Graves' Hyperthyroidism: Clinical Practice

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Thyrotoxicosis refers to excess circulating thyroid hormone for any cause related to hyperthyroidism (Franklyn & Boelaert, 2012; Sharma, Aronow, Patel, Gandhi, & Desai, 2011). There are several differential diagnoses for thyrotoxicosis including Graves' autoimmune thyroid disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. Pregnancy may exacerbate an existing diagnosis of thyrotoxicosis, known as gestational hyperthyroidism, which may resolve with or without treatment in the second or third trimester (Brent, 2008; Eastman, 2012; Franklyn & Boelaert, 2012).

Graves' disease accounts for 5% of thyroid autoimmunity and causes 50% to 80% of all hyperthyroidism cases (Brent, 2008; Ponto & Kahaly, 2012; Saranac et al., 2011). Franklyn and Boelaert (2012) note the prevalence of Graves' disease in the USA population is 1-3% primarily affecting women between 20 to 50 years of age Ponto and Kahaly (2012). Women, at a rate of five to ten times, are disproportionately likely to develop Graves' disease than men (Brent, 2008; Ponto & Kahaly, 2012). There is wide prevalence variability between race and geography, though overall Caucasians have the highest prevalence irrespective of geography (Franklyn & Boelaert, 2012; McLeod & Cooper, 2012). Saranac et al. (2011) note 80% of thyroid autoimmunity is genetic, while 20% is environmental. In addition to the other mentioned factors, concurrent autoimmune disease contributes to increased risk (Ponto & Kahaly, 2012).

Screening and Diagnosis

Graves' disease is characterized as an autoimmune disease of the thyroid resulting in increased levels of thyroid stimulating hormone (TSH). In addition to increased TSH levels, thyroxine (T_4) and trioiodothronine (T_3), hormones produced by the thyroid, which act systemically, are characteristically elevated in Graves' disease though they

may remain within normal limits (Brent, 2008; Grebe & Kahaly, 2012). Graves' disease causes a primarily humoral response whereby autoantibodies bind to thyroid peroxidase (TPO) or thyroglobulin (Tg) autoantigens within or on the cell surface of TSH receptors (Eastman, 2012; Franklyn & Boelaert, 2012; McLeod & Cooper, 2012; Morshed, Latif, & Davies, 2012; Schott et al., 2009b). TSH receptors are expressed in both thyroid tissue and other tissues including adipocytes and bone cells contributing to a systemic disease process (Ponto & Kahaly, 2012).

Diagnosis of Graves' disease is based on clinical presentation, laboratory findings, and imaging studies (i.e., ultrasonography and thyroid scintigraphy) (Brent, 2008; Franklyn & Boelaert, 2012; Saranac et al., 2011; Sharma et al., 2011). Symptoms of Graves' disease may present as a fine tremor, heat intolerance, anxiety, weight loss, irregular menses, sexual dysfunction, hair loss, tachycardia, osteoporosis, and fatigue (Brent, 2008; Ponto & Kahaly, 2012; Sharma et al., 2011). While some patients may require a more comprehensive work-up with imaging studies, diagnosis of Graves' disease is typically determined through an elevated TSH level (<0.01 mIU/L). Depending on the laboratory and immunoassay, a TSH reference range typically falls between 0.3 – 3.5 mIU/L, 0.4 – 2.5 mIU/L, or 0.4 – 4.5 mIU/L (Åsvold, Vatten, Midthjell, & Bjoro, 2012; Eastman, 2012; Schott et al., 2009b; Vanderpump, 2011). Additional laboratory testing of T_4 and/or T_3 levels to elaborate the cause of hyperthyroidism (e.g., subclinical hyperthyroidism, Graves' disease, TSH-secreting pituitary adenoma) may be necessary (Grebe & Kahaly, 2012; Schott et al., 2009b). Antibody immunoasays (i.e., TSH receptor antibodies, thyroid stimulating immunoglobulin, TPO antibodies) may be completed to discriminate Graves' disease

from non-autoimmune forms of hyperthyroidism (Brent, 2008; Franklyn & Boelaert, 2012; Grebe & Kahaly, 2012; Schott et al., 2009b; Srivastava et al., 2010). When used to confirm suspected thyroid disease in patients, serum TSH has a sensitivity and specificity greater than 90% (98% - 100% and 92% - 95%, respectively) for conventional and functional immunoassays (Grebe & Kahaly, 2012; Schott et al., 2009a; Vanderpump, 2011). Grebe and Kahaly (2012) suggest, however, accuracy and precision can only be accomplished at the extreme ranges of the significance level established for each assays. Despite standardization, clinical results of different assays are based on varying reference ranges and detection accuracy.

Treatment

Current treatment approaches to Graves' disease include surgery, radiation, and pharmaceutical therapies. Patients may or may not achieve a euthyroid state with therapies even including the more definitive approaches of radiation and surgery. Most patients require a mixed therapeutic approach. Treatment intervention can vary based on clinical presentation, country of residence, and therapeutic goals (Annerbo, Stalberg, & Hellman, 2012; Burch, Burman, & Cooper, 2012; Fumarola, Di Fiore, Dainelli, Grani, & Calvanese, 2010; Glinoer & Cooper, 2012). Patients, for example, in Scandinavia routinely undergo thyroidectomy due to the definitive outcomes and "perceived low complication rates" (Annerbo et al., 2012 p. 1943). Burch et al. (2012) undertook an international survey of 730 practicing clinicians involved in the care of Graves' disease patients. Respondents from North America, Europe, Latin America, Middle East, Africa, Asia, and Oceania completed an online survey (Burch et al., 2012). Burch et al. (2012) found clinicians strongly preferred pharmaceutical intervention (i.e., Europe= 85.7%,

Middle East= 66.7%, Latin America= 73.8%, Asia + Oceania= 70.6%, North America= 40.5%) versus radioiodine. Thyroidectomy, for all respondents, was an intervention of last resort recommended about one percent of the time (Burch et al., 2012).

Thyroidectomy is generally considered in the context of the following goals: intractable Graves' disease unresponsive to pharmaceutical intervention, failed radiation treatment, progression to dysthryoid opthalmopathy, or airway obstruction due to excessively enlarged goiter (Annerbo et al., 2012; Brent, 2008; Hoffmann, 2009; Sharma et al., 2011). Thyroid surgeons may opt for a subtotal thyroidectomy (both sides), near total (both sides), unilateral near total combined with contralateral total resection, or bilateral total resection (Annerbo et al., 2012; Hoffmann, 2009). Surgical risks include laryngeal paralysis, hypoparathyroidism, and recurrence with incomplete resection (Annerbo et al., 2012; Hoffmann, 2009). During the 2007 German Congress on Surgery, Eisenberger cautioned, "the extent of thyroid resection is the most important risk factor for complications" (Hoffmann, 2009 p. 241).

Patients may be treated with I-131, a radioactive form of iodine, administered orally as a pill to destroy hyperfunctioning thyroid tissue (Ross, 2011). Patients may require multiple doses to achieve therapeutic response (Ross, 2011). Clinical practice is currently divided on the appropriate dosing protocol (Ross, 2011). According to one randomized clinical trial, benefit was seen with calculated-dose regimens while another study suggests a fixed dose is appropriate (Ross, 2011). Patients often must take support medication post-treatment for hypothyroidism (Emiliano, Governale, Parks, & Cooper, 2010; Fumarola et al., 2010; Ross, 2011).

The most common therapy is one or of a combination of medications (Burch et al., 2012; Emiliano et al., 2010; Fumarola et al., 2010). Patients are typically treated with one of three thionamides- propylthiouracil (PTU), methimazole (MMI), or carbimazole (CBZ) (Burch et al., 2012; Emiliano et al., 2010; Fumarola et al., 2010). Data suggests patients should be treated a minimum of 12 months to achieve remission (Fumarola et al., 2010). Depending on clinical presentation and remission status, therapy may be suspended after 18 months of treatment (Fumarola et al., 2010). Current research suggests patients who do not complete at least 12 months of antithyroid therapy are likely to recur, though periods longer than 18 months do not show superiority (Fumarola et al., 2010). Burch et al. (2012) queried survey respondents on the typical length of therapeutic treatment. Responses ranged from 24 months (35.4%) to less than one year (13.9%) (Burch et al., 2012). While several randomized studies consider the dose of MMI versus PTU and rates of remission and found no relation, increasing dose is related to increased toxicity for both drugs (Emiliano et al., 2010; Fumarola et al., 2010). Despite being the drug of choice (in the United States) until 1995, the Food and Drug Administration issued a black box warning for PTU due to possible heptotoxicities and death (Burch et al., 2012; Emiliano et al., 2010). PTU is only indicated in patients refractory to MMI or intolerant as well as pregnant women in the first trimester given it does not cross the placental barrier in the same concentration as MMI (Emiliano et al., 2010; Fumarola et al., 2010; Glinoer & Cooper, 2012). Since 1996, MMI has been the drug of choice for Graves' disease with an expected event profile including pruritus, arthralgia, nausea, and olfaction disorders (Emiliano et al., 2010; Fumarola et al., 2010).

Prevention

Currently, there are minimal, indeterminate prevention measures for Graves' autoimmune thyroid disease. Data suggests genetic factors cause 80% of Graves' disease, while environmental factors contribute to the remaining 20% (Falgarone, Heshmati, Cohen, & Reach, 2013; Morshed et al., 2012; Saranac et al., 2011; Vos, Endert, Tijssen, & Wiersinga, 2012). The primary environmental risk factors are: stress, exposure to nicotine smoke, resident of an iodine-rich region, and a diet poor in selenium (Burch et al., 2012; Drutel, Archambeaud, & Caron, 2013; Falgarone et al., 2013; McLeod & Cooper, 2012; Saranac et al., 2011). Smoking appears to moderately increase the risk for Grave's disease (Burch et al., 2012; McLeod & Cooper, 2012; Saranac et al., 2011). According to a meta-analysis by McLeod et al. (2012), countries rich in iodine replacement programs, report a higher incidence of thyroid autoimmunity versus those countries with lower iodine levels. Additionally, Saranac et al. (2011) and Drutel et al. (2013) suggest a diet poor in selenium also contributes to thyroid disease given its antioxidant effects which protects the thyroid from excessive iodine exposure.

In a review of the literature, Effraimidis et al. (2012), Falgarone et al. (2013), Fukao et al. (2011), Paunkovic et al. (1998), Vos et al. (2012) suggest stress plays a pivotal role in exacerbation of Graves' disease and may potentially contribute to its genesis. Illustrative of extreme stress, Paunkovic et al. (1998) describe a dramatic increase in the incidence of Graves' disease during the Serbian Civil War between 1992 to 1995. The authors note the increase in Graves' disease incidence is challenging to explain and is likely multifactorial related to the Chernobyl accident as well as environmental causation including stress (Paunkovic et al., 1998). The authors are careful to point out there was not a corresponding increase in other forms of

hyperthyroidism though the quality of iodine-enriched salt during that period was inconsistent and very poorly regulated (Paunkovic et al., 1998). Alternatively, Vos et al. (2012) propose those with genotype susceptibility are a higher risk of developing Graves' disease or symptom exacerbation at a lower threshold of stress than those without genetic variants. Fukao et al. (2011) consider those with an existing depressive disorder and suggest their psychosis negatively impacts their Graves' disease rather than the Graves' disease influencing their level of stress.

To date, there have been no randomized studies examining stress and its role in Graves' disease (Falgarone et al., 2013). Effraimidis et al. (2012) conducted a prospective, nested case-control study of first and second-degree relatives with autoimmune thyroid disease including Graves' and Hashimoto's. Researchers found no difference in the incidence of stress and autoimmune thyroid disease between the two groups (Effraimidis et al., 2012). Falgarone et al. (2013) posit it is reasonable to criticize Graves' disease surveys which consider emotional context only as they are highly subjective in nature as there have been no quantifiable instruments to date to correlate results. Thus, any association between stress and Graves' disease is based on clinical evidence, rule in/out treatment response, and theoretical effect of stress on immune mechanism rather than validated evidence-based medicine and randomized clinical trials (Falgarone et al., 2013).

Health Policy

In 2011, the American Thyroid Association published practice guidelines on the management of hyperthyroidism. Burch et al. (2012) question the relevance of the guidelines noting, "…it is not clear to what extent current clinical practice differs from

these recommendations, because the last systematic survey of management practices for GD [Graves' disease] in the United States was published nearly a quarter of a century ago" (p. 4550). In that time, clinical practice has informally shifted therapeutic approaches, which have informed the larger therapeutic process. Thus, the guidelines appear to be a distillation of current practice with no new additional information or guidance.

Given the symptom differentials, immunoassay disparity, and interassay variability, an autoimmune thyroid diagnosis can easily be misdiagnosed or overlooked (Pal, Le, & Graves, 2013). As a preventive measure, should clinical practice guidelines include primary surveillance for autoimmune thyroid disease? Eastman (2012) notes screening is a vital part of public health and disease prevention. That said, there is controversy on the appropriate TSH cutoff levels as well as the appropriateness of therapeutic intervention for subclinical cases (Eastman, 2012; Vanderpump, 2011).

Åsvold et al. (2012) prospectively followed 15,106 Norwegian participants without a history of Grave's disease with a baseline TSH of 0.20 – 4.5 mU/liter for 11 years to assess the value of upfront intervention and screening evaluation. Åsvold et al. (2012) found participants' with a baseline TSH at the lower end of the reference range were at a higher long-term risk of developing hyperthyroidism than participants whose baseline was in the normal range. The discussion then becomes a matter of gradation including subclinical cases. The general consensus, however, is not to treat subclinical cases given the inconsistent accuracy of laboratory testing and bias of self-reported symptomology (Vanderpump, 2011) Furthermore, due to the range of lab results, fluctuating thyroid hormone levels, and numerous possible symptoms, primary

surveillance programs are not recommended for Graves' disease or other autoimmune thyroid diseases (Franklyn & Boelaert, 2012; Sharma et al., 2011; Vanderpump, 2011). Thus, clinicians rely heavily on patient symptomology coupled with laboratory correlation for individual diagnosis confirmation.

Discussion

Graves' disease is a complex autoimmune disorder of the thyroid primarily related to genetic susceptibility influenced by environmental factors. Typically, Caucasian women between 20 to 50 years old are affected. Diagnosis is most often a result of laboratory analysis and symptom assessment though some patients may require a more extensive work-up. Treatment is most frequently pharmaceutical intervention. Given Graves' disease is primarily a disease of genetics; there are limited prevention measures such as abstaining from nicotine, increase selenium intake, moderate iodine intake, and limit stress. Current health policies do not favor a screening surveillance program due to patient fluctuating TSH levels (even within the normal healthy population), those with subclinical disease, and immunoassay test variability.

Arguably, limited research has focused on genetics, gender, or environmental affects. Current efforts have focused on understanding the pathophysiology of Graves' disease and enhancing therapeutic approaches with existing treatments. Most research is needed to better understand the disease in all populations, environmental, and genetic risk factors and treatment affects.

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