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Journal of Endocrinology, Diabetes & Obesity

Research Article

Clinical Profile and Long-Term Remission in Patients with Graves' Disease: *The Tripoli Medical Centre Experience*

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Submitted: 20 November 2018

Accepted: 20 March 2018

Published: 22 March 2018

ISSN: 2333-6692

Keywords

- Graves disease
- Hyperthyroidism
- Anti-thyroid drugs
- Radioactive iodine therapy
- Tripoli medical center
- Libya

Abstract

Background: Graves' disease (GD) is an autoimmune disease characterized by goiter hyperthyroidism and ophthalmopathy. Treatment options include anti-thyroid drugs (ATD), radioactive iodine (RAI), and surgery.

Objective: To determine the clinical features at presentation, mode of treatment, and long-term outcome of GD in our region and to determine the whether the duration of ATD treatment, patient gender, and age at presentation can predict the long-term response rate.

Methods: Retrospective review of medical records of 145 consecutive Libyan patients with GD who were treated at the endocrine clinic of the Tripoli Medical Center (TMC) during the period between June 2005 and April 2007. Demographic data, presenting clinical features, and the results of thyroid function test at the time of the first presentation were obtained. Mode of treatment and the long-term outcome were recorded

Results: A total of 145 patients were reviewed, 71.7% were female and 28.3% were males. Mean age was 36.7±11.8 years (Range 16-70) and mean duration of follow up was 5.7±3.9 years (Range 1-12) years. Tremor (64.8%), weight loss (54.5%), and palpitation (53.1%) were the most common clinical manifestations. 76.6% were treated only with antithyroid drugs (ATD), 16.6% received radioactive iodine (RAI), and 6.9% underwent surgery. Long-term remission rates for ATD, surgery, and RAI were 59.1%, 88.9%, and 87% respectively.

Conclusion: Clinical manifestations of GD in our patients were comparable with those reported in the literature. There was an underuse of second-line treatment, namely surgery, and RAI therapy.

INTRODUCTION

GD is the most common cause of hyperthyroidism, accounting for 50 to 80 percent of all cases [1,2]. GD affects about 0.5% of the population. The peak incidence is in the age group 40 to 60 years, but any age can be affected [1,2].

GD occurs with greater frequency in females, with a female to male ratio of 5:1 to 10:1, which may relate to the effects of estrogens on the immune system [3,4] .

Graves' disease is an autoimmune disease caused by IgG antibodies, thyrotropin receptor antibodies (*TRAb*), which bind to and activate the TSH receptor, and causing thyroid enlargement (goiter), and increased thyroid hormone production (hyperthyroidism) [1].

Ophthalmopathy characterized by inflammation of periorbital and retro-orbital connective tissue, fat, and muscle are clinically evident in approximately one-third of patients [5]. Dermopathy and acropachy are rare extrathyroidal manifestations of GD. Several associated genetic loci have been identified, conferring susceptibility to GD [6]. In regions of iodine deficiency, iodine supplementation precipitates Graves' hyperthyroidism and other types of hyperthyroidism, by means of the Jod–Basedow phenomenon.

The current management strategies for the treatment of patients with GD include ATD, thyroid ablation with radioiodine and surgery (near total or total thyroidectomy).

In our center, ATD is the first line therapy, while radioiodine and surgery are utilized as a second line therapy. The evidence suggests the optimal duration of anti-thyroid drug therapy for the titration regimen is 12–18 months. Long-term remission rate after the first episode of hyperthyroidism varies considerably between geographical areas [7-10].

The geographical differences in iodine intake account for some variations in remission rates. High iodine intake has

been suggested to be associated with increased relapse rates in patients treated with ATD alone [11].

Considerable variability in clinical practices is seen both between and within countries in the diagnosis and treatment of the disease.

The aim of this study is to determine the clinical features at presentation, mode of treatment, and long-term outcome of treatment of GD in our region and to determine whether the duration of treatment, patient gender, and age at presentation can predict the long-term response rate to treatment.

PATIENTS AND METHODS

This was a retrospective analysis of medical records of Libyan patients with Graves' disease (GD) disease consecutively treated at the endocrine department of the Tripoli medical center during the period June 2005 through to April 2007.

Demographic data and clinical features at the time of presentation at our outpatient clinic were obtained. Results of thyroid function test, pulse and blood pressure at their initial presentation were also recorded.

Mode of therapy, antithyroid drugs, thyroidectomy, and/or radioactive iodide was reported. Long-term outcome of treatment was recorded only for patients who had completed a follow-up duration of two years or more.

Patients who had a follow-up period less than 2 years after their diagnosis were excluded.

The outcome of treatment was defined as hyperthyroid (Toxic), if still on antithyroid medications, euthyroid, if on no medication or hypothyroid if on replacement therapy with L-thyroxine.

The patient was considered in remission, if maintained a euthyroid, or hypothyroid state requiring replacement therapy, for at least one year prior to the last follow up visit.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS Inc., IBM, US), 19th version. Continuous variables are expressed as mean ± standard deviation (SD) and range. Categorical data are expressed as numbers and percentages. Student's t-test was used to compare continuous variables and qualitative variables were analyzed with the chi-square test.

This study was carried out in accordance with the principles of the Helsinki Declaration. A formal approval was obtained from institutional authorities.

RESULTS

Out of the 145 diagnosed cases of Grave's disease, their mean age was 36.7±11.8 years (Range 16-70). 117 (80.7%) were below the age of 46 years 41 (28.3%) were males and 104 (71.7%) were female, the female to male ratio was 2.5:1.

The mean age for males was 37.6±12.1 years and for females 36.4±11.8 years. No significant difference in age at presentation between male and female gender (p-value =0.598). Table 1 Tremor 94 (64.8%), weight loss 79 (54.5%), palpitation 77 (53.1%), followed by increased sweating 53 (36.6%) were the most common clinical manifestations.

Other clinical features were heat intolerance 51 (35.2%), nervousness 31(21.4%), fatigability 27 (18.6%), increase appetite 16 (11.0%) and diarrhea 14(9.7%).

Cardiac clinical feature were present in 24 (16.4%) patients: 22 patients (15.2%) had dyspnea and 4 patients (2.8%) had atrial fibrillation (AF). Exophthalmos was present at diagnosis in 55 (37.9%) Table 2.

The frequency of exophthalmos among males was higher (43.90%) than in female patients (35.60%), but the difference was statistically insignificant, p-value=0.352.

Exophthalmos frequency was higher among those with duration of follow up less than five years (46.20%) than those with longer follow up (28.40%), p-value=0.028 and among those ≤ 25 years of age (56.50%) compared to older age groups, 35.6% of the age group (25-50) years and 25.0% of patients ≥ 50 years of age p-value=0.081.

The mean duration of follow up was 5.7±3.9 years (Range 1-12). 25 (17.2%) lost to follow-up in less than 2 years after diagnosis and 120 (82.8%) had continued their follow up for 2 years or more. All patients received ATD thionamides as a first-line therapy. Carbimazole was the treatment of all patients, except one pregnant patient treated with propylthiouracil. 111 patients (76.6%) received only medical treatment, 10 patients (6.9%) underwent surgery and 24 patients (16.6%) received RAI. For those who had continued the follow up for 2 years or more, 88 patients (73.3%) received only medical treatment, 9 patients (7.5%) underwent surgery and 23 patients (19.2%) received RAI. The final outcome of treatment was reviewed only in patients who completed duration of follow up for 2 years or more. The rate post-therapy hypothyroidism was higher in those treated with I131 (82.60%) or surgery (66.70%) comparing to those who had received only medical therapy (13.60%) (p-value=0.000). 45.50% of those who had received only medical therapy had achieved euthyroid state compared to those who had undergone surgery (22.20%) or received RAI therapy (4.30%) (p-value=0.000) Table 3. Males were more likely to undergo ablative therapy (36.4%) than female (20.6%), although the difference was not significant (p-value=0.171).

Table 4 summarizes the effect of patient's gender, age, and duration of follow up with on the long-term outcome of treatment for hyperthyroidism in Libyan patients with Graves' disease. The rate of hypothyroidism was higher in older age group (≥ 50 years), and the rate of achieving euthyroidism was higher in the ≤ 25 years age group, p-value =0.025.

The rate of hypothyroidism was more in those who had continued a follow up period of more than five years (41.8%) than those with lesser follow up periods (17.0%), p-value =0.001, and in male (48.5%) than female patients (24.1%), while the rate of achieving euthyroidism was more in female (43.7%) than male (15.2%), p-value =0.006.

DISCUSSION

Graves' disease (GD) is an autoimmune disorder characterized

Table 1: Baseline characteristics of patients.

Variable		Patients n (%)
Total no. of patients		145 (100%)
Age (Years) *		36.7±11.8(16-70)
Gender	Female	104 (71.7%)
	Male	41(28.3%)
Age group	≤25	23(16.0%)
	25-50	101(70.1%)
	≥50	20(13.9%)
TSH (μIU/ml) *†		0.01±0.02(0.00-0.07)
Total T4 ((nmol/l) *‡		254.4±58.9(83.0-320.0)
Follow up duration (Years) *		5.7±3.9(1-12)
Duration of follow up	≤ 5 years	78(53.8%)
	> 5 years	67(46.2%)
Treatment modality	medical	111(76.6%)
	surgery	10 (6.9%)
	RAI	24(16.6%)

*Mean±SD (Range), †Normal range of total T4 in adults is 64 to 154 nmol/L.
‡Normal range of TSH is 0.1-5 μIU/ml.

Table 2: Frequency of thyrotoxic symptoms in decreasing frequency.

Hand Tremor	94 (64.8%)	*Headache*	5 (3.4%)
Weight loss	79 (54.5%)	Atrial fibrillation (AF)	4 (2.8%)
Palpitation	77 (53.1%)	*Hyperpigmentation*	3 (2.1%)
Exophthalmos	55 (37.9%)	*Weight* gain	3 (2.1%)
Increased sweating	53 (36.6%)	Hair loss	2 (1.4%)
Heat intolerance	51 (35.2%)	Decreased appetite	2 (1.4%)
Nervousness	31 (21.4%)	*Hyperemesis gravidarum*	1 (0.7%)
Fatigability	27 (18.6%)	*Hyperactivity*	1 (0.7%)
Breathlessness	22 (15.2%)	*lymphadenopathy* (*LAP*)	1 (0.7%)
Increased appetite	16 (11.0%)	Related to menstrual cycle *	8 (7.7%)
Diarrhea	14 (9.7%)	Incidental diagnosis	2 (1.4%)

* Oligomenorrhea, Amenorrhea or Menorrhagia (For female patients)

Table 3: Long term outcome according to the modes of therapy.

Mode of therapy	Euthyroid	Toxic	Hypothyroid	P value
ATD (88)	40 (45.50%)	36 (40.90%)	12 (13.60%)	0.000
Surgery (9)	2 (22.20%)	1 (11.10%)	6 (66.70%)	
RAI(23)	1 (4.30%)	3 (13.00%)	19 (82.60%)	
Total(120)	43 (35.80%)	40 (33.30%)	37 (30.80%)	

Abbreviations: ATD: Anti-thyroid drugs, RAI: Radioactive iodine.
$p < 0.05$ considered significant.

Table 4: The relationship of gender, age and duration of follow up with the long term outcome of treatment for hyperthyroidism in Libyan patients with Graves' disease.

Long term Response in all treatment modalities Total number =120		No (%)	Euthyroid 43 (35.8%)	Toxic 40 (33.3%)	Hypothyroid 37 (30.8%)	P value
Age group	≤ 25	18 (15.0%)	9 (50.0%)	7 (38.9%)	2 (11.1%)	0.025
	26-49	85 (70.8%)	33 (38.8%)	26 (30.6%)	26 (30.6%)	
	≥ 50	17 (14.2%)	1 (5.9%)	7 (41.2%)	9 (52.9%)	
Duration of follow up	≤5	53 (44.2%)	18 (34.0%)	26 (49.1%)	9 (17.0%)	0.001
	>5 years	67 (55.8%)	25 (37.3%)	14 (20.9%)	28 (41.8%)	
Sex	Male	33 (27.5%)	5 (15.2%)	12 (36.4%)	16 (48.5%)	
	Female	87 (72.5%)	38 (43.7%)	28 (32.2%)	21 (24.1%)	0.006

Long term Response to drug treatment Total number =88		No (%)	Euthyroid 40 (45.5%)	Toxic 36 (40.9%)	Hypothyroid 12 (13.6%)	P value
Age group	≤25	13 (14.8%)	7 (53.8%)	6 (46.2%)	0 (0%)	0.091
	26-49	65 (73.9%)	32 (49.2%)	23 (35.4%)	10 (15.4%)	(0.043)*
	≥ 50	10 (11.4%)	1 (10.0%)	7 (70.0%)	2 (20.0%)	
Duration of follow up	≤ 5	45 (51.1%)	18 (40.0%)	24 (53.3%)	3 (6.7%)	0.025
	>5 years	43 (48.9%)	22 (51.2%)	12 (27.9%)	9 (20.9%)	
Sex	Male	20 (22.7%)	4 (20.0%)	10 (50.0%)	6 (30.0%)	
	Female	68 (77.3%)	36 (52.9%)	26 (38.2%)	6 (8.8%)	0.01

*Difference in response between age group ≤25 & ≥50, $p < 0.05$ considered significant.
Abbreviations: ATD: Anti-Thyroid Drugs, RAI: Radioactive Iodine

by a variable combination of hyperthyroidism, ophthalmopathy, and dermopathy. Female sex is an important risk factor for GD in part as a result of the modulation of the autoimmune response by estrogen [1]. 71.7% of our GD patients were female, with a male to female ratio of 2.5:1. In studies from Saudi Arabia, the female to male ratio ranges from 1.4 to 3.8 [12].

Female predominance is typical of most thyroid diseases, including multinodular goiter and differentiated thyroid carcinoma [2]. One explanation is that the promoter for certain genes such as Class II HLA molecules may have estrogen receptor response elements and thus be activated more easily in women [4].

The mean age at onset in our study was 36.7 ±11.8 years and 64.8% of our patients were between 25-45 years, this is narrower than the age range reported in the literature [1,12].

The most common symptoms of GD are hand tremor, weight loss with a normal or increased appetite, palpitations, heat intolerance, and irritability.

Nordyke et al., reported that with increasing age, weight loss becomes more common, whereas heat intolerance is less common [13]. Compared to the present study where weight loss affected more than 50% of those younger than 55 and 28.6 % of those ≥ 55 years. In our study heat intolerance is less prevalent in those ≤25 years of age (13%) compared to older age groups. As reported elsewhere, cardiac symptoms are common at presentation in patients over 50 years of age [13,14]. In our patients, the mean heart rate was higher in the younger age group while the mean systolic blood pressure was higher in the older age group. Older patients are less likely to have tachycardia [14]. Graves' ophthalmopathy (GO) is clinically evident in about 30 - 50% of patients with GD, and in more than 80% of patients who undergo orbital imaging [1,15].

GO has a bimodal peak in the fifth and seventh decades of life. It is more frequent in females but tends to be more severe in males [5,15].

Our study showed that 37.9% of Libyan patients with GD had GO, which seems to be more prevalent in males, and younger patients compared to females and those older than 55 years of age.

All patients received ATD as a first-line therapy. Carbimazole is the ATD used in Libya. Carbimazole is a pro-drug as after absorption it is converted to the active form, methimazole, so it has similar efficacy to methimazole [16].

Studies showed that methimazole had a better efficacy in restoring the euthyroid state much faster than propylthiouracil, although no difference between them in the recurrence rate after withdrawal of medication [17].

Serious hepatic side effects were linked to propylthiouracil, thus methimazole is the preferred drug for treatment of GD patients as recommended as by ATA guidelines [16]. The only indication for PTU is pregnant women during the first trimester [16,7].

ATDs are effective in restoring the euthyroid state, but the long-term remission rates are low, varying between 30–50% [8-10,16].

The rest will need repeated courses of drug therapy to achieve remission or maintained on the drug for years or indefinitely or were given other treatment modalities [8,7,18].

The variation in remission rates with ATD between different studies may be related to geographical differences in iodine status, where increased iodine intake was associated with lesser response to medications. [11] Longer duration of treatment was found to be associated with increased response rate [19]. In the present study (27.9%) of patients who continue medical treatment for more than five years remained toxic compared to (53.3%) of those with lesser follow up duration (p-value=0.025). Those who failed to enter remission with antithyroid medication were well maintained the euthyroid status with small doses of thioamides. In a study with over 10 years of follow-up for 26 GD patients on low dose methimazole, no serious problems were reported, and the cost was approximated that of RAI therapy [20].

Some patients opt for long-term ATD therapy for years or even decades, and there is no theoretical reason why not to continue antithyroid drug therapy indefinitely if the euthyroid state is maintained with small doses of antithyroid drugs [9,16]. Graves' disease as other autoimmune diseases, may fluctuate in its activity, and patients may occasionally enter remission without any specific therapy being given [21]. Although such spontaneous remission may be the reason that a fraction of patients treated with ATD remains euthyroid after the stop of medication, evidence accumulated that treatment with anti-thyroid drugs was accompanied by remission of GD beyond the natural history of the autoimmune aberration [22].

Most patients who become euthyroid with drug therapy will eventually develop spontaneous hypothyroidism [23,24]. The annual incidence of subclinical hypothyroidism is 2.5%, and of overt hypothyroidism 0.6% [24].

Many retrospective studies showed that younger age (<40 years), smoking, male gender, thyroid gland size, the presence of ophthalmopathy and high titers of *TRAb* at the beginning and at the end of therapy are associated with a relatively poor response to ATD and higher recurrence risk [25-27].

The prevalence of cigarette smokers was low in our study, therefore, future large cohort studies with more smokers are required in order to investigate the association between GD and smoking among Libyan patients.

Age less than twenty-five years (53.8%) and female gender (52.9%) were more likely to be associated with the euthyroid state with medical treatment compared to older age groups (10.0%) and male gender (20.0%) ($p<0.05$).

The rate of hypothyroidism in response to medical treatment was higher in those ≥ 50 years of age (20.0%) and with a male gender (30.0%) compared to those younger than 25 years (0%) and female gender (8.8%) ($p<0.05$).

In a retrospective study of long-term prognosis after the medical treatment of GD in northern Swedish patients with a median follow-up of 2.8 years and maximal follow-up of 10 years, the long-term remission rate during 10 years was 56.5% and age, gender, current smoking, and ophthalmopathy did not predict relapse. [10] Another prospective study included 306 Chinese patients with GD treated with ATD demonstrated that gender, family history of thyroid diseases and smoking, did not significantly affect disease relapse rates [27].

Medical treatment with ATD requires adherence to the prescribed medications and follow up schedules for many months or years, more frequent visits to the doctor, monitoring for the occasional side effects, and it has a lower permanent remission rate compared to other treatment modalities.

In Europe, most physicians prefer to treat Graves' disease initially with antithyroid drugs, and secondarily with 131-I or less frequently surgery [28].

In the United States, RAI has been the therapy most preferred by physicians, but a trend has been present in recent years to increase use of ATDs and reduce the use of RAI [7].

Less than 10% of our patients underwent surgery as a second line treatment for Graves' disease. Surgery is seldom recommended for the treatment of hyperthyroid Graves' disease, it may be appropriate when other modalities are contraindicated, or when a thyroid nodule thought to be malignant also requires surgical intervention.

The disadvantages of surgery include the expense, the risks of surgery itself, and the risks of damage to recurrent laryngeal nerve, hypoparathyroidism, hypothyroidism, and recurrence.

None of them developed complications, the remission rate was better than RAI, and more patients achieved euthyroid state than those in the RAI group.

In presence of experienced surgeons, thyroidectomy is a safe and effective treatment for GD. Furthermore, surgical treatment gives the fastest results with lower recurrence rates than RAI or ATD [29]. Only 19.2% of GD patient in our study were treated with RAI as a second line after medical treatment failure. Although radioiodine is a more effective means of curing hyperthyroidism and is used as both first-line treatment and in those who relapsed disease after medical therapy, the risk of permanent hypothyroidism is high and it is difficult to titrate doses for individual patients accurately in order to guarantee a euthyroid state [30].

Nevertheless, RAI treatment early in the course of GD management will allow the patient to achieve a stable thyroid status earlier in the course of therapy and save several years of regular outpatient clinic visits and possible upsets caused by the frequent relapses of the hyperthyroid state. Thus, RAI treatment should be discussed at an early stage with patients.

One randomized, controlled trial compared the effects of the three modalities of therapy of Graves' hyperthyroidism. After 18 months of treatment with methimazole, 16% had adverse reactions, 6% had an inadequate response to therapy, and 37% had a relapse. Of patients who underwent surgery, 6% had a relapse and none had complications. And hypothyroidism developed in all patients treated with radioiodine [31].

Our study has highlighted the current practice in the treatment of Grave's thyrotoxicosis in our center. Considerable variability in clinical practices is seen both between and within countries in the diagnosis and treatment of the disease.

The initial management of GD among American thyroidologists is to prescribe radioiodine therapy at an early stage of management, although a trend has been present in recent years to increase the use of ATDs and reduce the use of RAI. A 2011 survey of clinical endocrinologists showed that 59.7% of respondents from the United States selected RAI as primary therapy for an uncomplicated case of GD, compared with 69% in a similar survey performed 20 years earlier [7].

While in Europe and Asia GD was treated initially with antithyroid drugs, and secondarily with 131-I or less frequently surgery [7,8].

Our study has a number of limitations, including its retrospective nature, a small sample size, and the fact that it was conducted at a single endocrine center.

Further large-scale prospective studies are needed to assess the protocols adopted by Libyan endocrinologists for the management of GD patients in real practices.

CONCLUSIONS

Clinical manifestations of GD in our patients were comparable with those reported in the literature. There was an underuse of second-line treatment, namely surgery, and RAI therapy. Longer duration of ATD treatment seems to increase the remission rate in our GD patients.

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Cite this article

El-Shareif HJ (2018) Clinical Profile and Long-Term Remission in Patients with Graves' Disease: The Tripoli Medical Centre Experience. J Endocrinol Diabetes Obes 6(1): 1116.