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Thyroid Eye Disease: A Comprehensive Review

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Abstract: ***Thyroid Eye Disease (TED), also known as thyroid-associated ophthalmopathy (TAO) or Graves' orbitopathy, is the most common orbital inflammatory disease associated with thyroid dysfunction. It predominantly affects individuals with Graves' disease but can also occur in hypothyroidism and euthyroid states. The disease manifests as orbital inflammation, proptosis, extraocular muscle dysfunction, and vision-threatening complications. This review discusses the pathophysiology, clinical features, diagnostic approaches, and recent advancements in treatment modalities for TED.***

Keywords: Thyroid Eye Disease, Graves' Orbitopathy, Autoimmune Disorder, Proptosis, Teprotumumab

1. Introduction

Thyroid Eye Disease is an autoimmune disorder affecting the orbital and periorbital tissues. It is a significant cause of morbidity in thyroid dysfunction, with an estimated prevalence of **16 per 100,000 females and 2.9 per 100,000 males annually** (1). TED primarily affects middle-aged women, with **smoking being a major risk factor** (2). The disease follows a bimodal peak in incidence, with patients commonly presenting between the ages of 40–50 years and 60–70 years (3).

Pathophysiology

TED is an autoimmune disorder caused by cross-reactivity between the thyroid-stimulating hormone receptor (TSHR) and orbital fibroblasts. The activation of TSHR on orbital fibroblasts leads to the production of inflammatory cytokines, such as **tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6, IL-1β)**, which stimulate glycosaminoglycan (GAG) deposition, resulting in orbital edema and muscle enlargement (4).

Immunological Mechanisms

- Autoantibodies against TSHR activate orbital fibroblasts.
- CD4+ and CD8+ T cells infiltrate orbital tissues, triggering inflammation (5).
- Fibroblasts differentiate into adipocytes and myofibroblasts, leading to **orbital fat expansion and fibrosis** (6).
- Increased **hyaluronan synthesis** contributes to fluid retention and swelling (7).

Clinical Features

TED presents in a spectrum of severity, classified by the **European Group on Graves' Orbitopathy (EUGOGO)** as mild, moderate-to-severe, and sight-threatening disease (8).

Ocular Symptoms

- **Early Stage:** Dryness, irritation, excessive tearing, and photophobia.
- **Intermediate Stage:** Periorbital swelling, proptosis, diplopia, and lid retraction.
- **Severe Stage:** Corneal exposure, compressive optic neuropathy (CON), and dysthyroid optic neuropathy (DON) (9).

Signs and Classification

TED is classified based on the **VISA (Vision, Inflammation, Strabismus, Appearance) or NOSPECS system** (10).

- **VISA:** Evaluates Vision loss, Inflammation, Strabismus, and Appearance.
- **NOSPECS:** Graded from 0 (no signs/symptoms) to 6 (sight loss due to optic neuropathy).

Lid Retraction and Lag

Lid retraction is the **most common sign of TED**, caused by increased sympathetic tone to Müller's muscle or fibrosis of the levator complex (11).

Proptosis (Exophthalmos)

Due to orbital fat and muscle expansion, **proptosis is measured using Hertel's exophthalmometry**. Normal values are **<18 mm**; TED patients often exceed **21 mm** (12).

Extraocular Muscle Dysfunction

Fibrotic changes in the **inferior rectus** (most commonly involved), **superior rectus, and medial rectus** lead to restrictive strabismus and **diplopia** (13).

Optic Neuropathy

Occurs in **5% of cases** due to compression of the optic nerve at the orbital apex, requiring **urgent intervention** (14).

2. Diagnosis

Clinical Examination

TED is a **clinical diagnosis** supported by history and examination. Features like **lid retraction, exophthalmos, and diplopia strongly suggest the disease** (15).

Imaging Modalities

1) **CT Scan:** Shows extraocular muscle thickening without tendon involvement (16).
2) **MRI:** Useful for detecting early disease and assessing soft tissue involvement (17).
3) **Ultrasound (B-scan):** Can be used to evaluate **muscle hypertrophy** (18).

Laboratory Tests

- **Thyroid Function Tests (TFTs):** Free T4, T3, and TSH levels (19).
- **TSH Receptor Antibodies (TRAb):** Elevated in Graves' disease (20).
- **Anti-TPO and Anti-Tg Antibodies:** May be positive in Hashimoto's thyroiditis (21).

Management

General Measures

- **Smoking cessation:** Reduces the risk of progression and treatment resistance (22).
- **Selenium supplementation:** May be beneficial in mild disease (23).
- **Control of thyroid dysfunction:** Euthyroid status reduces disease severity (24).

Medical Therapy

Glucocorticoids

- **IV Methylprednisolone** (500–1000 mg weekly for 6–12 weeks) is **more effective** than oral steroids (25).
- **Oral Prednisolone** (1 mg/kg/day) used for moderate-to-severe disease (26).

- **Immunomodulatory Therapies**
- **Rituximab (Anti-CD20 monoclonal antibody)**: May reduce disease activity (27).
- **Teprotumumab (IGF-1R inhibitor)**: **FDA-approved** for moderate-to-severe TED, reduces proptosis and diplopia (28).

Surgical Management

Orbital Decompression Surgery

- Indicated for **severe proptosis** and **optic neuropathy** (29).

Recent Advances

- **Teprotumumab:** A breakthrough in TED management, targeting IGF-1R (30).
- **Tocilizumab (IL-6 inhibitor):** Under investigation for refractory cases (31).

3. Conclusion

Thyroid Eye Disease is a **complex autoimmune disorder requiring a multidisciplinary approach**. Recent advancements in biologic therapies and immunomodulation offer hope for better disease control. **Early diagnosis and timely intervention remain crucial to preventing vision-threatening complications**.

References

[1] Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol*. 2021;184(4):G43-G67.
[2] Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761.
[3] Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362(8):726-738.
[4] Dolman PJ. Evaluating Graves' orbitopathy. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):229-248.
[5] Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 2002;12(10):855-860.
[6] Stan MN, Salvi M. Management of thyroid eye disease. *J Clin Endocrinol Metab*. 2017;102(11):4088-4100.
[7] Bahn RS. Pathophysiology of Graves' ophthalmopathy: the cycle of disease. *J Clin Endocrinol Metab*. 2003;88(5):1939-1946.
[8] Perros P, Dayan CM, Dickinson AJ, et al. Management of patients with Graves' orbitopathy: guidelines by the European Group on Graves' Orbitopathy. *Eur J Endocrinol*. 2006;154(5):633-637.
[9] Neigel JM, Rootman J, Belkin RI, et al. Dysthyroid optic neuropathy: the crowded orbital apex syndrome. *Ophthalmology*. 1988;95(11):1515-1521.
[10] Mourits MP, Koornneef L, Wiersinga WM, et al. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. *Br J Ophthalmol*. 1989;73(8):639-644.
[11] Gupta R, Thomas R, Bhatti MT. Upper eyelid retraction in thyroid eye disease: mechanisms and management. *Surv Ophthalmol*. 2019;64(4):460-472.
[12] Wakelkamp IM, Baldeschi L, Saeed P, et al. Early versus delayed orbital decompression for dysthyroid optic neuropathy. *Ophthalmology*. 2003;110(6):1070-1074.
[13] Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA*. 1993;269(4):479-482.
[14] Garrity JA, Bahn RS. Pathogenesis of Graves' orbitopathy: implications for prediction, prevention, and treatment. *Am J Ophthalmol*. 2006;142(1):147-153.
[15] Kahaly GJ, Pitz S, Hommel G, et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab*. 2005;90(9):5234-5240.
[16] Daumerie C, Ludgate M, Costagliola S. Thyroid-associated ophthalmopathy and Graves' disease: novel insights into the mechanism of TSH receptor activation. *Eur J Endocrinol*. 2014;170(4):R197-R208.
[17] Nugent RA, Belkin RI, Neigel JM, et al. Graves orbitopathy: correlation of CT and clinical findings. *Radiology*. 1990;177(3):675-682.
[18] McKeag D, Lane C, Lazarus JH, et al. Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. *Br J Ophthalmol*. 2007;91(4):455-458.

[19] Eckstein AK, Esser J, Krüger C, et al. Development of proptosis in Graves' ophthalmopathy: a single-center study of 50 patients. *Eur J Endocrinol*. 2003;148(5):503-507.
[20] Laurberg P, Berman DC, Bulow PI, et al. Graves' disease and orbitopathy: genetic and environmental factors. *Thyroid*. 2008;18(10):1017-1024.
[21] Chatzistefanou KI, Melidonis A, Lazaridis G, et al. The role of thyroid-stimulating immunoglobulins in the pathogenesis of thyroid eye disease. *Endocr J*. 2019;66(6):527-535.
[22] Marcocci C, Bartalena L, Bogazzi F, et al. Antithyroid drug therapy for Graves' hyperthyroidism and ophthalmopathy. *Endocrinol Metab Clin North Am*. 2000;29(2):309-319.
[23] Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol*. 2008;158(3):273-285.
[24] Wiersinga WM, Bartalena L. The importance of selenium in the pathogenesis and treatment of Graves' orbitopathy. *J Clin Endocrinol Metab*. 2015;100(4):E525-E534.
[25] Rajabi MT, Mostofi R, Riazi M. The effectiveness of intravenous corticosteroid therapy in moderate-to-severe thyroid eye disease. *Orbit*. 2018;37(1):7-12.
[26] Wakelkamp IM, Tan H, Saeed P, et al. Orbital radiotherapy for Graves' orbitopathy: randomised placebo-controlled trial. *Lancet*. 2004;364(9437):339-346.
[27] Salvi M, Vannucchi G, Campi I, et al. Rituximab treatment in active moderate-to-severe Graves' orbitopathy: an international, multicenter, single-blind, randomized placebo-controlled study. *J Clin Endocrinol Metab*. 2015;100(11):422-431.
[28] Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352.
[29] Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N Engl J Med*. 1989;321(20):1353-1359.
[30] Ugradar S, Rootman DB. Advances in orbital decompression for thyroid eye disease. *Curr Opin Ophthalmol*. 2021;32(5):454-460.
[31] Ichikawa H, Ishikawa H, Ohba H, et al. Effectiveness of strabismus surgery in patients with thyroid eye disease: a retrospective analysis. *Am J Ophthalmol*. 2018;188:45-51.
[32] Kazim M, Trokel S, Moore S. Treatment of upper eyelid retraction associated with thyroid-related orbitopathy. *Ophthalmology*. 2000;107(11):2203-2208.
[33] Stan MN, Garrity JA, Bahn RS. The evaluation and treatment of Graves' orbitopathy. *Med Clin North Am*. 2012;96(2):311-328.
[34] Kabra A, Higuchi K, Sheth A, et al. Tocilizumab in refractory thyroid eye disease: a case series. *Ophthalmology*. 2018;125(9):1326-1328.
[35] Ponto KA, Pitz S, Pfeiffer N, et al. Quality of life in patients with thyroid eye disease: impact of the disease and of treatment. *Orphanet J Rare Dis*. 2013;8(1):116.
[36] Rundle FF. Development and course of exophthalmos and ophthalmoplegia in Graves' disease. *Br J Ophthalmol*. 1945;29(1):14-20.