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Short Communication

Hyperthyroidism in children: treatment outcomes and preferences in Eastern India

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Introduction

Graves' disease (GD) accounts for majority of hyperthyroidism in children. The best treatment option for hyperthyroidism in children has been controversial for many years. There is poor long term remission with antithyroid drugs in children, though the duration of therapy in children is also debatable. So, many children are treated with radioiodine-131(RAI) ablation or surgical thyroidectomy as "definitive therapy". But acceptance of these definitive therapies in children is limited because of side effects and also customary beliefs. So the policy is variable between countries, institutions and endocrinologists. Drug-based therapy is usually the initial treatment for GD hyperthyroidism in children. There is paucity of data from India regarding treatment outcomes and acceptability of therapy for hyperthyroidism in children. Our objective was to assess the long-term outcome and acceptability of hyperthyroidism treatment in a referral clinic in eastern India.

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Materials and Methods

Data on sixty two hyperthyroid patients due to GD (excluding multinodular goitre and toxic nodule), aged 5 to 18 yrs seen between 1996 and 2013 in a single referral centre in Kolkata in eastern India, were analysed. Twenty patients (32.2%) were 5 to 12 yrs and the remaining 42 (67.8%) patients were between 12–18 yrs (Table 1). The study was reported to the Ethics Committee of the Institute who felt that given its retrospective nature informed consent could be dispensed with. All were accompanied by at least one parent. All patients had a full clinical examination. Free T3, Free T4 and TSH were measured by a chemiluminescence assay. All the patients had GD diagnosed by eye disease and thyroid stimulating hormone receptor antibody (TRAb) positivity by radio receptor assay (competitive binding assay method) or elevated and diffuse thyroid radioactive iodine uptake (RAIU). All forms of thyroiditis (including painless and destructive) was excluded in all by a Tc99 thyroid scan.

Treatment Protocol

Treatment options were discussed. All patients and their parents were given a choice of treatments and were made aware of the poor remission rate on medical treatment. All patients chose medical therapy as their preferred first choice of treatment. Only carbimazole was used

Table 1 Characteristics of patient population

Variables	Patient (n)	Patient (%)
Age: 12–18 yrs	42	67.74
Age: 5–12 yrs	20	32.23
Male / Female	15 / 47	24.19 / 75.81

for medical therapy, with an initial dose of 0.6 to 0.8 mg/Kg body weight. Patients were seen every 3 mo for the first 6 mo and then every 6 mo. The ATD dose was gradually reduced in a titration regimen by 50% or more to maintain euthyroidism. Patients agreed to consider RAI therapy if there was nonresponse or relapse after 2 yrs. Remission was defined as maintenance of euthyroidism for more than 12 mo after discontinuing ATD treatment. Relapse was defined as elevated serum fT4 and fT3 levels together with suppressed TSH level and high RAIU. TRAb measurements were available to us from 2004 and were done on 41 patients, all but one were positive.

Results

Thirty three patients (53.23%) remained on regular follow-up of more than 25 mo. The longest duration of follow-up was 53 and 67 mo in two patients who remained on carbimazole. Twenty nine (46.7%) patients out of 62 dropped out. All had dropped out because of physician initiated request to consider radio iodine therapy. All said that they could not accept radio iodine therapy. Seven (21.21%) patients out of 33 patients on follow-up went into remission after 24 mo of treatment. Three (42.86%) of the 7 patients in remission had documented relapse. 2 (66.67%) relapsed within one yr and one between 1–2 yrs of discontinuing ATD. 4 (12.12%) patients are in remission for 18–30 mo, out of the initial cohort of thirty three patients on regular follow-up (Fig. 1). There were no clinical or laboratory features (including TRAb measurement at diagnosis) which could predict remission or relapse after ATD withdrawal. None of the study patients had any adverse reactions with carbimazole therapy. We have not reported the clinical features and laboratory data of the study subjects as we feel the list would be too long without adding much scientific value.

Thus, the long term remission rate of regular follow-up patients on carbimazole therapy was only 12%, with 42.8% relapse. When the entire cohort of 62 patients (including 29 drop-outs after 2 yrs) were considered, the initial and long-term remission rate was 11.29% and 6.45% respectively (Fig. 1). All patients continuing carbimazole for 18 mo or more were counselled on each visit to stop the treatment and have radioiodine ablation. One patient, who relapsed, accepted this advice and successfully remitted after radioiodine ablation. She was 17 yrs old at that time and had TRAb positive GD. Her mother had earlier received I-131 treatment for the same condition. The remaining patients refused radioiodine ablation and preferred to continue on carbimazole indefinitely.

Discussion

Hyperthyroidism is less frequent in children (1) than in adults and is mainly caused by GD (1). But GD is rare under the age of 5 yr and has a peak incidence at 10–15 yrs of age. Majority (92.5%) of our patients had hyperthyroidism due to GD, with 79% females. Only 31% of the current study patients were 12 yrs or younger. The optimal therapy for hyperthyroidism and GD in children is controversial. Current treatment options involve antithyroid medications, surgery, and RAI. Drug-based therapy is usually the initial treatment for GD in children.

All our patients were treated with carbimazole. In this study 21% of our patients went into remission, but of them 42.8% relapsed, majority (66.67%) relapsed within one yr. There were no specific features which could predict remission. In a large series of 186 children by Glaser *et al.*, less than 30% of children went

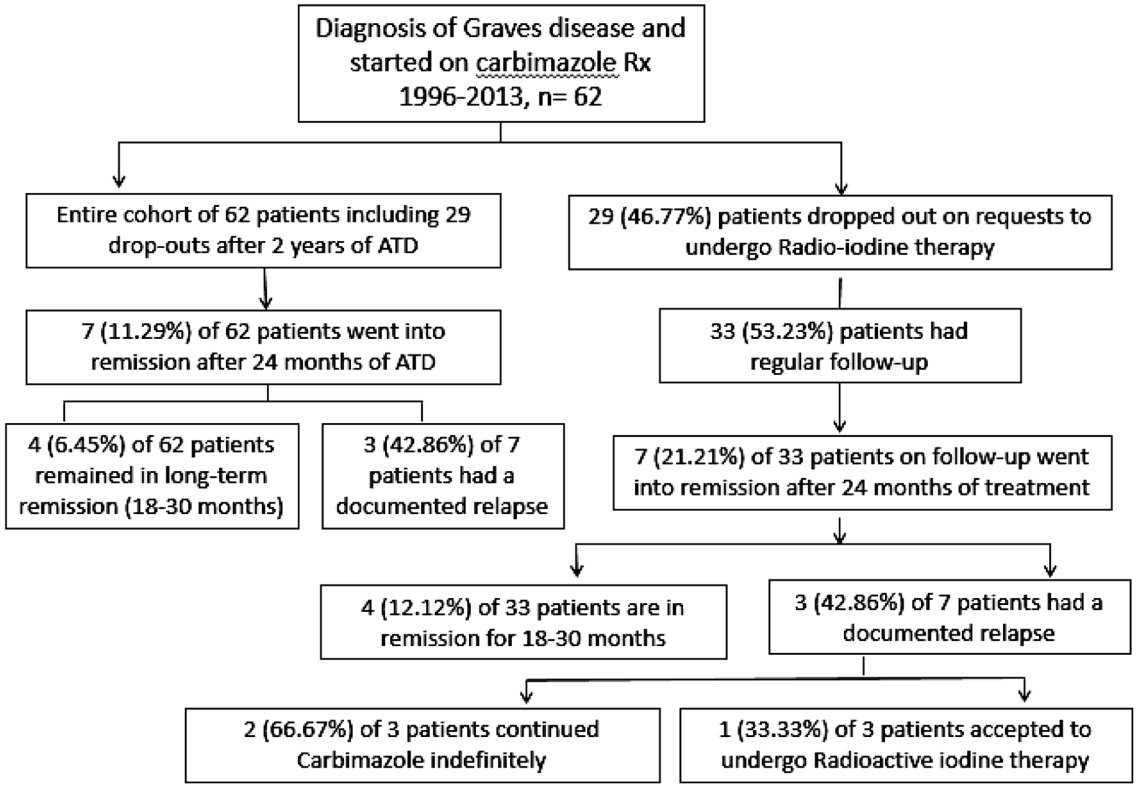

Fig. 1. Clinical characteristics of the 62 paediatric patients with Graves' disease initially treated with an antithyroid drug (ATD), carbimazole.

into remission (2). Though several markers were associated with a decreased likelihood of achieving and maintaining remission, no single marker has 100% predictability (3). In our series, of the 41 patients who had TRAb measurements, just 18 remained on follow-up. No meaningful conclusion could be drawn from the antibody data. Recently, Léger *et al.* estimated relapse rate for hyperthyroidism was 59% at 1 yr and 68% at 2 yrs after the end of treatment (4). Léger *et al.* found an association between ethnicity, age, and disease severity at diagnosis and risk of relapse, moreover longer courses of ATD treatment was associated with a better outcome. Every additional year of treatment was associated with a decrease in relapse rate (4). Ohye *et al.* reported in a recent single institution large retrospective study of children with GD in Japan, showed 46.2% remission on long term ATD (median duration of treatment: 3.8 yrs; range: 0.3–24.8 yrs), 34.2% had relapse. 73.7% of relapses occurred within 2 yrs after discontinuing ATD. The cumulative remission rate increased with the duration of ATD treatment up until 5 yrs (5). American Thyroid Association has considered RAI therapy for children five years of age and over, but Japan Thyroid Association does not recommend RAI therapy for children under 18 yrs of age because of concerns about RAI-associated carcinogenesis in the thyroid or other organs (5). There is no unanimity regarding duration of carbimazole therapy. Glaser *et al.* found that most children need 36–48 mo of treatment (2). Léger *et al.* reported, in a recent prospective observational study of 154 patients below 18 yrs with GD treated with three cycles (each lasting 2 yrs) of carbimazole, 20%, 37%, 45% and 49% remission after 4, 6, 8 and 10 yrs of carbimazole therapy respectively (4). In the same study by Léger *et al.* 17% of study patients

were lost to follow-up, while we had a much higher lost to follow-up because of patients' refusal to radioiodine therapy after failure to achieve remission. There is a background fear of radioiodine therapy in the community.

Lippe *et al.* also reported 25% remission rates with ATD in children, which increased by 25% for every additional 2 yrs of therapy (6). The mechanism underlying remission may be linked to the restoration of euthyroidism. Hyperthyroidism itself has been shown to perpetuate or even to worsen autoimmunity, leading to generation of more TRAb and aggravation of hyperthyroidism (4). Up to 0.5% of proylthiouracil (PTU) or methimazole (MMI) treated children develop serious complications like increases in liver enzymes, and leukopenia (7). 25% of children have minor side effects, including pruritus, hives, myalgia, small increases in liver enzymes, and leukopenia (7). Léger *et al*. reported only three serious adverse events (AE) of allergic reaction, neutropenia, and arthralgia (4). A study by Ohye *et al*. had 21.4% and 18.8% overall AEs with MMI and PTU respectively, without any fatal AEs (5). Most AEs (91.6%) occurred within first three months of ATD treatment, seven of eight late-onset AEs were induced by PTU. None of our patients had any serious adverse reactions with carbimazole therapy, PTU was not used.

When relapse occurs, thyroidectomy or RAI treatment is considered, but these therapeutic options in children remains controversial (8). Remission rates exceed 95%, with rare complications (8).

Conclusions

In conclusion, this study shows that in children with hyperthyroidism, medical therapy with carbimazole is safe and preferred as both initial and long-term treatment modality despite a low remission rate. On the contrary, patients are extremely reluctant to accept radioiodine as alternative treatment because of background fear in the community.

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