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Analysis of Graves' disease from the origins to the recent historical evolution

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Abstract. Graves' disease (GD), also called Basedow's disease, owe the names respectively to the Irish physician Robert James Graves, who described the disease in 1835, and to Karl Adolph von Basedow, who reported the same clinical picture in Germany in 1840. Indeed, it was the Englishman Caleb Hillier Parry to firstly report a case of hyperthyroidism and goiter in 1786, but his report was not published until 1825. Earlier, in 1802, the Italian physician Giuseppe Flajani, described a disease characterized by the coexistence of palpitations and exophthalmos. Graves' disease is an autoimmune, organ-specific, disorder sustained by auto-antibodies stimulating the thyroid-stimulating hormone (TSH) receptor (R). It is believed that the interaction between susceptible genes and environmental/endogen factors triggers the development of the disease. As a consequence of TSH-R improper stimulation, hyperthyroidism and goiter are the main clinical manifestations of the disease, accompanied, in the 25% of cases, by Graves' orbitopathy (GO). GD is primarily diagnosed by demonstrating the presence of thyrotoxicosis and the pathognomonic TSH-R antibodies (TSH-RAb). In this manuscript we will refer to the disease as Graves' disease.

Key words: thyroid, Graves' disease, autoimmunity, hyperthyroidism, ophthalmopathy, James Graves, Basedow disease

Graves' disease

Graves' disease is an autoimmune thyroid disorder, clinically characterized by the presence of hyperthyroidism, diffuse goiter, and, in some patients, ophthalmopathy (1).

GD is finally caused by auto-antibodies directed to TSH-R, which mimic the effect of TSH peptide (physiologically released by the pituitary gland) and induce the uncontrolled synthesis of thyroid hormones (THs), as well as the hypertrophy and hyperplasia of thyroid cells, resulting in diffuse goiter (2).

History

The Persian physician Avicenna (Ibn Sina) firstly described in 1000 AD the coexistence of goiter and exophthalmos in patients with increased appetite. A century later, another Persian physician, Sayyid Ismail al-Jurjani, reported this association in the medical dictionary of its time (Thesaurus of the Shah of Khwarazm) (3). Centuries would pass before this clinical picture attracted again the scientific attention.

The most famous Author associated whit the discovery of the disease is the Irish physician Robert

James Graves (1796-1853), who described the association of palpitations, goiter, and exophthalmos in 1835. Graves delivered a series of lectures with the title "Newly observed affection of the thyroid gland in females" at the Meath Hospital, in Dublin, in 1834-1835 (4), describing three patients suffering from goiter and palpitations. The fourth patient, evaluated by his colleague Sir William Stokes, was a young lady in her twenties, with palpitations, thyroid swelling, nervousness. Symptoms were assumed to be manifestation of "Hysteria", aggravated by the coexistence of exophthalmos. "The eyeballs were visibly enlarged, to the point that the eyelids could not close during sleep and when trying to close the eye; when the eyes were open, the whites of the eyes could be seen in the width of several lines around the entire cornea" (4). In 1843, Graves published his textbook "Clinical lectures on the practice of Medicine" (5), and the disease gained the name of Graves' disease (GD). Graves and Stokes believed that this disease represented a cardiac syndrome due to important palpitations.

In the same period, the German physician Karl Adolph von Basedow (1799-1854) described three patients sharing the same clinical picture, characterized by goiter, palpitations, and exophthalmos. Since Basedow practiced in Merseburg, the characteristic signs of the disease were defined as the "Merseburg triad" (6, 7). Von Basedow emphasized the symptoms of heat intolerance, profound asthenia, diarrhea, and weight loss despite increased appetite, thus, integrating the already known clinical picture of the disease; but missed Graves's report of 1835 and he had no hypothesis on the pathogenesis. His description focused the attention of clinician on the presence of eyes symptoms to address the diagnosis. The German physician also recommended the first treatment with mineral water containing iodide and bromide (7). Given that, in continental Europe, the disease is alternatively called GD or Basedow's disease (BD), while in the United States the eponym GD is more common.

Neither von Basedow nor Graves were the first to notice this disorder in modern Medicine. A similar clinical picture was reported by the Italians Giuseppe Testa in 1810 (8) and by Giuseppe Flajani in 1802 (9). In 1786 the Welsh physician Caleb Hillier Parry (1755-1822) described 6 out of his patients as follow "The swollen part was the thyroid gland; eyes were protruded from their sockets, faces exhibited an appearance of agitation and distress, especially on any muscular exertion, which I have seldom seen equaled; the heartbeat was so violent that each systole of the heart shook the whole thorax..." (10). He described a woman who developed these symptoms in the postpartum period and a second patient who developed the same symptoms after the exposure to an acute stress factor. Both the postpartum period (11) as well as strong stress are now recognized as risk for the onset of autoimmune thyroid disorder in susceptible subjects (12). Although Parry never published the descriptions of these cases until 1825, his report represents the first description of the disorder. In 1898, Sir William Osler unsuccessfully suggested to update he name "Graves' disease" into "Parry's disease" (13).

As stated before, Graves thought that the disease was a cardiac syndrome. Afterwards, in 1857, Jean Martin Charcot attributed the pathogenesis to a neurologic disorder (14), and so did Trousseau in 1868 (15), even in the absence of strong evidence to support this hypothesis. At that time, thyroid functions were unknown. In the late nineteenth century, Physicians noticed that thyroid surgery could improve the patient's conditions and the attention was addressed to the thyroid gland (16, 17). It was in 1886 that P.J. Moebius suggested that the cause was a dysfunction of the thyroid gland itself. The most accredited hypothesis was that the thyroid gland produced a poisoning toxin (16, 17). In 1910, Charles Horace Mayo (1865-1939) introduced the term "hyperthyroidism" (www.Thyroid.org). In 1911 Marine and Lenhart attributed to hyperfunctioning thyroid the origin of GD (18). The identification of the thyroid stimulating hormone in the 1930s (19) led to the suggestion that Graves' disease was caused by an excess of TSH. In 1958, Adams and Purves identified a thyroid-stimulating factor in the serum of patients with GD, different from TSH, which they named long-acting thyroid stimulator (LATS) because of its prolonged activity (20). Further studies demonstrated the ability of LATS to bind to the TSH receptor and that this binding was able to stimulate the receptor activity, beyond the physiological negative pituitary feedback control (20). LATS were recognized to be immunoglobulin G antibodies

(20). Due to their ability to compete with TSH for binding to thyroid membranes, LATS were called TSH receptor antibodies (TSH-RAb) (21). From this moment on, GD was recognized to be an autoimmune thyroid disorder.

Epidemiology and pathogenesis

GD accounts for the 60-80% of the cases of hyperthyroidism, depending on regional factors and especially on iodine intake, being the most common form of hyperthyroidism in iodine-replaced area, such as the United States (22). GD predominantly affects women, and this is likely because of estrogens effect on the autoimmune response. Although it may occur at any age, and also in children, the peak of incidence is between 40-60 years old and the annual incidence in over-20 years old women is around 0.5 per 1000 (23).

GD is brought on by the combination of genetic susceptibility, endogen and environmental triggers (24). When a susceptible individual meets a trigger, thyroid-specific T cells are synthetized, infiltrate the thyroid gland and activate B cells. The B cells in turn produce TSH-RAb. Hence, this immune dysfunction, finally leading to autoantibody production, involves T cells, B cells, and certain autoantigens such as peptides from the extracellular TSH-R domain, thyroglobulin and thyroid peroxidase (TPO) (25). These autoantibodies recognize TSH-R and mimic the effects of TSH on thyroid cells, thus stimulating the uncontrolled production of thyroxine (T4) and triiodothyronine (T3), leading to the development of hyperthyroidism. Thyroid infiltrating T cells can activate anti-apoptotic pathways and induce thyrocyte proliferation and thyroid gland enlargement (goiter). Certain genes, such as CD28 and Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), induce opposing signals on activation state of T cells (26).

Key factors for inducing/unmasking GD are environmental, including iodine intake, cigarette smoking, stress, external and internal irradiation by 131-I and drugs, such as antiretroviral and interferon-alpha (27).

Besides the well-known effect of iodine status on thyroid function, other micronutrients are on study for their potential role in GD pathogenesis and treatment. Animal models suggested that vitamin D supplementation succeeded in decreasing thyroid inflammation and prevent thyroiditis induction. Recent observational studies suggested that vitamin D levels were lower in subjects with autoimmune disorders, including GD patients (28, 29). Accordingly, a randomized clinical test of 30 naïve GD observed a higher decrease of thyroid hormone levels in the vitamin D-supplemented-group (30).

Infectious agents can trigger an autoimmune response by molecular mimicry. The latter occurs when there is structural similarity between infectious agents and thyroid antigens resulting in the formation of thyroid-specific T cells and antibodies. At the time being, several microbes, including enterovirus, Yersinia enterocolitica and Epstein-Barr Virus have been linked to the development of GD, but results are still preliminary (27, 31). Other viruses such as Hepatitis C Virus and Parvovirus B19 have also been associated with autoimmune thyroid diseases but equally these data need further validation (32).

Finally, other etiological factors might involve the microbiota and dysbiosis, since it has been shown that a modified microbiota composition raises the prevalence of autoimmune thyroid diseases, including GD (33). Still possible therapeutic interventions are in their infancy (34).

Thyroidal injury, due to surgery, radiotherapy, infection, or excess iodine might be implicated in GD pathogenesis causing the exposure of cryptic epitopes of thyroidal proteins. This condition promotes the secretion of cytokines and chemokines and stimulates thyroid inflammation, infiltration by T cells and finally, TSHR-Ab production by B cells (35).

Clinical manifestations and changes of disease phenotype

The Merseburg triad (hyperthyroidism, goiter, and orbitopathy) represented the classical and historical description of the disease (7).

In GD, the thyroid gland is often enlarged. Microscopic evaluation reveals hypertrophy and hyperplasia of the thyroid follicular cells and lymphocytic infiltration; thyroid follicular cells have an elongated

columnar appearance, are folded in papillary configurations, and protrude into the lumen of the follicle. Goiter has been described as a typical feature of GD in historical cohorts. Indeed, in the 80', Lauberg et al. found that goiter (assessed by palpation) was present in 81% of newly diagnosed Graves' patients, being small in 58 % and moderate to large in 23 %; similarly, 20 years later, Vitti et al. found that the 52% of GD patients had a large goiter. More recently, Bartalena et al. observed that goiter is often smaller than in the past, probably due to repletion of iodine status (36).

Ophthalmopathy, also known as Graves' orbitopathy (GO), occurs in more than 25% of patients with Graves' disease (37). The characteristic signs of Graves' orbitopathy are proptosis (exophthalmos) and inflammatory symptoms including dry and sandy ocular sensation, pain during eye movement, excessive tearing, photophobia and periorbital edema. In most severe cases, double vision and loss of vision/colors acuity might occur (38, 39). Recently, Tanda et al. observed that, as goiter, orbitopathy is milder than in the past, probably due to a prompter diagnosis and better treatment of hyperthyroidism (40).

Several studies recently suggested that GD became milder in the last decades in term of disease severity and prevalence. By a systematic search of studies published between 1980 and 2017, Ippolito and coworkers confirmed that GD phenotype at diagnosis is nowadays milder than in the past; the Authors hypothesized the impact of iodine prophylaxis and micronutrient supplementation, decrease in smoking habits, larger use of contraceptive pill, as well as earlier diagnosis and management as other possible causes (41, 42).

Despite this milder phenotype, GD diagnosis might not be neglected, as a poor treatment might increase mortality risk (42). It is likely that all cells in the body are targets for THs, which largely impact on the main physiologic and metabolic process. The clinical extrathyroidal manifestations of hyperthyroidism include tremor, weight loss, anxiety, insomnia, heat intolerance, fatigue, weakness, and myalgia. Several complex actions of THs on cardiac muscle and blood vessels lead to cardiovascular morbidities including increased cardiac output, cardiac contractility, and systolic blood pressure. Since THs directly stimulate the sinus node pacemaker, sinus tachycardia, and in most alarming cases, supraventricular arrhythmias might occur. The cardiac signs are particularly severe in older patients as they could develop atrial fibrillation and heart failure. During an 8-years follow-up of 500,000 adults, a 13% cumulative incidence of atrial fibrillation was shown among people with thyrotoxicosis and over 65 years old (43).

Frequently, hyperphagia without weight gain as well as bowel movements are present. Other common manifestations include alterations in menstrual cycles, erectile dysfunction or decreased libido, fatigue (44, 45). Dermopathy is a rare manifestation in GD patients, and it is characterized by a waxy, discolored induration of the skin, primarily involving the pretibial area (46, 47). Acropachy, which is the rarest extrathyroidal manifestation of GD, is characterized by clubbing of the fingers and toes caused by bone changes (48).

Almost 20% of GD patients develop another autoimmune disease, which suggests that GD patients who develop new unspecific symptoms should be evaluated for other autoimmune disorders (49).

The history of available treatments

At the time being three different approaches exist to treat GD: Thionamide compounds, radioactive iodine (RAI) and total thyroidectomy. Thionamide compounds were found in 1943 during experiments on animals and were firstly applied by Prof. Edwin B. Astwood to treat human hyperthyroidism (50). Their primary effect is to inhibit TPO-mediated iodination of thyroglobulin, and thereby the synthesis of THs. Currently, Thionamide represent the first line therapy for GD in Europe, Asia and, more recently, in USA also (2).

A different treatment option is offered by iodine (I)-131, whose therapeutic goal is to render the patient hypothyroid (2). In 1811, the French chemistry Bernard Courtois (1777-1838) discovered iodine in burnt seaweed, but the element was named by Joseph Louis Gay-Lussac (1778-1850) (51). A few years later, Jean-Francois Coindet (1774-1834), in Genève, recommended the use of iodine in the preoperative treatment of goiter to decrease vascularity and the operative risk (52). In 1831, he was awarded by the Paris Academy

of Sciences for the discovery. Finally, in 1911, iodine was recommended to treat Graves' disease. The first report on radioactive iodine as diagnostic tool for thyroid disorder dates 1936, when J. Howard Means and Saul Hertz, at the Massachusetts General Hospital, realized that iodine could be used as a tracer (53). A couple of years later, at the Massachusetts Institute of Technology, the physicists Robley Evans and Arthur Roberts tested the short acting I-128 tracer on rabbit's thyroid gland. In 1940 the same group built a cyclotron and generated two long-life radioiodine isotopes for an innovative therapeutic approach. By march 1941, RAI was used by different groups and demonstrated to be effective in hyperthyroidism treatment. The first two studies on human case series were published in 1946 on the Journal of the American Medical Associations (54).

The first reports on thyroid surgery to treat nontoxic goiter dated back to Albucasis in 952 AD, but hyperthyroidism was considered a limitation for surgery for years. In 1884, Ludwig Rehn (1949-1930) reported that surgical treatment of large goiter was able to relieve toxic symptoms (55). Since that moment on, thyroidectomy was performed to treat hyperthyroidism (56, 57).

Future perspectives on cell-mediated immune responses

More than 40 years ago, it was suggested that immune system and THs have a close relationship, due to the fact that staphylococcus-stimulated lymphocytes might de novo produce a TSH-like molecule, similar to the canonical form (58) and subsequently that bone marrow hematopoietic cells, i.e. lymphocytes and innate myeloid cells, such as dendritic cells could synthesize TSH (59). However, the effective role of extra-pituitary TSH remains to be clarified. At the same time, interest in the characterization of immunological features in GD has increased over the years. Several researches showed that immune cells possess all elements required for THs metabolism and action. (60, 61). For example, TH and especially T3 can modulate dendritic cell maturation and function (61) and enhanced dendritic cell numbers (62).

Moreover, TSH-R is expressed on myeloid and lymphoid cells (63, 64), and the triggering of the receptor might act as a cytokine-like signal, inducing secretion of various cytokines, such as TNFα (65, 66). In vitro studies showed that TSH, combined to classical cytokines (e.g. IL-2, IL-12), can function as a costimulus for increased lymphocytes and natural killer cell proliferation (66-69).

Thyroid function may regulate the immune system; on the other hand, immune cells dysfunction might favor the development of thyroid disorders. For example, several studies investigated the potential contribution of natural killer cells (NK) in the development and progression of GD, but results are still incomplete and sometimes conflicting (70).

Large granular lymphocytes that comprise NK cells, were decreased in untreated GD patients compared to euthyroid GD patients on antithyroid drug therapy and to controls; also, the proportion of large granular lymphocytes was inversely correlated to T4 and T3 levels (71). Therefore, while normal THs levels are crucial to maintain an adequate activity of the immune system, excessively high THs levels exerted a negative effect, as well as enhanced cortisol release (72, 73).

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