PRIMEVIEW

GRAVES' DISEASE

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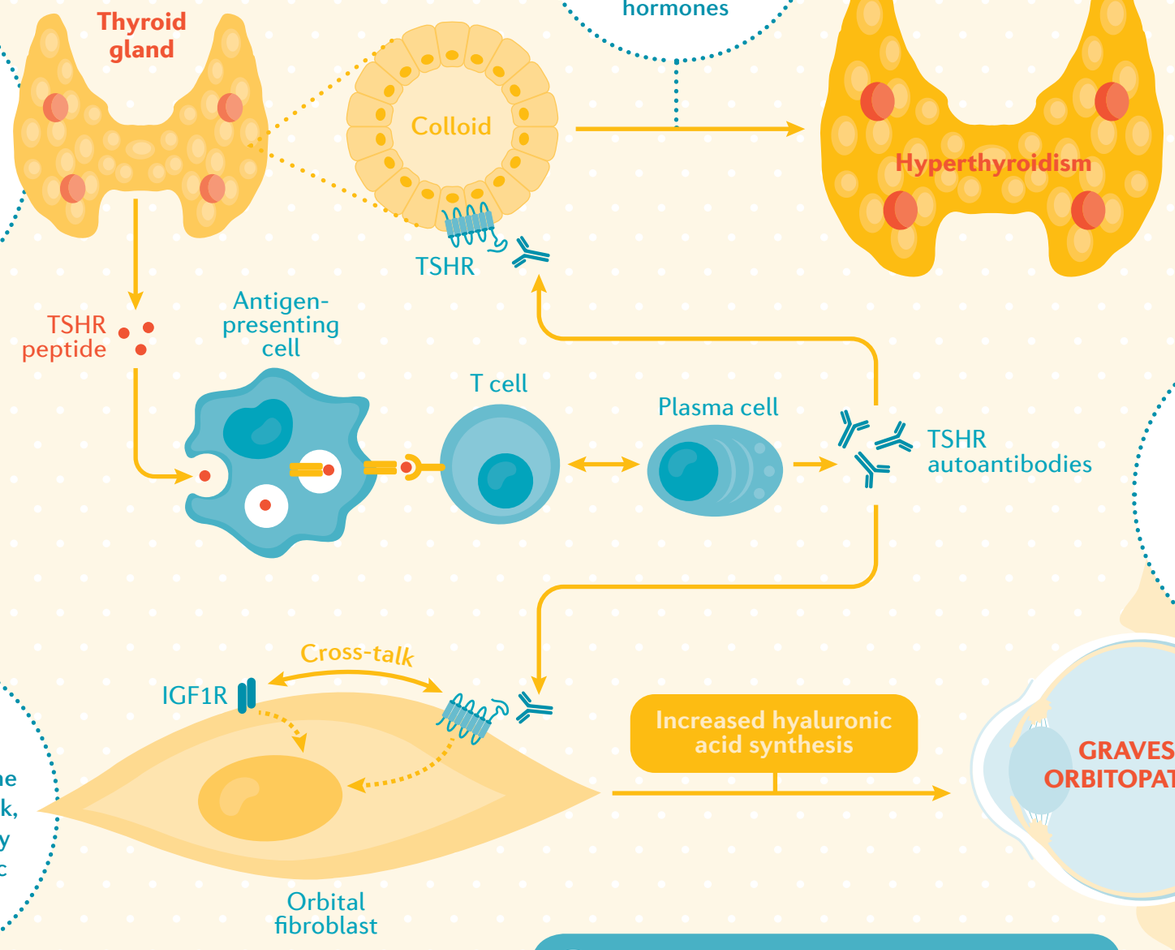
Graves' disease (GD) is an autoimmune disorder caused by autoantibodies to the thyroid-stimulating hormone receptor (TSHR), causing overactive thyroid gland (hyperthyroidism). In severe cases, patients develop extrathyroidal complications such as sight-threatening ocular disease (Graves' orbitopathy, GO) and infiltrative dermopathy (pretibial myxoedema, PTM).

MECHANISMS

GD is thought to occur when a combination of genetic and environmental insults exceeds a certain threshold in a susceptible individual, causing an immune response

T cells sensitized to the TSHR antigen become activated by pro-inflammatory cytokines, which in turn activate B cells to secrete TSHR autoantibodies

The TSHR autoantibodies act as agonists of the TSHR, inducing the thyroid to secrete excess thyroid hormones



Binding of TSHR autoantibodies to TSHR expressed in the eye induces cross-talk, which synergistically increases hyaluronic acid production

In severe cases, proptosis (protrusion of the eyes forward) occurs owing to the tissue expansion and accumulation of glycosaminoglycans

EPIDEMIOLOGY

GD occurs at all ages, but its incidence is higher in women (~2%) than in men (0.2%). The global incidence of GD is ~20–40 cases per 100,000 population per year. GO is observed in ~5% of patients with GD and is prevalent in 10–16 per 10,000 persons, whereas the prevalence of PTM is reported to be 0.15 per 10,000 persons.

Risk factors for GD include genetic susceptibility, female sex, pregnancy, stress, viral infection, exposure to iodine and iodine-related drugs, immune-modulating agents and microbiotal diversity. In addition to these, high TSHR autoantibody titres are associated with an increased risk of GO and PTM. Smoking and radioiodine treatment are specifically associated with GO development, and physical trauma has been shown to exacerbate PTM.

DIAGNOSIS

The diagnosis of GD can often be established based on clinical symptoms. A confirmation of hyperthyroidism (by measuring serum TSH and free thyroxine levels), visible signs of GO and a diffuse goitre (enlarged thyroid gland) typically confirm a diagnosis. However, if a diagnosis is not evident from clinical presentation, in addition to TSH levels, detection of TSHR autoantibodies can support GD diagnosis. However, if the antibody test is negative, a thyroid scan and uptake (which evaluates the function of the gland) should be performed to establish the diagnosis.

MANAGEMENT

The main goal in the management of GD is to establish normal thyroid hormone levels. Antithyroid drugs such as methimazole or propylthiouracil are used to treat hyperthyroidism in most people. Radioiodine is recommended for some patients but is generally disfavoured owing to its inherent risk and as it exacerbates GO. Intravenous glucocorticoid is the recommended first-line therapy for patients with moderate to severe GO. Second-line therapies include teprotumumab, a monoclonal antibody to IGF1R, amongst others. Partial or total thyroidectomy, although conventional, is still the preferred treatment for patients with large goitres and with severe GO. The treatment of PTM remains challenging and inadequate to date.

OUTLOOK

! The exact aetiology of GD remains unknown

Progress in understanding the contributions of various genetic factors and environmental insults has been hindered by a lack of animal models. Hence, robust animal models that truly replicate the disease features are needed. Although treatment of GD has not changed in several years, many new potential drugs are in clinical trials, the outcomes of which are awaited.

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