Original Article

Graves' disease in saudi arabia: a ten-year hospital study

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Abstract

Objective: To determine clinical manifestation and mode of treatment of Graves' disease at King Khalid University Hospital Riyadh, Saudi Arabia.

Methods: A retrospective study of all cases of Graves' disease diagnosed at the hospital in the period between January 1995 and December 2004, who received a minimum of two years treatment were included in the study.

Results: A total of 194 patients were seen with female: male ratio of 2.9: 1 and mean age of 32 ± 0.9 years. Sixty nine percent of the patients had positive thyroid antibodies. Palpitations, tremors, weight loss and nervousness were the most common presenting manifestations. Forty nine percent of patients were treated with radioiodine, 38% with antithyroid drugs, and 13% underwent subtotal thyroidectomy.

Conclusion: Clinical manifestations of Graves' disease in our patients distinctly differed from those reported in the West and Pacific Islanders with notable rarity of pretibial myxoedema and hyperpigmentation respectively. We also noted higher male to female ratio and an increasing utility of radioactive iodine therapy while use of antithyroid drugs and surgery are declining (JPMA 58:302;2008).

Introduction

Graves' disease is a common endocrine disorder worldwide. Being an autoimmune disorder characterized by diffuse enlargement of the thyroid gland, ophthalmopathy and sometimes associated with pretibial myxoedema.[1] Yet, its clinical features are not universal. For instance change in skin colour was reported to be a predominant clinical feature of the disease in some communities[2,3], interestingly this clinical sign is rarely seen in Caucasians.[4] On the other hand, thyroid dermopathy was thought to be not an uncommon presentation of Graves' disease in the West yet it has been reported to be rare in Negroid population.[5,6] As far as we know only few studies have been done on adult hyperthyroidism in Saudi Arabia.[7-11] Of those reports, none specifically addressed Graves' disease peculiar clinical features in the local population despite being identified to be the commonest autoimmune endocrine disease in hospital practice.[7,8] Furthermore, with the reported safety profile of radioactive iodine treatment, there is a shift from usage of medical and surgical therapy to radioiodine worldwide.[12] Nevertheless, there is no documented change in pattern of first choice of mode of therapy in the Saudi local practice. The aim of the study therefore was to identify clinical and treatment profile of Graves' disease in Saudi subjects.

Patients and Methods

The study was conducted at King Khalid University Hospital (KKUH) Riyadh on patients who satisfied the inclusion criteria highlighted below. This large tertiary center caters for patients referred from all over the Kingdom. All hospital admissions were recorded electronically by the same medical record staff using codes according to the international classification of diseases (ICD). We retrieved files of patients admitted with Graves' disease between January 1995 and December 2004 following approval from the ethics committee of the hospital. We also reviewed the following data: age, sex, presenting signs and symptoms as well as duration of symptoms prior to presentation, routine biochemical and hormonal investigations and nuclear scans. Graves' disease was defined as the presence of biochemical hyperthyroidism (elevated serum free T4 concentration and undetectable TSH) together with an elevated diffuse thyroid uptake seen in 99mTc-pertechnetate scan. If an uptake scan was not available, the presence of biochemical hyperthyroidism with two of the following was required: diffuse goiter, significant titer of thyroid peroxidase and/or thyroglobulin autoantibodies (a titer of 1:100 was considered significant), and presence of thyroid ophthalmopathy. Data were also collected from archived laboratory data, and, when needed, from discussion with the patients endocrinologist. Free T4, Free T3 and TSH were measured by ELISA (Enzymun-Test, Boehringer Mannheim Immunodiagnostics, Mannheim, Germany) until year 2000, and then by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA). Thyroid autoantibodies were measured by an antibody agglutination test (SERODIA-AMC and SERODIA-ATG, FUJIREBIO INC., Tokyo, Japan). The presence or absence of goiter was assessed clinically by a staff endocrinologist during

the patient's first visit to the endocrine clinic. The size of goiter could not be retrieved due to lack of documentation. Eye disease was defined according to the presence of eye signs in categories 2-6 of the NOSPECS classification.[13] The following factors were assessed and recorded in the database: presence of diffuse goiter, presence of eye disease, autoantibody status and titer, and serum concentration of TSH, free T4 and free T3.

Results

The demographic, clinical, and laboratory characteristics at presentation of the 194 patients with Graves' hyperthyroidism are summarized in table 1. Over two-thirds were females, while males were less than a third of the patients M:F::1:2.9. Mean age at diagnosis was 32 ± 0.9 years (range 8-69). All the patients had high levels of free T4 and T3, with a mean of 53 ±1.8 pmol/L and 28 ± 1.8 pmol/L respectively. Of the 108 patients tested for the thyroid antibodies, 69.4% were shown to be positive as against negative values in 33 patients (30.6%).

Table 2 depicts clinical features of patients with Graves' disease at first clinic visit. The most common symptoms were palpitation, tremors and weight loss each representing over 50%. Other symptoms recorded included excessive sweating (45%), heat intolerance (31%), and nervousness (27%), while menstrual disturbances and diarrhea accounted for 16% and 11% of patients respectively. On the other hand, exophthalmos, tremors, and tachycardia ranked top on the list of clinical signs representing over 40% for each. Proximal myopathy was seen in 8% and atrial fibrillation was recorded in 4% of patients. Graves' ophthalmopathy was noted in 54% of patients; the vast majority had mild disease, consisting of exophthalmos and/or conjunctival irritation, i.e. categories 2 and 3 of the NOSPECS classification.

Figure shows comparison mode of therapy of hyperthyroidism in three major studies in Saudi Arabia from 1989 to date. Medical therapy was the definitive treatment of choice in 66% of patients in 1989 study as compared to 38% in the present study. On the other hand, radioiodine was used in 9% in early days in contrast to a higher value of 49% in the present study. The choice of surgery fell gradually from 25% to current level at 13%.

Table 1. Clinical and biochemical characteristics of patients with Graves' disease.

Patients	Number (%)
Total	194 (100)
Males	54 (28)
Females	140 (72)
Male: Female ratio	1:2.9
Age (Mean + SEM)	32 + 0.9
FT4 at diagnosis (Mean + SEM)	53 + 1.8
FT3 at diagnosis (Mean + SEM)	28 + 1.8
Positive thyroid antibodies	75 (69.4)
Negative thyroid antibodies	33 (30.6)

Table 2: Clinical signs and symptoms of patients with Graves' disease at presentation.

Symptom	Number (%)	Sign	Number (%)
Palpitation	140 (72)	Exophthalmos	95 (49)
Tremors	99 (51)	Tremors	90 (46)
Weight loss	98 (51)	Tachycardia	79 (41)
Sweating	88 (45)	Sweaty palms	51 (26)
Heat intolerance	60 (31)	Brisk tendon reflex	39 (20)
Nervousness	52 (27)	Bruit	33 (17)
Fatigue	48 (25)	Proximal myopathy	16 (8)
Eye symptoms	44 (23)	Atrial fibrillation	7 (4)
Goiter	42 (22)	Lymphadenopathy	2 (1)
Anxiety	42 (22)	Vitiligo	2 (1)
Irregular menses	31 (16)	Acropathy	1 (0.5)
Diarrhea	19 (10)	Pretibial myxoedema	1 (0.5)
Irritability	11 (6)	-	-
Asymptomatic	7 (4)	-	-
Decreased appetite	4 (2)	-	-
Others	7 (4)	-	-

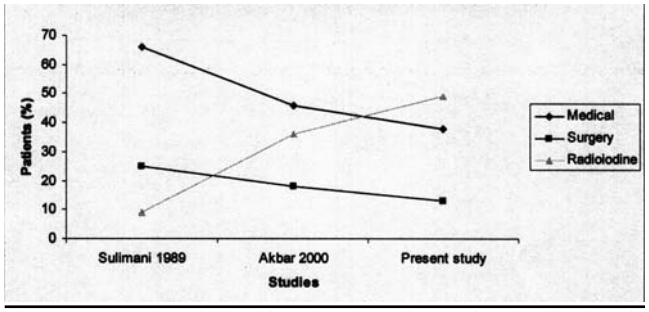

Figure. Comparison of 3 modalities of therapy in patients with Graves' hyperthyroidism in Saudi Arabia from 1999 to 2007.

Discussion

Although Graves' disease in Saudi subjects, though a predominant disease of young females, a higher proportion of males are also affected as seen earlier.[7] The patients in the study group were representative of the adult Saudi population as KKUH is a national referral center from all over the country. In our study, we reported male: female ratio of 1:2.9 which is lower than the reports from the western series of 1:5 to 1:7 with higher female preponderance.[1,14] The reason for the relatively higher proportion of males affected in our population as compared to Caucasian population is not known. Remarkably, Saudi Arabia is not known to have endemic goiter due to low iodine in which repletion with iodized salt tends to uncover excess Graves' disease in the

population.[15,16] Furthermore, there was no disproportionately high level of autoimmune markers in our male cohorts. More studies are needed to clarify this observation.

Interestingly, sympathetic over-activity in the form of palpitation and tremors was noted to be the commonest mode of presentation of Graves' disease in Saudi subjects as is seen in most parts of the world.[17,18] However, a notable observation in our study was the rarity of pretibial myxedema in which we recorded 0.5% of patients with this clinical sign in contrast to 5% reported in Caucasian subjects with the disease.[19] Similar observation was made in Arabs and Negroid population of Africa.[6,7] The reason for the apparent disparity is still yet to be explored.

Another interesting aspect of our study was the absence of hyperpigmentation which was reported in 71% of Malenesian patients with thyrotoxicosis thought to be due to excessive secretion ACTH or melanin.[3,20] The lack of documented hyperpigmentation in our Graves' disease subjects might not be due to smaller sample size as others did not find this clinical sign in their studies.[7,8] However, it is important to note that observations from other studies may contain some missing information. Nevertheless, our result is in agreement with other reports.[17,20]

The three most commonly used therapies for Graves' disease are RAI, anti-thyroid drugs and surgery. In a landmark survey it was noted that physicians' preference for treatment of hyperthyroidism in different parts of the world varied widely.[21,22] For instance, majority of physicians in Europe and Japan preferred antithyroid agents as a first line therapy than radioiodine, which is favoured in North America.[12,23] However, approach to treating hyperthyroid diseases changed substantially in recent years among physicians in the West with a shift towards RAI and away from anti-thyroid drugs and surgery as a result of established safety profile of radioiodine therapy.[24] Clearly, we have shown similar drift towards RAI use in treatment of Graves' hyperthyroidism in Saudi patients where only 9% of patients received the therapy in a similar study conducted by Sulimani et al almost 2 decades ago[7]; increased to 36% 10 years later[8], and to a much higher percentage of 49% in the current study. On the other hand, use of antithyroid drugs as a definitive therapy for our patients fell from 66% in earlier report[7] to 38% in the current study. Use of surgical option in the management of Graves' disease in our patients remained relatively low, similar to the current trend worldwide.[11,25]

In conclusion, the clinical manifestation of Graves' disease in our hospital is comparable with those reported in the literature with the exception of relatively higher males affected and rarity of pretibial myxedema and hyperpigmentation. In addition, there is a noticeable increased utilization of RAI as compared to previous studies in the same region.

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