

# Hyperthyroid graves disease – A 5 year retrospective study

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## Summary

The clinical, biochemical and immunological features of 180 patients with hyperthyroid Graves' disease managed at the Universiti Kebangsaan Malaysia (UKM) Endocrine Clinic from 1983 to 1987 were examined. The prevalence of the disease is highest in Chinese and lowest in Indians. The female: male ratio is 2.8:1. Hypokalaemic periodic paralysis and hypercalcaemia were present in 5.0% and 1.7% of the cases respectively. Pretibial myxoedema was extremely rare. Thyrotropin – binding inhibitory immunoglobulins, anti-thyroglobulin and anti-microsome antibodies were positive in 61.5%, 25.8% and 42.3% of the patients respectively. A eumetabolic state could be achieved in the majority of patients with antithyroid drugs alone. Definitive therapy with subtotal thyroidectomy or radioiodine were needed in 31.3% of cases.

*Key words:* Hyperthyroid Graves' disease, complications, autoantibodies, treatment outcome.

## Introduction

There is a paucity of local reports on Graves' disease. Our knowledge of this common thyroid disorder is adduced mainly from Western literature. The emergence and subsequent course of this disease are known to be modified by constitutional factors.<sup>1</sup> Population studies revealed an increased frequency of HLA – B8 in Caucasians, HLA – BW 46 in Chinese and HLA – BW 35 in Japanese patients with Graves' disease.<sup>2,3</sup> The incidence of relapse following withdrawal of antithyroid drug has been reported to be higher in patients with HLA – Drw 3 positive,<sup>4</sup> although other studies could not confirm this.<sup>5</sup>

We examined the clinical, biochemical, immunological and therapeutic aspects of the 180 patients with the disease seen at the Universiti Kebangsaan Malaysia (UKM) Endocrine Clinic from 1983 to 1987 inclusive to ascertain local variations in presentations and response to treatment.

## Materials and methods

Consecutive records of 180 patients with hyperthyroid Graves' disease attending the UKM Endocrine Clinic from January 1983 to December 1987 were analysed. The data collected include prevalence of the disease among the major races; clinical, biochemical and immunological aspects of the disease, and treatment modalities and outcome. The diagnosis of Graves' disease

was based on the presence of the clinical features of thyrotoxicosis with a smooth and diffuse goitre and raised serum concentrations of thyroxine (T4) and/or triiodothyronine (T3).

Serum T4 and T3 were measured using radioimmunoassay (RIA) kits from Abbott laboratories, North Chicago, USA. The normal ranges for T4 and T3 were 70 to 167 nmol/l and 1.3 to 2.6 nmol/l respectively. Thyroid autoantibodies, anti-thyroglobulin (aTG) and anti-microsome (aMic), titres were determined using enzyme immunoassay technique as described previously.<sup>6</sup> Titres of 1:100 or higher were considered as positive. Gamma-B Thyrotropin Receptor Antibody Kit from RIA (UK) Limited (Usworth Hall, Washington, Tyne and Wear, United Kingdom) was employed to detect the presence of thyrotropin – binding inhibitory immunoglobulins (TBII); inhibition of TSH binding of >10% was considered significantly positive.

Statistical analysis was done using the Chi-Square Test.

## Results

From the 180 records of patients with hyperthyroid Graves' disease reviewed, the ethnic composition and sex ratio of patients are as shown in Table 1. Comparing these with the racial distribution of UKM Physician Clinic patient population, the adjusted prevalence of Graves' disease in the Chinese is significantly higher than those of the Malays and Indians. The relative excess of prevalence of Graves' disease in Chinese compared to that of Malays and Indians are 1.5 and 7.5 respectively. The adjusted female:male ratio is 2.8:1. The age at presentation ranged from 7 to 58 years (mean 31.8 years), with the 20 to 40-year age-group comprising 82.8% of the total (Figure 1).

The autoimmune features in these 180 patients with Graves' disease are shown in Table 2. Exophthalmos and family history of thyroid disorders were common features, whilst pretibial myxoedema was extremely rare. The serum concentrations of T3 and T4 at presentation, and

**Table 1**  
**Race and sex distribution of 180 patients with hyperthyroid Graves' disease**

	M (%)	C (%)	I (%)	O (%)	Female:Male
No. of patients	91 (50.6)	82 (45.6)	6 (3.3)	1 (0.6)	3.1:1
UKM PC Population (1987)	9621 (51.2)	5690 (30.3)	3253 (17.3)	230 (1.2)	1.1:1
Relative prevalence compared to Malay (95% c.i)+	1.0	1.5* (1.1 to 2.0)	0.2** (0.1 to 0.4)	(-)	2.8:1** (2.1 to 3.8)

M – Malay    C – Chinese    I – Indian    O – Others

\*P < 0.01    \*\*P < 0.001    +c.i – confidence interval

(-) Number too small for statistical analysis

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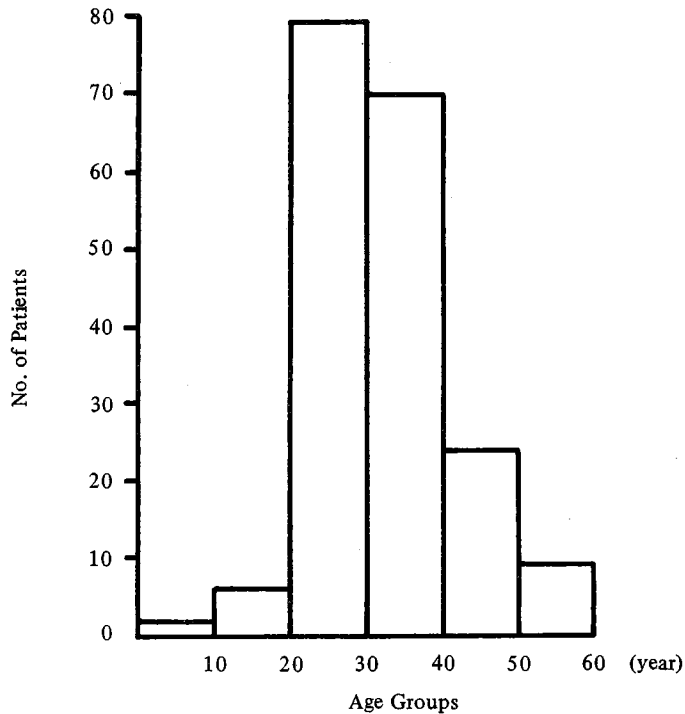


Fig. 1 Age distribution at presentation to UKM Endocrine Clinic.

**Table 2**  
Associated autoimmune features in 180 patients with Graves' disease

Condition	No. of patients (%)
Exophthalmos	60 (33.3)
Acropachy	6 (3.3)
Pretibial Myxoedema	1 (0.6)
Alopecia	6 (3.3)
Vitiligo	6 (3.3)
Myasthenia Gravis	3 (1.7)
Primary Ovarian Failure	1 (0.6)
Family History of Thyroid Dysfunction	23 (12.8)

the percentage positivity of aTG, aMic and TBII are shown in Table 3. The associated 'complications' encountered in this group of patients are shown in Table 4; the most frequent being cardiovascular (40.3%).

The mean duration of illness prior to presentation was 33.9 months with the majority of

**Table 3**  
**Biochemical and immune parameters of patients with Graves' disease**  
**at the UKM Endocrine Clinic (1983–1987)**

T4 nmol/l (mean +/- SD) (Range)	243.7 +/- 51.6 (91 to 309)
T3 nmol/l (mean +/- SD) (Range)	6.1 +/- 2.9 (2.1 to 15.0)
Positive aTG	25.8%
Positive aMic	42.3%
Overall Positive TBII	61.5%

**Table 4**  
**Complications in patients with hyperthyroid Graves' disease**  
**at the UKM Endocrine Clinic (1983–1987)**

Complication	No. of patients
Dysrhythmias	8 (4.4%)
Hypokalaemic Periodic Paralysis	9 (5%)
Hypercalcaemia	3 (1.7%)
Congestive Cardiac Failure	2 (1.1%)
Osteoporosis	1 (0.5%)

patients, (56.7%) having had some form of treatment prior to attending our Clinic (Table 5). Thirty cases (16.7%) ceased follow-up after the first consultation.

**Table 5**  
**Treatment modalities in 180 patients with Graves' disease**

	Thionamide alone	Thionamide & surgery	Thionamide & Radioiodine
At presentation	98 (54.6%)	3 (1.7%)	1 (0.6%)
At UKM Endocrine Clinic (n = 150)*	103 (68.7%)	21 (14.0%)	26 (17.3%)

\*25 patients defaulted follow-up and 5 patients referred back after the initial consultations.

The outcome of the medical treatment of the remaining patients (150 cases) is summarised in Table 6. Clinical and biochemical (defined as T3 and T4 within normal ranges) euthyroidism was achieved with the medical treatment in 90.6% of patients. The mean (+/- SD) duration of treatment before achieving euthyroidism was 4.7 (+/- 3.7) months. With antithyroid drugs, remission was obtained in 58.7% of the patients. Whilst long term remission (>/ 1 year) was observed in 26.6% of the 150 patients. Subtotal thyroidectomy and radioiodine therapy were employed in those who did not respond to the medical treatment or those at presentation, considered appropriate for the mode of treatment. These constituted 31.3% of the 150 patients.

**Table 6**  
**Outcome of medical treatment in 150 patients with hyperthyroid Graves' disease**

Euthyroid on treatment	136 (90.7%)
Remission (>/ 1 year)	40 (26.6%)

### Discussion

The clinical impression of a higher prevalence of Graves' disease among Chinese is confirmed. While, interestingly, Indians have the lowest prevalence. HLA pattern in Chinese with Graves' disease has been reported<sup>2</sup> but there is as yet no data regarding the haplotypes in Malays and Indians with the disease. In Western populations<sup>2,7</sup> the female:male ratio is 7-10:1. However, in this series and that reported by Suyuno et al.,<sup>8</sup> the ratios were 2.8:1 and 3.8:1 respectively. In our population, as in others,<sup>2,8</sup> presentation is most common in the third and fourth decades. The disease is rare before ten years and after 60 years of age.

Exophthalmos (33.3%) and a positive family history of thyroid disorders (12.8%) are the two common autoimmune features associated with Graves' disease in this study; while pretibial myxoedema was noted to be extremely rare (0.6%).

Thyroid autoantibodies are commonly present in Hashimoto's and Graves' disease.<sup>9</sup> In the latter, aTg and aMic were reported to be present in 25% and 80% of cases respectively.<sup>9</sup> Our report for aTg was comparable; however, aMic was detected in only 42.3% of the patients tested. TBII, is reported to be of value in predicting long term remission after treatment<sup>4,10</sup> and the occurrence of neonatal thyrotoxicosis in the offsprings.<sup>11</sup> In active Graves' disease, TBII activity has been reported to be present in 76%<sup>12</sup> to more than 90%<sup>13</sup> of cases. In this series only 61.5% of the cases tested were positive for TBII. This low percentage could be due to the fact that some of the patients were already on treatment with thionamides when referred. Thionamides are known to be immunosuppressive.<sup>5</sup> When only active cases were considered, 75.5% were found to be positive for TBII.

Hypokalaemic periodic paralysis, a relatively common complication of thyrotoxicosis in Asians, was noted in 5.0% of our cases (two Chinese males, five and two Malay males and females respectively). Its occurrence is reported in some 2% of all thyrotoxic patients.<sup>14</sup> The reported incidence in Chinese thyrotoxics is about 6%, being more common in males than females.<sup>15</sup> In this study, the Malays thus appear as predisposed to hypokalaemic paralysis, perhaps even more so, as the Chinese. Hypercalcaemia, however, with reported incidence of between 8-22% in thyrotoxicosis<sup>16</sup> is often not actively looked for and therefore probably under-diagnosed in our series (1.7%).

The majority of patients presented late and had some forms of treatment before being seen at our clinic. Nevertheless, a large proportion (58.7%) of these patients attained remission just on thionamides alone, with carbimazole being the commonest thionamide used. However, only 26.6% of the 150 patients achieved long term remission without resorting to surgery or radioiodides. This figure is similar to that of Ingbar's and others.<sup>2,17,18</sup> The mean duration of treatment required, in this group of patients studied, before a normal metabolic state was achieved, is relatively long (4.7 months). This is probably an overestimation as the mean interval between follow-ups is about three months. Usually a eumetabolic state could be restored in six weeks.<sup>2</sup> More rapid acquirement of a euthyroid state could be accomplished using Lugol's solution.<sup>18</sup>

The inherent limitations of a retrospective study are recognised. Certain features of a disease studied may be under – reported because they are either not actively looked for or not recorded when present. Despite these drawbacks, several useful and interesting observations were made of the 180 patients with Graves' disease seen at the UKM Endocrine Clinic.

### Acknowledgements

This study was funded by UKM Research grant 30/88. We thank assistant nurses Aion Alyias and Zainon Mohd. Nor for their dedication and help in the Endocrine Clinic. We also thank the Dean of the Faculty of Medicine, UKM, for the permission to publish this paper.

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