

# Graves' Disease in Senegal: Clinical and Evolutionary Aspects

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## Abstract

**Objectives:** To assess the clinical particularities and management of Graves' disease at the Medical Clinic II of the Abass Ndao Hospital Centre in Dakar. **Patients and methods:** This was a retrospective, descriptive study on records of patients monitored for Graves' disease from 1 January 2010 to 31 December 2014 (5 years). Socio-demographic, clinical treatment and changing parameters were evaluated. **Outcomes:** 878 patients were included and among them 542 had been monitored for at least 18 months. The sex ratio (M/F) was 0.2 and the average age was  $34.8 \pm 12$  years. The average consultation period was  $10.7 \pm 2$  months. Free T4 at diagnosis was  $> 80$  pmol/l (36.6%). Prolonged medical treatment was reported in 96.7% of patients. The average dose for initial therapy with Carbimazole was  $37 \pm 9$  mg/day. Beta-blockers were used in 64% and anxiolytics in 40.5% of cases. The average period for administering the maintenance dose was 5.6 months. Patients' attendance and compliance stood at 17.7% and 53.1% respectively. Complications, mainly cardiothyreosis, were found in 13% of cases. Goitre regression was found in 13.9% of cases and that of exophthalmos stood at 19.5%. Among our patients, 38.2% were lost to follow-up. The remission rate was 36.5% and thyroidectomy involved 14.5% of patients. Only stage of goiter ( $p = 0.007$ ) and initial free T4 value ( $p = 0.003$ ) were statistically associated with remission. **Conclusion:** Graves' disease management raises follow-up problems. Indeed, the medical treatment is long while the number of patients lost to follow-up is high. As the only radical alternative available is surgery, it is therefore essential to promote the development of radioactive iodine therapy to expand the therapeutic choice.

## Keywords

Graves' Disease, Treatment, Remission, Senegal

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## 1. Introduction

Graves' disease is an autoimmune hyperthyroidism characterized by a thyrotoxicosis syndrome, vascular diffuse goitre, exophthalmos and presence of anti-TSH receptor antibodies. It is the most common cause of hyperthyroidism with frequencies ranging from 45% to 60% [1] [2]. It usually occurs in young women 91.3% [1]. The choice of treatment differs depending on schools and continent. It is based on three methods of treatment: conservative medical treatment by synthetic anti thyroid drugs, thyroidectomy and radioactive iodine therapy [3]. In United States, radioactive iodine therapy is mostly used [4]. However, in Europe and in Africa Senegal, the extended treatment with synthetic anti thyroid drugs remains the first line option [1] [2]. However, this treatment is a source of relapse, a rate of 53.9% as reported in China [5]. We deemed it appropriate to review progress made in the clinical presentation and the evolving profile of the Graves' disease in a Senegalese population under supervision at the Medical Clinic II of the Abass Ndao Hospital Centre.

## 2. Patients and Methods

This was a retrospective, descriptive study conducted at the Medical Clinic II of the Abass Ndao Hospital Center of Dakar. It focused on records of patients monitored for Graves' disease from 1 January 2010 to 31 December 2014 (5 years). All patients over 15 years old monitored for Graves' disease, on the basis of a thyrotoxicosis table associated with one or more of the following signs, were included: exophthalmos acquired, vascular diffuse goitre and pretibial myxoedema. Thyrotoxicosis was confirmed by excess thyroid hormones (free T4 and free T3) or a decrease in the ultra-sensitive Thyroid-Stimulating Hormone (TSHus). Incomplete files (lack of assessment confirmation of hyperthyroidism, incomplete clinical data) were excluded from the final analysis. A pre-arranged sheet was used as the basis for data collection. It covered the following:

**-Socio-demographic data:** age, sex, marital status, history and comorbidities. To study the hyperthyroidism trigger or self-maintenance factors, the patients were grouped into three categories: category 1 (marital and/or social and family conflicts such as divorce, single mothers, celibacy, difficulties within the couple and/or family or in-laws); category 2 (economic, professional, educational difficulties); category 3 (psych emotional shocks such as death of a close relative, infertility, sentimental disappointment).

**-Clinical data:** signs of thyrotoxicosis and signs specific to Graves' disease (goitre, exophthalmos, dermopathy). The classification of the World Health Organization, 1962, was used to classify goitre in stages. The associated pathologies were evaluated.

**-Paraclinical data:** values of thyroid hormones, ultra-sensitive TSH determined by immuno-radiological methods. Standards ranged from 0.17 to 4.05 mIU/l for TSHus, from 9 to 22 pmol/l for free T4 and from 2.5 to 5.8 pmol/l for free T3 were used. Cervical ultrasound, electrocardiogram and cardiac ultrasound were performed if required.

**-Treatment data:** the study of the medical treatment concerned the time limit for receiving appropriate care, prescription of drugs (synthetic anti thyroid drugs, beta-blockers and anxiolytics), dosage and treatment duration. The evaluation of surgical treatment focused on indications and the type of surgery.

**-Evolution data:** data on changes in patients who were monitored for at least 18 months. Complete remission was defined as a sustainable stabilization of the disease after 12 months of discontinuation of medical treatment. The complications that were investigated were cardiothyreosis, acute thyroid crisis and malignant exophthalmos.

For descriptive analysis purposes, data were presented in percentage for qualitative variables and in averages for quantitative variables. Chi-2 test were used for bivariate analysis and Fisher test for quantitative data. A p value < 0.05 was considered statistically significant with a confidence interval of 95%. Data were evaluated with Epi Info and SPSS 24.

## 3. Outcomes

### 3.1. Sociodemographic Aspects

878 cases were included. These were 709 women and 169 men, or a sex ratio (M/F) of 0.2. The average age was  $34.8 \pm 12$  years (range of 16 - 83 years). The most affected age group was that of 31 - 59 years old with 55.1% of cases and subjects who were at least 60 years old accounted for 4.2% of cases. Married patients represented 52.8% of cases; a family thyroid dysfunction was found in 18.2% of cases. With regard to the trigger or self-

maintenance factors, social and family and/or conjugal conflicts (category 1) predominated in 22.8% of cases followed by psycho emotional shocks (category 3) in 14.9% of cases. In 55.5% of cases, no specific psycho emotional situation had been described.

### 3.2. Clinical Aspects

The average time for consultation was  $10.7 \pm 2$  months. The patients seen in the first six months accounted for 46.8% of cases. Thyrotoxicosis signs are shown in **Table 1**. Signs associated with thyrotoxicosis were exophthalmos in 65.9% of cases (including 62.3% bilateral), pretibial myxoedema in 1%, melanoderma (9.1%), alopecia (7.5%). Goiter was found in 97.3% of which 75.3% of stages 2 and 3. Diabetes mellitus was found in 6.5% and impaired fasting glucose in 15.1% of cases. Associated pathologies were arterial hypertension (17.1%) and obesity (3.7%).

### 3.3. Treatment and Evolutive Data

The average starting treatment dose with synthetic anti thyroid drugs (SAT) was  $37 \pm 9$  mg/day of Carbimazole. This dose was 30 - 40 mg/day in 62.7% and more than 40 mg/day only in 25.5% of cases. Beta-blockers were prescribed in 64% and anxiolytics in 40.5% of cases.

Among our patients, 336 (38.2%) were lost to follow up. These were mainly women (95.4%), subjects aged 31 - 59 years (61.3%). The number of lost to follow-up was the highest one (11%) after the first consultation, then 10% after the first check of the 3<sup>rd</sup> month.

Among the 542 patients who were monitored for more than 18 months, the average duration of treatment of attack was 5.6 months. This duration was 3 months in 42.2% and 6 months in 25% of cases. In 56 patients (10.3%), the maintenance treatment could not be administered within 12 months of follow-up because of a lack of thyroid balance. Patients' attendance was only 17.7% while their compliance stood at 53.1%.

The rate of free T4 achieved in the follow-up consultations was 95% while that of TSH us and blood count stood at 12% and 80%, respectively. The normalization of the free T4 stood at 31.1% in the 3<sup>rd</sup> month and 24.7% from the 6<sup>th</sup> month after the start of treatment with SAT. The average time until the occurrence of iatrogenic hypothyroidism was 15.6 months. The latter was found in 10% of patients in each quarterly check. Complete goitre regression was observed in 16.4% and that of exophthalmos in 11% of cases. Complications were found in 13.9% of cases. These were cardiothyreosis (11.9%) and malignant exophthalmos (1.1%).

Remission was achieved in 198 cases (36.5%). Only stage of goiter ( $p = 0.007$ ) and initial free T4 value ( $p = 0.003$ ) were statistically associated with remission. **Table 2** shows the characteristics of patients in remission. The relapse rate stood at 28.4%.

**Table 1.** Distribution of clinical signs.

Clinical signs	Number of patients (n = 878)	Percentage
Palpitation	730	83.1%
Weight loss	702	79.9%
Trembling	610	69.4%
Insomnia	447	56.7%
Thermophobia	486	55.3%
Asthenia	471	53.6%
Excessive perspiration	440	50.1%
Irritability and nervousness	417	4.4%
Sign of weakening of muscles	255	29%
Diarrhoea	209	23.8%
Polyuria and polydipsia	172	19.5%
Genito-sexual disorders	121	1.3%

**Table 2.** Characteristics of patients in remission.

Parameters studied	Patient in remission (n = 198)		p value
Age groups (years)	(16 - 40)	129 (65.2%)	0.63
	≥40	69 (34.8%)	
Sex	Female	165 (83.4%)	0.90
	Male	33 (16.6%)	
Stage of goiter	Stage 0 - 1	65 (32.8%)	0.007*
	Stage 2 - 3	134 (67.2%)	
Exophthalmos	yes	127 (64.2%)	0.10
	No	71 (35.8%)	
SAT starting dose (mg/l)	<40	85 (42.9%)	0.22
	≥40	113 (57%)	
Initial free T4 Value (pmol/l)	<50	89 (45%)	0.003*
	≥50	109 (55%)	

\*Statistically significant link.

Seventy patients (14.5%) had received total thyroidectomy. The average age of patients was 34 years and among them, there were 52 women and 18 men. The indication for surgery was a recurrence in 37.1%, a medical treatment failure in 34.2%, a cardiothyreosis in 27.1% and a malignant exophthalmos in 1.4% of cases.

## 4. Discussion

### 4.1. Sociodemographic Aspects

Graves' disease turns out to be basically a predominantly female disease. In the literature a frequency of 7 - 10 women for one man is reported [1]. The average age of our patients was 35 years with a peak between 31 and 59 years. This corroborates the results reported by Krull *et al.* [4] in Switzerland who reported a peak of Graves' disease incidence between 30 and 50 years. In our study, social and family and/or conjugal conflicts were found in 22.8% of patients. Family and especially conjugal stress in women married may be major aetiological factors for Graves' disease. Diop *et al.* [1] and Sidibé *et al.* [6] have shown the role of these factors in the onset and maintenance of the disease.

### 4.2. Clinical Aspects

The more or less complete thyrotoxicosis syndrome was intense with a predominance of general, cardiovascular and neuropsychic signs. The frequency of associated signs such as goitre and exophthalmos is in line with the local data sets [1]. None of our patients received the dosage of anti thyroid antibodies or TSH receptor antibodies. Yet, according to data from the literature, TSH receptor antibodies offer diagnosis sensitivity higher than 90%, especially in the absence of exophthalmos [5]. The high cost is the limiting factor of their prescription in our context.

### 4.3. Therapeutic Aspects

The therapeutic strategy is different depending on the school and continents. In our series 85.5% of patients were under medical treatment. The treatment of Graves' disease in Africa and Europe is based on the medical option [1] [2] [4]. However, in the United States, 69% of patients receive first-line treatment with radioactive iodine [4].

Our preference for SAT is linked to their availability, in the absence of treatment with radioactive iodine, and finally the lack of access to thyroidectomy [1]. However, antithyroid drugs have only a suspense effect pending

a spontaneous remission of the disease. In literature the recommended SAT loading dose is 40 - 60 mg [7]. In our series, it averaged 37 mg/day. The usual treatment regimen includes an initial treatment phase from 1 to 6 months then a maintenance treatment in reduced quantities for the following 12 months [7]. In our series 67.2% of patients received attack treatment during 1 to 6 months. The average time for the administration of the maintenance treatment in our series was 5.6 months.

Only 14.5% of our patients underwent surgery. Madieng *et al.* [8] in a general surgery service report a 25.3% frequency of Graves' disease in a series of 402 thyroidectomise. None of our patients had received treatment with radioactive iodine because the latter was not available. In a study conducted in 2015 in Tunisia, Ben Sellem *et al.* [9] showed good efficacy of the administration of high doses of iodine at the very first treatment. Iratherapy has then established itself as being an alternative choice in Graves' disease, especially in developing countries. In Nigeria, Onimede *et al.* [10] shared their experience regarding iratherapy. Hypothyroidism is recognized as a major side effect of it [11].

#### 4.4. Evolutionary Aspects

The regression of goitre was found in 16.4% cases, and that of exophthalmos in 11% of cases. The volume of goitre and presence of exophthalmos were correlated with a greater frequency of relapse in some series [5] [12]. However in the series of Cappeli *et al.* [13] the goiter size and FT4 level were not predictive factors of the long-term prognosis. In the series of Shingai *et al.* [14] in India, a higher Technetium uptake was found to be significantly associated with relapse.

The TSH us was requested in only 12%. Yet its lowered rate is a predictive factor of relapse occurrence. It is the same for the increase in TSH receptor auto antibodies [5]. Unfortunately none of our patients could receive it because of the high cost of its dosage.

Approximately 35% of patients were lost to follow-up. Among the patients who reached the legal treatment duration, only 36% had a sustained remission. Our results are consistent with those reported of 32.7% in India [14], 46% in China [6] and 41.9% in Pakistan [15]. However, in Mexico Bolanos *et al.* [12] reported a lower remission rate of 17.5%. Our low rate can be explained by the low level of compliance and attendance of our patients but also by the high grade of goitre and the high level of free T4 value at diagnosis.

The relapse rate was 28.4% in our series. Rates of 53.9% and 82.5% were reported by Lin *et al.* [5] in China and Bolanos *et al.* [12] in Mexico, respectively. In India 19.2% of patients in remission in the series of Shingai *et al.* [14] relapsed.

Limitation of our study was:

-It's a retrospective study.

-Para clinical data like TSH receptor auto antibodies were not performed in patients because their cost is expensive.

## 5. Conclusion

Graves' disease is a common disease in Senegal as evidenced by the number of cases compiled over five years. Socio-demographically, it remains a disease affecting young women and does not show any clinical feature except the severity of thyrotoxicosis and the significant volume of goitre associated with late treatment. Therapeutically prolonged medical treatment is the preferred option, but the number of patients lost to follow-up is significant and relapses are common. It is therefore essential to expand the indications for surgery but also to promote the development of treatment with radioactive iodine.

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