Observational Study

Presentation and management of Graves' disease — Experience from a tertiary care center in Eastern India

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Graves' disease has varied presentation and preference for therapeutic modality varies from country to country. We report the presentation and mode of therapy we perform in a tertiary care center in Eastern India. This is a retrospective data of 60 patients with Graves' disease evaluated and treated at Institute of Post-graduate Medical Education and Research (IPGMER), Kolkata. Patients were recruited consecutively between March 2017 and May 2017. Baseline characteristics revealed median (±IQR) age of presentation 33.1±10.1 years, F:M ratio 2.3:1, median duration 7.7±6.8 months, 28% were overweight and 20 % were smoker. Most common mode of presentation was tremor (93%), followed by palpitation (86.6%), weight loss (85%) and hyperdefecation (25%). Overall 31 (51.6%) patients had eye signs and active eye disease was present in 5 (8.3%) patients. Only 30 patients were screened for glycemic status at disease onset and 12 (40%) were found to have dysglycemia. Diagnosis of Graves' was mostly done by clinical examination (57%), followed by Isotope studies (38%) and only 3 (5%) patients by Anti TSH receptor antibodies (TRAb). Majority of the patients (70%) underwent medical therapy alone, followed by radioiodine ablation (21.6%) and surgery done in 5 (8.3%) patients only. Average radioiodine dose was 11.9 ± 2.1 mCi and only 2 (13.3%) patient needed repeat dose. 2 patients out of 5 who underwent total thyroidectomy developed permanent hypoparathyroidism. A comprehensive overview of management of Graves' disease in Eastern India is described. There is high prevalence of dysglycemia but often not screened. Requirement of usage of TRAb is still minimal and restricted to special cases only.

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Graves' disease during its first recognition in 19th century was known for a cachexic look, enlarged thyroid gland, an accelerated heart rate, and ocular abnormalities[1].With gradual increase in understanding and awareness among doctors and patients, this disease is diagnosed at much earlier stage and thus the mode of presentation has changed. Again preference for diagnostic and therapeutic modality varies from country to country. Bartalena L *et al*[2] conducted a survey among endocrinologists in Europe, North America and Asia regarding the diagnosis and management strategy of Graves. Recently Hussain YS *et al*[3] reported real life data regarding epidemiology, management and outcomes of Graves' disease in United Kingdom. Diagnostic modalities include pathognomonic clinical findings (orbitopathy, dermopathy, acropachy, brui on thyroid gland auscultation), ultrasonograhy (increased vascularity), radioisotope scan (diffuse increased uptake) and Anti thyrotropin receptor antibody (TRAb) positivity[4]. In general, medical therapy is started to control thyroid hormone production and release, with an aim to relieve symptoms and to normalise thyroid hormone levels. Following failure of medical therapy or sometimes denovo, definitive treatment with either surgery or RIA is considered. However, good quality data information on short and long-term outcomes of treatment in consecutive cohorts of patients with Graves' disease from India is lacking.

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Materials and Methods

This is a retrospective survey which included patients diagnosed as Graves' disease from Endocrinology outpatient department (OPD) Institute of Post-graduate Medical Education and Research (IPGMER), Kolkata. Sixty patients of documented Graves' disease on at least 3 month follow up were included consecutively in this survey.Data on these patients such as demographics (age, gender, BMI-body mass index and smoking status), presentation, biochemical features at onset (TSH -Thyroid Stimulating Hormone, FT4 - Free Thyroxine, T4-Total T4, T3 -Triiodothyronine, TRAb - TSH Receptor Antibody, FPG-Fasting plasma glucose, PPPG-Post prandial plasma glucose), imaging study if any, mode of treatment, outcomes and current status of disease was collected from previous documents. Those having incomplete data or those with un-

clear diagnosis were excluded from the study.

The reference ranges for normal values for the various laboratory investigations include 0.4–4 mIU/L for TSH, 0.8–1.9 ng/dl for FT4, 4.5-12 µg/dlfor T4 and 80-180 ng/dl for T3. Thyroid function was estimated mostly in our institute by the electrochemiluminescence (ECL) technique using commercially available kits from Siemens Diagnostics (Germany) with Immulite 1000 analyzer. TRAb was done from outside lab as this is not available in our hospital, so the method and interpretation was heterogeneous. Fasting plasma glucose (FPG) and post prandial plasma glucose (PPPG) reports were traced to determine glycemic status and it was defined as per American Diabetes Association (ADA) 2018 criteria[5].

The outcome of initial medical treatment was defined from biochemical response (FT4 and TSH) and clinical examination and recorded as follows: Controlled disease—normalization of biochemistry whilst on ATDs or within 1 month of withdrawal of ATDs, Disease remission—patients whose disease was controlledwith ATDs and where control was maintained for at least a month after withdrawal of medical treatment, Uncontrolled disease—persistently abnormal biochemistrydespite ATDs or intolerant to ATDs.

Statistical Package for the Social Sciences (version 14.0, SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Results on continuous measurements were presented on mean ± standard deviation (for scewed data, it was presented as median ± interquartile range--IQR) and results on categorical measurements were presented in number (N) and percentage (%). Given the observational nature of the study, approval from the regional ethics committee or individual patient consent was not deemed necessary.

Results

Consecutive 60 patients were included in this survey. Baseline characteristics revealed age of presentation 33.1 ± 10.1 [median (±IQR)] years, 4 (6.6%) patients were less than 18 years of age. Female: Male ratio was 2.3: 1 and median duration of symptoms was 7.7 ± 6.8 months. In 55 out of 60 patients had goiter Ib or more (91.6%), although only 27 (49%) patients actually noticed it. Median ± IQR BMI (in kg/m^2) was 20.7 ± 3.2 and contrary to popular belief 28% of patients suffering from Graves' disease were overweight at presentation. 12 out of 18 male patient were smoker, however none of the female patients were smoker. Glycemic status was screened only in 30 patients (50%) at onset and 3 patients (10%) patients were found to be suffering from diabetes. Another 30% patients were suffering from either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The baseline characteristics are depicted in Table 1.

Table 1 — *Baseline characteristics of Study population*

Characteristics (n=60)	Values	Comments
Age at diagnosis	33.1 ± 10.1 years	4 paediatric patients
Sex (Female:Male)	42:18	
Duration of symptoms before presentation	7.7 ± 6.8 months	4 patients were suffering for more than 24 months
Goiter (Grade Ib or more)	55 (91.6%)	Only 27 (49%) complained neck swelling
Smoking	12 (20%)	All smokers are male
BMI (kg/m^2)	20.7 ± 3.2	28% overweight
Glycemic status at presentation (n=30)	10% diabetic 30% IFG or IGT	categorisation of dysglycemia could not be done
FT4 at presentation (n=46)	4.09 ± 1.89 ng/dl	

BMI-body mass index, IFG-impaired fasting glucose, IGT- impaired glucose tolerance, FT4- free thyroxine

Mode of presentation varied widely. Most common mode of presentation was tremor (93%), followed by palpitation (86.6%), weight loss (85%) and hyperdefecation (25%). Less than 50% patients complained of neck swelling among those having Goiter 1B or more. Thyroid brui was documented in 10% patients. Two patients presented with only eye symptoms. Overall 31 (51.6%) patients had eye signs and active eye disease was present in 5 (8.3%) patients. Dermopathy and acropachy were rare and was present only on clinical examination in 2 (3.3%) and 1 (1.6%) patients respectively. Table 2 summarises different modes of presentation. Diagnosis was mostly done by clinical examination (57% cases) such as presence of orbitopathy, dermopathy, acropachy, brui on thyroid gland auscultation. 23 patients (38%) needed help of isotope studies (99m Tc pertecnatate scan) which is the preferred modality in our institute. Use of TRAb for diagnosis was seldom used. Two patients with euthyroid graves orbitopathy and one pregnant patient was diagnosed as Graves' on basis of TRAb positivity. Table 3 summarises the use of different diagnostic modalities.

The preferred mode of therapy is medical. All patients were started with medical therapy (Carbimazole is the preferred drug). More than 90% patients achieved biochemical control within 3 month. 3 patients developed sore throat (but no neutropenia), 3 patient developed jaundice and 1 patient developed skin rashes. Those who developed jaundice and skin rash were started on lithium and sent for radioiodine ablation (RAI) therapy. All others were given choice between medical therapy and RAI therapy explaining all

Table 2 — *Presenting features of Graves' disease*

Clinical features	Comments
Features of thyrotoxicosis :	
Tremor (93%)	2 patients presented
Palpitation (86.6%)	with only eye
Weight loss (85%)	swelling
Neck swelling (45%)	
Brui (10%)	
Hyperdefecation (25%)	
Extrathyroidal manifestations :	
Orbitopathy 52%	CAS = 3/7
Dermopathy 3.3%	in 5 patients
Acropachy 1.8%	

CAS = clinical activity score

Table 3 — *Use of different diagnostic modalities*

Modality	Percentage
Clinical	57%
Isotope studies	38%
Anti TSH-R antibody	5% (2 Euthyroid GO and 1 pregnant)

pros and cons. A total of 13 patients had chosen RAI therapy. Average dose required was 11.6 ± 2.9 mCi which rendered 8 patients hypothyroid, 3 patients euthyroid. 2 patients (15% of those undergoing RAI therapy) remained hyperthyroid despite 2 doses of RAI therapy, but required much less dose of carbimazole as compared to initial dose. Five patients underwent total thyroidectomy (2 patients had huge goiter, 2 patients had suspicious nodule and 1 patient had active eye disease with raised liver enzyme with carbimazole). Unfortunately 2 out 5 patients who underwent surgery developed permanent hypoparathyroidism. None of them developed vocal cord palsy. All the treatment modalities are summarised in Table 4. Among the 31 patients with orbitopathy, only 5 patients clinical activity score (CAS) = 3/7 and was treated with intravenous methylprednisolone as per our institutional protocol (Table 5). None of these patients required rituximab or orbital decompression for eye disease.

Discussion

Multiple literature worldwide have described the natural history, mode of presentation, diagnostic pitfalls and therapeutic options for graves' disease[2,6,7] but literature from India is scarce[8,9,10]. Boelaert K[11] *et al* reported weight loss, tremor and palpitations were presenting features in only 50-60% cases, whereas our study reports these symptoms to be present in 80-90% patients. Eye symptoms are also much higher in our cohort (51% *versus* 11%) as compared to that study. One of the main reason for these differences may be the age of patients as the study by Boelaert et al included only elderly individuals. Our cohort also reported a very high prevalence of goiter (91%) as compared to previous studies, possibly indicating delay in diagnosis and/or irregular treatment before presenting to us.High prevalence of dysglycemia at presentation is another interesting finding in our study. This is supported by previous literature where thyrotoxicosis per se was associated with glucose intolerance in approximately one-third of individuals, with frank diabetes occurring in a further 8% of patients[12]. Pre-existing diabetes mellitus may be aggravated or Graves' disease may be associated with type 1 diabetes as a part of polyglandular autoimmune syndrome. Also, excess thyroid hormone itself causes increased glucose production and expression of the hepatocyte glucose transporter 2 (GLUT-2) protein expression in liver[13] and there is some evidence for insulin resistance as the primary defect[12]. However despite these strong association, screening for diabetes was done only in 50% cases in our cohort.

Table 5 — *Institutional protocol for Intravenous methylprednisolone for Graves' orbitopathy*

Clinical Activity score (CAS)	Mode of treatment
CAS 1 or 2	Conservative (Methycellulose eye drop, eye ointment if lagophthalmos, Dark glasses to wear, head end elevation)
CAS = 3/7	Checklist: Blood count, Plasma glucose, renal function, LFT, Chest X Ray Infusion Methyl prednisolone 500 mg IV for consecutive 3 days? repeat this dose monthly for 4 months (Cumulative dose 6g)

In a survey done by Bartalena L[2], TRAb was an underutilised tool for diagnosis of graves' disease in 1991, but its use has gone up in 2011 due to its wide availability and being easy to perform. More than 50% doctors in North America and 70% in Europe now rely on TRAb for diagnosis of graves' disease. Our survey shows use of TRAb is bare minimal 11% and that's too for special cases only (Two patients with euthyroid graves' orbitopathy and one pregnant patient) (Fig 1). In that same survey by Bartalena L, it was found that RAI therapy was more popular in North America as first line treatment for graves but in Europe and Asia, medical therapy is the preferred one. Our survey results are keeping with them (Fig 2). In India, a report from 1993 indicated that antithyroid drugs were the preferred first-line treatment for Graves' disease[8], recently, in a tertiary referral centre in North India, 131I-radiotherapy has gained widespread acceptance[10]. Pradeep PV *et al*[9] from Uttarpradesh reported surgery for hyperthyroidism has negligible mortality and acceptable morbidity in experienced hands. Our survey reports high prevalence of surgical hypoparathyroidism among those undergoing surgery, may be this was due to selection bias as the cases were collected from an endocrine OPD. The advantage and disadvantages of medical, RAI therapy and surgery are summarised in Table 6.

Table 4 — *Mode of therapy used for Graves' disease*

Mode of therapy	Percentage	Side effects	Comments
Medical	70% 40 carbimazole 2 methimazole 0 PTU	5% sore thorat 5% liver dysfunction 1 skin rash	Mostly used
I^{131} ablation	21.6% (dose 11.6 ± 2.90 mCi)	61% hypothyroid	15% hyperthyroid (after 2 doses)
Surgery	8.3%	2 out of 5 developed permanent hypoparathyroidism	

Conclusion

A comprehensive overview of management of Graves' disease in Eastern India is described. Contrary to popular belief, a significant number of patients are overweight. There is high prevalence of dysglycemia at disease onset but often clinicians are

Table 6 — *Advantages and disadvantages of treatments for Graves disease (Adapted from Bartalena L2, permission not taken)*

Treatment	Advantages	Disadvantages
Antithyroid drugs	Conservative treatment No hospitalization required Low risk of subsequent hypothyroidism No radiation exposure No adverse effect on Graves ophthalmopathy Safe to use during pregnancy and breastfeeding	High relapse rate Requires frequent clinic visits for monitoring Poor adherence Adverse events (rarely major)
^{131}I-radiotherapy	Definitive treatment Low cost No hospitalization required No need for surgery or anaesthetic	Lifelong hypothyroidism Radiation exposure Slow control of hyperthyroidism Possible progression or *de novo* occurrence of Graves ophthalmopathy
Thyroidectomy	Definitive treatment No radiation exposure Prompt control of hyperthyroidism	Lifelong hypothyroidism Adverse events related to surgical procedure and anaesthetic Hospitalization High cost Permanent scar

reluctant to screen. Diagnosis is primarily made clinical examination, radioisotope studies done in doubtful cases. Requirement of usage of TRAb is still minimal and restricted to special cases only.Treatment is primarily medical therapy, which is reasonably safe. Radioiodine therapy is also a safe alternative, surgical therapy should be reserved for refractory cases.

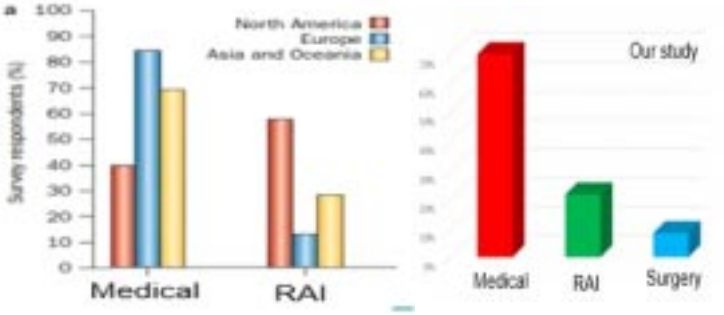

Fig 1 — Comparison of use of diagnostic tests for Graves' disease (Left side panel taken from Bartalena L2 and right side panel our data)

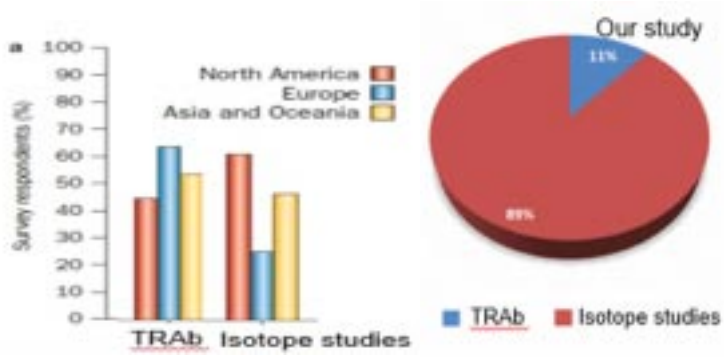

Fig 2 — Comparison of use therapeutic options for Graves' disease (Left side panel taken from Bartalena L 2 and right side panel our data)

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