The management of Graves' disease by Indian thyroidologists

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ABSTRACT

Background. Although effective modes for treating Graves' disease are available, there is controversy over their choice. We conducted a nation-wide survey to determine trends in the diagnosis and management of Graves' disease in India.

Methods. A proforma was mailed to 45 practising thyroidologists who were members of the Endocrine Society of India or the Thyroid Association of India. One index case and 5 variations were provided, and the members were asked to indicate the investigations of choice, therapeutic modality and details about its implementation.

Results. The overall response rate was 71% (32). For diagnosis, serum T3, T4, TSH, sensitive TSH, free T3, and free T4 were asked for by 24, 25, 6, 13, 5, and 10 responders respectively. Radioactive iodine uptake with or without a scan was obtained by 19 of the responders. Antithyroid drugs were the choice of the majority in most situations (index case: 40-year-old female with first episode of typical Graves' disease--23; 40-year-old male--20; 16-year-old male--32; 40-year-old female without goitre--25), except for the patient with relapse and the 65-year-old female where radioiodine was the choice of the majority (20 and 23 respectively).

Conclusion. Antithyroid drugs are the mainstay of treatment of Graves' disease in India. The predominant use of these drugs was similar to European data, but different from the practice in the USA, where radioiodine is used much more liberally.

INTRODUCTION

Graves' disease is a common condition encountered in endocrine practice. The available modes of therapy are antithyroid drugs (ATDs), radioiodine ($^{131}$I) and surgery. While all the available modes of treatment are effective, they have disadvantages, and there is a general lack of agreement among thyroidologists about the best method of treating an individual patient. The choice usually depends on the availability of the therapeutic modality, the personal preferences of the treating physician and the patient. However, the patient relies on the information provided by the physician; although, many have their own apprehensions of radiation, surgery or lifelong medication.

Surveys conducted in Europe and the United States have yielded insights into the methods of management of Graves' disease. In India, its management is complicated by the variation in the amount of iodine intake in different parts of the country, and the paucity of centres which have facilities to provide the three main modalities of treatment. We, therefore, decided to conduct a postal survey on how patients with Graves' diseases are being managed by thyroidologists in India.

METHODS

We mailed a proforma to forty-five practising clinical thyroidologists who were members of the Thyroid Association or the Endocrine Society of India. The index case described was a 40-year-old female with moderate thyrotoxicosis, diffuse thyromegaly (60 g) and mild exophthalmos. She had three children and did not plan to have any more. The clinical diagnosis was uncomplicated Graves' disease.

In addition to the index case, five variations were also described (Table I). The physicians were asked to select the in vivo and in vitro tests of choice for the diagnosis of the index case. They were also asked to choose between ATDs alone, surgery, $^{131}$I, or any other treatment for the index case and the five variations. In relation to ATDs, the answers sought included the drug of choice, the initial dose, the
TABLE I. Index case and variations

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Goitre size (g)</th>
<th>Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (index)</td>
<td>40</td>
<td>F</td>
<td>60</td>
<td>First</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>M</td>
<td>60</td>
<td>First</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>M</td>
<td>60</td>
<td>First</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>F</td>
<td>40</td>
<td>First</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>F</td>
<td>-</td>
<td>First</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>F</td>
<td>60</td>
<td>Relapse (ATDs)</td>
</tr>
</tbody>
</table>

ATDs  Antithyroid drugs

period of treatment after which the dose was modified, the criteria for assessment of euthyroidism, the use of adjunctive therapy and the duration of use of ATDs.

The questions asked about $^{131}$I therapy included definition of the goal of treatment, the method for dose determination, the usual initial dose range, whether single or split doses were used and the use of ATDs before and after $^{131}$I administration.

The last part of the proforma contained questions on what facilities were available locally and whether the responder was working in an iodine-deficient area.

RESULTS

Thirty-two (71%) of the forty-five thyroidologists responded from different parts of India.

Choice of laboratory test for diagnosis

Serum total triiodothyronine (T3) and thyroxine (T4) were the most commonly employed tests to establish the diagnosis (Table II).

Antithyroid drugs

The therapeutic options for the index case and its variants are shown in Fig. 1. The most commonly used drug was carbimazole (31 responders); only one responder preferred propylthiouracil. Twenty-eight would use an initial dose of 20 to 40 mg/day of carbimazole while four preferred to use 40 to 60 mg/day. Twenty-one responders would modify the dose after 6 to 8 weeks, three after 8 to 12 weeks, and eight used the attainment of euthyroidism (rather than any particular time period) as an indication to modify the dose of the drug. A combination of clinical and laboratory criteria was used to diagnose euthyroidism by twenty-six of the responders, while the rest depended solely on clinical criteria. Thirty-one thyroidologists would use beta-blockers as adjunctive therapy and one only radiocontrast agents. The preferred duration of treatment with ATDs was greater than 12 months (27 responders); two would use it for 6 to 12 months, and one for less than 6 months.

Radioiodine therapy

The majority (27) would aim for euthyroidism while using $^{131}$I, only five would aim to achieve hypothyroidism. Twenty-five thyroidologists recommend the use of 5 mCi or more, five would use less than 5 mCi, and two would calculate their dose based on the weight of the thyroid gland (100–150 µCi per g of thyroid tissue). Single dose $^{131}$I was preferred by seventeen thyroidologists, but as many as fifteen preferred split dose treatment.

Twenty-seven responders preferred to use ATDs before $^{131}$I treatment (<4 weeks by six, 4 to 12 weeks by thirteen and till achievement of euthyroidism by eight). Nineteen would stop ATDs a week before administering $^{131}$I, while the rest would stop it more than a week (1 to 4 weeks) before.

Twenty-four responders would like to restart ATD after $^{131}$I therapy. Out of these, five would like to restart within a week, twelve between 1 to 4 weeks, and seven after 4 to 6 weeks. This would be continued by ten for 8 to 12 weeks, by seven for more than 12 weeks and by four till euthyroidism.

TABLE II. Frequency of employment of tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T4</td>
<td>25 (78)</td>
</tr>
<tr>
<td>Total T3</td>
<td>24 (75)</td>
</tr>
<tr>
<td>Free T4</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Free T3</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Sensitive TSH</td>
<td>13 (41)</td>
</tr>
<tr>
<td>TSH</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Free T4 index</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Radioactive iodine uptake</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Radioactive iodine scan/99mTc scan</td>
<td>12 (39)</td>
</tr>
</tbody>
</table>

Fig 1. Therapeutic options in the index case and variations
was achieved. Three of the responders would like to continue ATDs till the next dose of $^{131}$I was due.

**Availability of facilities**

Facilities for immunoassay for T3, T4, and thyrotropin (TSH) levels were available to all the responders. Free T4 and T3, and free T4 index measurement was available to ten, nine and six responders respectively. Twenty-four had access to a sensitive TSH assay, while facilities for isotope scans and uptakes were available to twenty-six of the responders.

**DISCUSSION**

Our study provides an indication of the methods of management of Graves' disease in India by specialist thyroidologists. There was a fairly high response rate of 32 (71%), with representation from all parts of the country.

The tests most frequently asked for diagnosis are serum T3 and T4 levels. Tests for free hormones are used less frequently, while the sensitive TSH assay was only used by 13 clinicians (Table II). The use of total T3 and T4 levels for the diagnosis is comparable to the USA and Europe but assays for free hormones are used less often probably due to their lack of availability (less than one-third have access to such assays) as well as their high cost.

*In vivo* tests such as radioactive iodine uptake and scintigraphic scans are used less frequently in India than in the West. Since these tests are useful for differentiating conditions with low uptake thyrotoxicosis from hyperthyroidism, it is possible that some errors in diagnosis and management might be occurring. The reason for this difference in practice is unclear. Possibly it may again reflect availability and cost factors, but may also be related to a greater reliance on clinical findings by Indian physicians.

Antithyroid drugs continue to be the mainstay in the management of Graves' disease in India. Twenty-three (72%) of the responders in our study preferred ATDs as the first choice for the index case. While this practice is similar to Europe, it is different from the USA where $^{131}$I is the choice of the majority of experts. No change in therapy was recommended when the sex of the index case was changed, except that one of the thyroidologists preferred surgery if the patient was a male. There was complete unanimity in the treatment of a 16-year-old patient with all the responders recommending ATDs. While this is somewhat similar to the practice in Europe where 93% of responders preferred ATDs in younger patients, only two-thirds of American physicians would use ATDs, while the rest would advise $^{131}$I or surgery.

For elderly females, 20 of the responders would advise $^{131}$I, again almost identical to their European counterparts, while the Americans again incline towards using $^{131}$I, 86% of them advising this treatment. These differences also occur in the treatment of patients without goitres. While the majority of Indians and Europeans would opt for ATDs, 52% of thyroidologists in the USA would still use $^{131}$I treatment. For the patient who has relapsed after a course of ATDs, 24 of the responders preferred $^{131}$I therapy, similar to European figures. In the USA, the choice of $^{131}$I was made even more frequently.

Nearly all the responders used carbimazole as the drug of choice, since this is the only antithyroid drug available in India. Only one respondent (from Bombay) indicated that he would prefer to use propylthiouracil which would presumably need to be imported from abroad. In Europe methimazole is the most commonly used drug, while in the USA propylthiouracil is preferred by the majority. In practice there seems to be no major difference in the efficacy of different ATDs, except perhaps that carbimazole or methimazole can be used as a single daily dose, while propylthiouracil is best used in divided daily doses. The initial dose of carbimazole employed by most Indian thyroidologists was 20 to 40 mg—similar to their western counterparts. The overwhelming majority of responders would use ATDs for more than one year, like their colleagues in the West. This is hardly surprising since evidence is now accumulating which suggests that a longer duration of therapy enhances remission rates.

While most thyroidologists in India and Europe agree that the goal of $^{131}$I treatment is to achieve euthyroidism, as many as one-third of physicians in the USA would consider hypothyroidism to be the target. Regarding single versus divided dose $^{131}$I treatment, American and European physicians are almost unanimous in recommending a single curative dose, but almost half the Indian responders advocate split doses. ATDs are used by the majority of Indian physicians before administering $^{131}$I, and by 58% of Europeans, but most Americans would administer $^{131}$I directly, without preceding drug treatment. The duration of use of ATDs preceding $^{131}$I was variable in our study, but there was unanimity in the decision to stop ATDs before administering $^{131}$I.

Our study has brought out certain important points about the management of Graves' disease in India which is quite similar to the practice in Europe. In general, ATDs are the mainstay of treatment while $^{131}$I is preferred for the elderly and those who have relapsed after other forms of treatment. Among the possible reasons why ATDs are preferred over $^{131}$I might be the ease and convenience of their administration, their almost universal availability, as well as their more predictable responses, at least in the short term. The lower iodine intakes in India (even in the so-called iodine sufficient areas) as compared to the USA (the average iodine intake in the USA is higher) might also modify the profile and treatment of hyperthyroidism. It has been shown that lower iodine intakes enhance responses to ATDs. The major problem with drug treatment remains the unacceptably high relapse rates, a problem not addressed in this study. There is a suggestion that relapse rates may be lower in areas of poor iodine intake, although no hard data is available to support this contention. The high relapse rates have been attributed in the past to the inability of ATDs to modify the underlying disease process in Graves' disease, which is autoimmune in nature. Recent studies have, however, suggested that ATDs may be more than just inhibitors of thyroid hormone synthesis and may actually be acting as immunomodulators or as free radical scavengers.

While we think this study provides valuable information, it has certain limitations as it was limited to expert thyroidologists who had access to relatively sophisticated facilities. It does not, therefore, represent the opinion of a large number of internists practising in peripheral areas of the country with very limited facilities who probably see the bulk of patients with Graves' disease.

**REFERENCES**

Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attractions of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors in a new section ‘Obituaries’. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his education and training and highlight the achievements as well as the disappointments. A photograph should accompany this article.

—Editor