptoms like upper eyelid retraction. It has been estimated that 79% of the chance of getting Basedow's disease is determined by heredity, and environmental variables influence 21%. Twin studies have revealed that perhaps the incidence of Basedow's disease is up to 30% in monozygotic twins (13, 14).

Numerous investigations have documented polymorphisms in the genes that encode thyroid-specific proteins such as TG and immune system protein genes like interleukin (IL)-2RA, PTPN22, CD40, CTLA 4, FCRL3, and IL-23R. Patients

with TAO have been found to have "single-nucleotide polymorphisms (SNPs)" in the "tyrosine phosphatase gene" that regulates the TSH receptor, as well as the genes for the inflammatory cytokines IL-13, IL-21, and IL-23. The progression and starting age of ophthalmopathy has been linked to NF-κB1 gene polymorphism, a transcription regulator (15).

The HLA-DRB1 allele was shown to be associated with extraocular muscle engagement in a study examining the link between "MHC class II human leukocyte antigen (HLA) alleles" and ophthalmopathy (16). Twenty-four SNPs found in the NRXN3 and ARID5B genes have been linked to Basedow's disease and may also control fat deposition (17). It has been demonstrated that individuals with autoimmune thyroid illness were more likely to have a nucleotide alteration in a TG gene promoter linked to interferon-alpha (IFNα). The attachment of "IFN regulatory factor-1" to the "variant TG promoter" by IFNα directly influenced the gene expression driving thyroid autoimmunity (18). A genetic marker for TAO was suggested for the "calsequestrin-1 gene" in additional studies (19, 20).

Environmental factors

Environmental triggers such as stress, viral diseases, iodine, IFN and interleukin therapy, and sex hormones may cause ophthalmopathy in people who carry the relevant genes (21).

Infections

By promoting the expression of "costimulatory molecules" like MHC class II or by changing how their own proteins are presented, bacteria can cause an inflammatory response. Even though there are findings in the literature connecting "Yersinia enterocolitica infection" and "human foamy virus" to Basedow's disease, causative linkages could not be shown (22).

Smoking

Each patient's TAO progresses differently. Severe illness is more likely to affect men and smokers. In a trial of 59 untreated individuals with mild conditions who were followed for a year, 13.5% of patients experienced worsening of their clinical condition. Additionally, it is well-known that extraocular muscle augmentation is more common in older patients, while orbital fat expansion is more common in younger individuals (23).

A proposed mechanism by which smoking may contribute to disease progression and potentially serious clinical manifestations is that "hypoxic cell culture conditions" enhance adipogenesis in ocular fibroblasts (24). Additionally, studies on children with TAO have revealed that passive or second-hand smoking exposure can exacerbate Basedow's disease and may exacerbate ophthalmopathy (25, 26). The link between smoking and poorer clinical outcomes, including an increased chance of blindness, should be explained to all smokers. Additionally, during clinic visits, the significance of quitting smoking should be highlighted. Furthermore, smoking causes the treatment for ophthalmopathy to be delayed and to work less effectively (5).

Standard treatments and therapies

A group of experts, general endocrinologists, ophthalmologists and surgeons may need to work together to provide treatment. They must develop and offer a treatment plan in a methodical, thorough manner. Support on the psychosocial front is also crucial.

Medical devices

Some patients with mild thyroid eye conditions may get supportive care in the form of artificial tears, ointments, dark shades to reduce light sensitivity or prisms that are fitted to spectacles. Double vision can be fixed with prisms. To prevent double vision, some patients may use eyepatch.

Teprotumumab

Teprotumumab, the first medication authorised to treat thyroid eye disease, was given FDA approval in January 2020. The protein "insulin-like growth factor-1", which is thought to be a key player in the emergence of the disease, is inhibited (or blocked) by teprotumumab. When consuming teprotumumab, affected people have demonstrated a considerable improvement in double vision, proptosis, and general quality of life.

Corticosteroids

Corticosteroids, which do not decrease diplopia and proptosis but decrease inflammation and oedema, may be administered to patients with moderate-to-severe conditions. Prednisone is a typical corticosteroid often used to treat people with thyroid eye disease.

Surgery

Surgery might eventually be needed for some people with moderate to severe illnesses. Surgery is typically postponed until after the disease's aggressive phase has passed; however, if doctors believe that a patient's vision is in danger due to the disease's development during the active period, surgery may be required.

Orbital decompression, lid surgery, and motility are among the surgical alternatives. Proptosis, or protruding eyes, and retraction of the eyelids can both be improved surgically. In order to lessen or get rid of double vision, motility surgery requires moving muscle attachments around the eyes.

CONCLUSION

A condition that impairs eyesight and is debilitating is thyroid-related orbitopathy. The pathophysiology is not yet fully understood. TAO, however, is thought to be an inflammatory condition. The symptoms and indicators of TAO should be discussed with patients who have thyroid problems. Surgery is still necessary for serious diseases that endanger eyesight and are resistant to medical treatment and restorative care while the illness is dormant.

A person's facial features may change noticeably due to thyroid eye disorder, which is not totally curable. Individuals with the disease frequently experience depression, and cosmetic changes can significantly worsen mental trauma. People with thyroid eye illness are advised to include a psychologist in their treatment plan to work with the afflicted people both during and after treatment.

The management of TAO has changed a lot and will keep changing. With the introduction of forthcoming biologic medicines and targeted therapy, we predict considerable progress in the care of TAO patients.

REFERENCES

1. Davies TF, Andersen S, Latif R, et al. Graves' disease. *Nature Reviews Disease Primers*. 2020;6(1):1-23. doi:10.1038/s41572-020-0184-y
2. Kahaly GJ. Management of Graves Thyroidal and Extrathyroidal Disease: An Update. *The Journal of Clinical Endocrinology & Metabolism*. 2020;105(12):3704-3720. doi:10.1210/clinem/dgaa646
3. Wémeau JL, Klein M, Sadoul JL, Briet C, Vélayoudom-Céphise FL. Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors. *Annales D'endocrinologie*. 2018;79(6):599-607. doi:10.1016/j.ando.2018.09.002
4. Wiersinga WM, Kahaly GJ, eds. *Raves' Orbitopathy: A Multidisciplinary Approach-Questions and Answers*. Karger Medical and Scientific Publishers; 2017.
5. Şahlı E, Gündüz K. Thyroid-associated Ophthalmopathy. *Turkish Journal of Ophthalmology*. 2017;47(2):94-105. doi:10.4274/tjo.80688
6. Wu L, Zhou R, Diao J, et al. Differentially expressed circular RNAs in orbital adipose/connective tissue from patients with thyroid-associated ophthalmopathy. *Experimental Eye Research*. 2020;196:108036. doi:10.1016/j.exer.2020.108036
7. Shen J, Li Z, Li W, et al. Th1, Th2, and Th17 Cytokine Involvement in Thyroid Associated Ophthalmopathy. *Disease Markers*. 2015;2015:e609593. doi:10.1155/2015/609593
8. Łacheta D, Miśkiewicz P, Głuszko A, et al. Immunological Aspects of Graves' Ophthalmopathy. *BioMed Research International*. 2019;2019:1-12. doi:10.1155/2019/7453260
9. Dik WA, Virakul S, van Steensel L. Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. *Experimental Eye Research*. 2016;142:83-91. doi:10.1016/j.exer.2015.02.007

10. Taylor PN, Zhang L, Lee RWJ, et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. *Nature Reviews Endocrinology*. 2019;16(2):104-116. doi:10.1038/s41574-019-0305-4
11. Khong JJ, McNab AA, Ebeling PR, Craig JE, Selva D. Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. *British Journal of Ophthalmology*. 2016;100(1):142-150. doi:10.1136/bjophthalmol-2015-307399
12. Mishra S, Maurya VK, Kumar S, Ankita, Kaur A, Saxena SK. Clinical Management and Therapeutic Strategies for the Thyroid-Associated Ophthalmopathy: Current and Future Perspectives. *Current Eye Research*. 2020;45(11):1325-1341. doi:10.1080/02713683.2020.1776331
13. Du J, Wang X, Tan G, et al. Predisposition to Graves' disease and Graves' ophthalmopathy by genetic variants of IL2RA. *Journal of Molecular Medicine*. 2021;99(10):1487-1495. doi:10.1007/s00109-021-02111-0
14. González-García A, Sales-Sanz M. Treatment of Graves' ophthalmopathy. Tratamiento de la oftalmopatía de Graves. *Med Clin (Barc)*. 2021;156(4):180-186. doi:10.1016/j.medcli.2020.07.031
15. Chen DP, Chu YC, Wen YH, Lin WT, Hour AL, Wang WT. Investigation of the Correlation between Graves' Ophthalmopathy and CTLA4 Gene Polymorphism. *Journal of Clinical Medicine*. 2019;8(11):E1842. doi:10.3390/jcm8111842
16. Shin DH, Baek IC, Kim HJ, et al. HLA alleles, especially amino-acid signatures of HLA-DPB1, might contribute to the molecular pathogenesis of early-onset autoimmune thyroid disease. *PloS One*. 2019;14(5):e0216941. doi:10.1371/journal.pone.0216941
17. Carballo MCS, de Sá BPC, Rocha DRTW, Arbex AK. Pathophysiology of Graves' Ophthalmopathy: A Literature Review. *Open Journal of Endocrine and Metabolic Diseases*. 2017;07(01):77-87. doi:10.4236/ojemd.2017.71008
18. Mammen JS, Ghazarian SR, Rosen A, Ladenson PW. Patterns of Interferon-Alpha–Induced Thyroid Dysfunction Vary with Ethnicity, Sex, Smoking Status, and Pretreatment Thyrotropin in an International Cohort of Patients Treated for Hepatitis C. *Thyroid*. 2013;23(9):1151-1158. doi:10.1089/thy.2012.0565
19. Lahooti H, Cultrone D, Edirimanne S, et al. Novel single-nucleotide polymorphisms in the calsequestrin-1 gene are associated with Graves' ophthalmopathy and Hashimoto's thyroiditis. *Clinical Ophthalmology (Auckland, NZ)*. 2015;9:1731-1740. doi:10.2147/OPTH.S87972
20. Lombardi A, Menconi F, Greenberg D, et al. Dissecting the Genetic Susceptibility to Graves' Disease in a Cohort of Patients of Italian Origin. *Frontiers in Endocrinology*. 2016;7:21. doi:10.3389/fendo.2016.00021
21. Antonelli A, Ferrari SM, Ragusa F, et al. Graves' disease: Epidemiology, genetic and environmental risk factors and viruses. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2020;34(1):101387. doi:10.1016/j.beem.2020.101387
22. Dittfeld A, Gwizdek K, Michalski M, Wojnicz R. A possible link between the Epstein-Barr virus infection and autoimmune thyroid disorders. *Central European Journal of Immunology*. 2016;3:297-301. doi:10.5114/ceji.2016.63130
23. Ben Simon GJ, Katz G, Zloto O, Leiba H, Hadas B, Huna-Baron R. Age differences in clinical manifestation and prognosis of thyroid eye disease. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*. 2015;253(12):2301-2308. doi:10.1007/s00417-015-3156-2
24. Eckstein A, Dekowski D, Führer-Sakel D, Berchner-Pfannschmidt U, Esser J. Endokrine Orbitopathie. *Der Ophthalmologe*. 2016;113(4):349-366. doi:10.1007/s00347-016-0239-3
25. Hodgson NM, Rajaii F. Current Understanding of the Progression and Management of Thyroid Associated Orbitopathy: A Systematic Review. *Ophthalmology and Therapy*. 2019;9:21-33. doi:10.1007/s40123-019-00226-9
26. Jarusaitiene D, Verkauskiene R, Jasinskas V, Jankauskiene J. Predictive Factors of Development of Graves' Ophthalmopathy for Patients with Juvenile Graves' Disease. *International Journal of Endocrinology*. 2016;2016:1-9. doi:10.1155/2016/8129497