Children with Graves' hyperthyroidism may have a poor therapeutic response to ^{131}I if it is delayed or if they have recently been treated with antithyroid drugs or have Graves' ophthalmopathy

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SUMMARY

BACKGROUND

Antithyroid drugs are usually the first-choice therapy for children and young adults with hyperthyroidism. However, minor and major complications may occur with antithyroid drugs, making surgical or radioiodine (^{131}I) therapy necessary. Yet there is controversy concerning the merits of each treatment, which may make this decision difficult. Also, it is not entirely clear what patient or therapeutic features predict a response to ^{131}I in children and adolescents. The aims of this study were to describe current referral practices in an academic pediatric center and an adolescent endocrine practice, to assess the responses of hyperthyroidism to ^{131}I therapy, and to further identify the factors predicting outcome in this group of patients.

METHODS

This was a retrospective electronic chart review of 720 consecutive patients treated in the Pediatric Endocrine Unit of the Mass General Hospital for Children (MGH) or the Thyroid Unit of the Massachusetts General Hospital.

How Patients Were Selected

Patients were selected from the 720 cases in the hospital database that had had any thyroid-function test abnormality and ranged in age from 30 days to 21 years. Among this group were 131 patients who had thyroid-function tests diagnostic of hyperthyroidism and a follow-up of at least 6 months. Also included in the search were medical records of pediatric patients who were treated during the same period with methimazole (MMI) or propylthiouracil (PTU) or had a diagnosis of thyroiditis, thyrotoxicosis, or postablative hypothyroidism. Among the latter group, the medical records of adolescent patients with hyperthyroidism treated with ^{131}I and had follow-up in the adult endocrinology clinic were selected for study. Excluded from the study were asymptomatic children with mild laboratory evidence of hyperthyroidism that spontaneously resolved.

How the Patient Data Were Collected

Data collected included patient sex and Tanner stage at the time of diagnosis, thyroid size estimated by palpation, prior use of MMI or PTU, with or without β–blockers, and the administration of ^{131}I. Tanner stage I was considered prepubertal, whereas other Tanner stages were considered pubertal or postpubertal. A diagnosis of Graves' disease was made if there was laboratory evidence of hyperthyroidism and at least two of the following: goiter, thyrotropin (TSH) receptor–binding immunoglobulins (TSHR-Ab) or thyroid-stimulating immunoglobulins, Graves' eye disease, and significantly increased thyroidal ^{131}I uptake. Patients with benign thyroid nodules and hyperthyroidism were assigned to a separate diagnostic category.

What Were the Indications for ^{131}I Therapy?

The major indication for ^{131}I therapy was identified from the primary clinician's electronic notes. Other possible indications were an adverse reaction to antithyroid drugs, poor control of

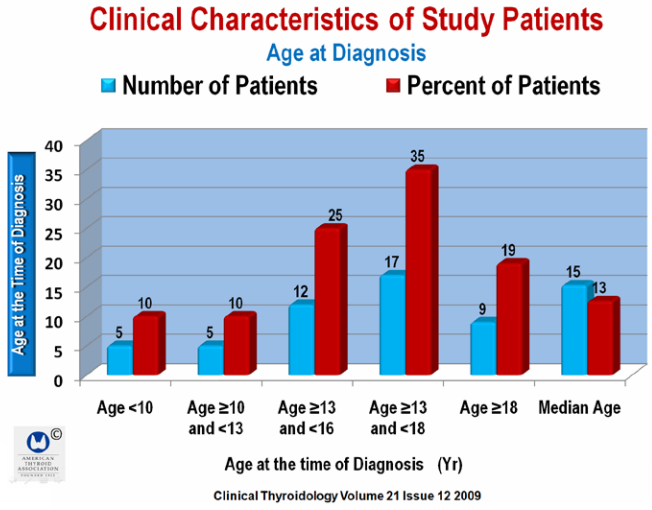

Figure 1. This figure shows the age of patients in this study. The data in this figure and Figures 2 through 4 and 6 are derived from Table 1 of McCormack et al.

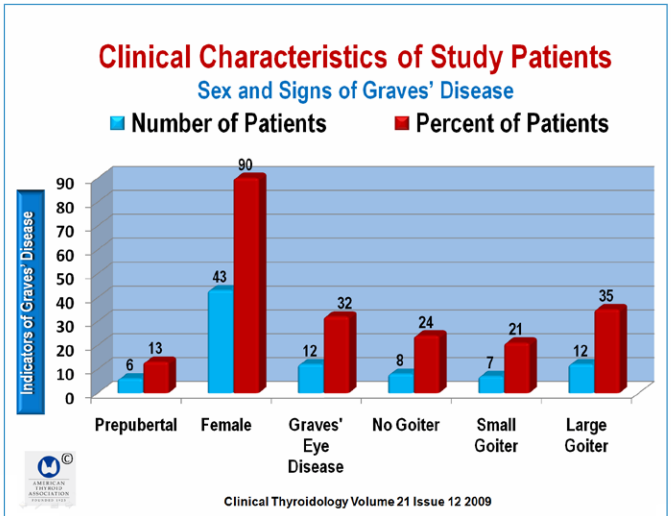

Figure 2. This figure shows the number of patients who were prepubertal and female and the number with signs of Graves' disease (ophthalmopathy and goiter).

hyperthyroidism on antithyroid drugs, or patient preference.

A single primary indication for ^{131}I was assigned using an iterative process. First, if an adverse reaction to antithyroid drugs was cited, then this was considered the primary indication; second, if poor control of hyperthyroidism was found, as defined by clinical signs of hyperthyroidism with or without persistent TSH suppression and with or without persistent elevation of free thyroxine (FT_4) while the patient was taking antithyroid drugs, despite attempts to optimize therapy, and without adverse reaction to the drugs, then poor control was considered the primary indication; third, if nonadherence was found in the record, excluding other reasons such as adverse effects of antithyroid drugs, then this was considered as the primary indication; and lastly, if evidence of patient preference was found in the clinical notes, then this was cited as the primary indication for ^{131}I therapy unless the report was incomplete, in which case it was labeled as unknown.

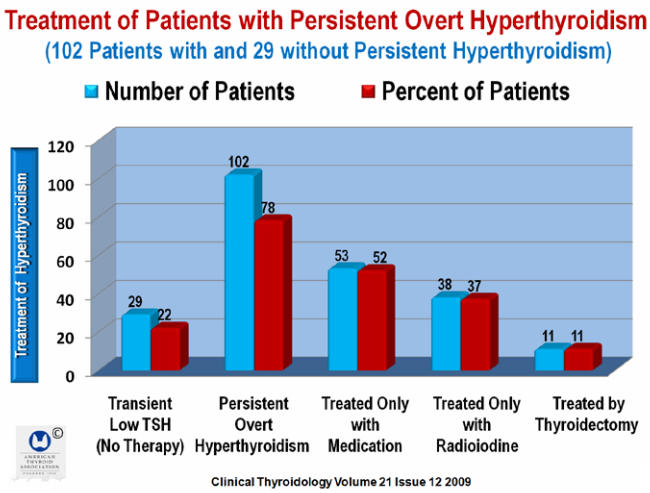

Figure 3. This figure shows the treatment of 102 patients with persistent overt hyperthyroidism and 29 other patients with transient low serum TSH for less than 6 months that spontaneously returned to normal without therapy.

How Radioiodine Therapy Was Administered

All patients treated at MGH who received ^{131}I were treated by one of two endocrinologists. Antithyroid drugs were discontinued 3 to 5 days before ^{131}I was administered, using 160 μCi per gram of thyroid tissue as estimated by palpation.

How Outcome Was Determined during Follow-up

All patients had follow-up for at least 6 months after ^{131}I therapy was administered or until hypothyroidism occurred. This typically included laboratory studies every 2 weeks and at least monthly clinic visits or more as required until hypothyroidism occurred. Time to development of hypothyroidism was defined from the initiation of therapy to the first visit at which hypothyroidism was diagnosed without antithyroid drugs or when thyroid-hormone replacement was necessary to treat hypothyroidism. However, if hypothyroidism did not occur well after 6 months, then this was used to identify patients who had a poor response to ^{131}I. If hyperthyroidism recurred or persisted after ^{131}I, then a second ^{131}I treatment was given to some patients, depending on the patient's and family's wishes.

How the Possible Predictors of a Poor Response to ^{131}I Therapy Were Determined

The following were considered possible predictors of a poor therapeutic response to ^{131}I: diagnosis before the onset of puberty, thyroid size, presence of ophthalmopathy, preceding antithyroid drug therapy, very elevated FT_4 or total triiodothyronine (T_3) at the time of diagnosis, previous β-blocker therapy and the time to administer ^{131}I therapy. These variables were largely chosen from the existing literature on children treated with ^{131}I for hyperthyroidism. Proxy measures of the severity of hyperthyroidism were thyroid-gland size, very elevated serum

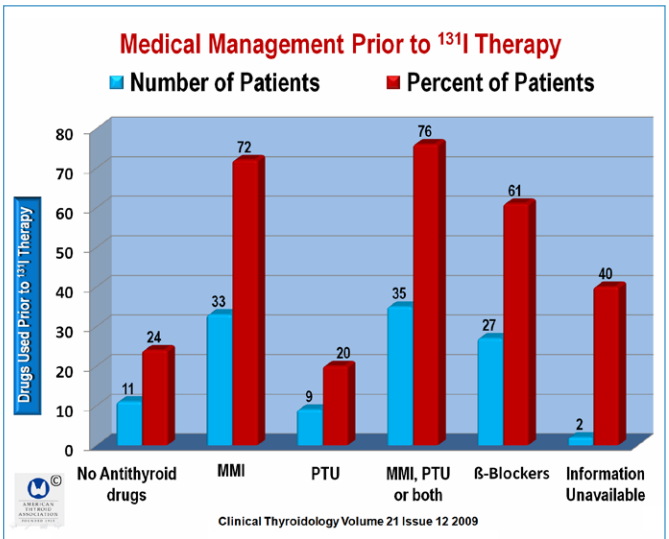

Figure 4. This figure shows the indictions for ^{131}I in 47 of the 48 patients treated with ^{131}I for whom the indications were known. Poor control of hyperthyroidism was the indication for ^{131}I in 9 patients, 4 of whom had poor control as the result of poor adherence to therapy.

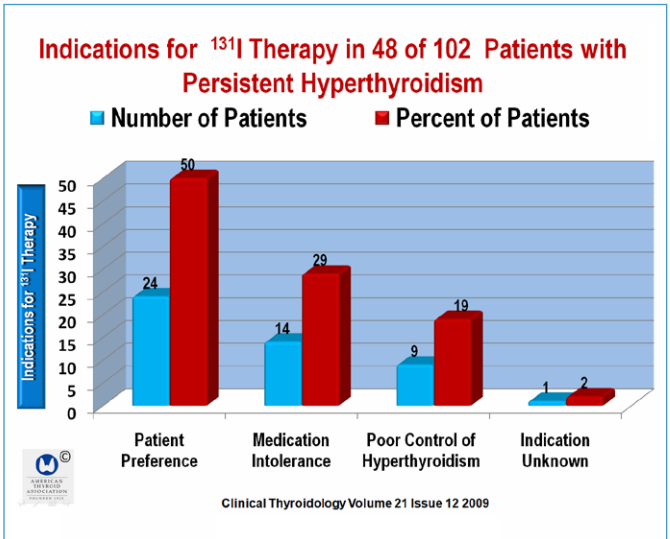

Figure 5. This figure shows the indictions for thyroidectomy in 11 of the 131 patients who had hyperthyroidism.

FT_4 or T_3, defined as threefold the upper limit of normal (69 mol/L for T_4 and 8.36 nmol/L for T_3). However, FT_4 and T_3 test results were not available for all patients because the tests were performed elsewhere. Also assessed was the effect of ^{131}I therapy after waiting more than 12 months from the time of diagnosis.

RESULTS

Clinical Characteristics and Course of Patients with Hyperthyroidism (Figures 1 to 3)

Of the 720 cases reviewed, 131 (18%) met the study criteria for hyperthyroidism. The primary clinical characteristics of this group are shown in Figures 1 and 2. Of these 131 cases, 29 (22%) had transient TSH suppression for less than 6 months that spontaneously resolved without additional therapy (Figure 3). Follow-up thyroid-function tests in this group disclosed normalization of the tests with or without subsequent hypothyroidism, which occurred in patients with subacute or silent thyroiditis or chronic lymphocytic thyroiditis. Persistent overt hyperthyroidism was found in 102 patients (78%), 53 (52%) of whom were treated only with medication; 38 (37%) were treated with ^{131}I, and 11 (11%) had thyroidectomy (Figure 3). Ten adolescent patients who had follow-up in the adult endocrinology clinic also were treated with ^{131}I and were included in this study.

The Preparation and Indications for ^{131}I Therapy (Figures 4 and 5)

Medical management before ^{131}I therapy comprised no antithyroid drugs in 11 patients (24%), MMI in 33 (72%), PTU in 9 (20%), MMI, or PTU, or both in 35 (76%), β-blockers in 27 (61%), and incomplete information in 2 (40%). (Figures 4 and 5)

The Indications for Thyroidectomy (Figure 6)

The indication for ^{131}I therapy was judged as patient preference (50%) followed by intolerance to medications (29%) and poor control while taking medications (19%), which was due to poor adherence to therapy in 4 of the 9 patients (44%). (Figure 6) All 48 patients who were treated with ^{131}I had Graves' disease.

Thyroidectomy was performed in patients with hyperthyroidism and thyroid nodules; it was also performed in 4 of 11 patients with persistent overt hyperthyroidism (36%), in 1 (9%) with a palpable thyroid >80 g, in 1 (9%) with ophthalmopathy, in 2 (18%) with significant ophthalmopathy, in 2 (18%) with intolerance to medical therapy in 2 (18%), and in 1 (9%) because of patient preference.

Predictors of a Poor Response to ^{131}I Therapy (Figure 7)

Thirteen of the 48 patients treated with ^{131}I (27%) had a poor response to ^{131}I or required a second treatment with ^{131}I. The main indicators that portended a poor response were the use of antithyroid drugs prior to ^{131}I, poor control of hyperthyroidism, the presence of ophthalmopathy, and a delay of ^{131}I treatment of more than 12 months after the diagnosis of hyperthyroidism (Figure 7). However, a poor therapeutic response to ^{131}I was not associated with a diagnosis of hyperthyroidism before puberty, prior use of β-blockers, goiter size, or a very elevated serum FT_4 or T_3. A Kaplan–Meier analysis of 46 patients for whom information was available on the use of antithyroid drugs showed that the median time to hypothyroidism was 2.2 months (95% confidence Interval [CI], 1.9 to 2.4 months) for those who did not take antithyroid drugs before ^{131}I as compared with 4.2 months (95% CI, 2.7 to 4.4 months) for those who did take antithyroid drugs before ^{131}I therapy ($P<0.01$)

CONCLUSION

Children with Graves' hyperthyroidism may have a poor therapeutic response to ^{131}I if treatment is delayed or if they were recently treated with antithyroid drugs or have Graves' ophthalmopathy.

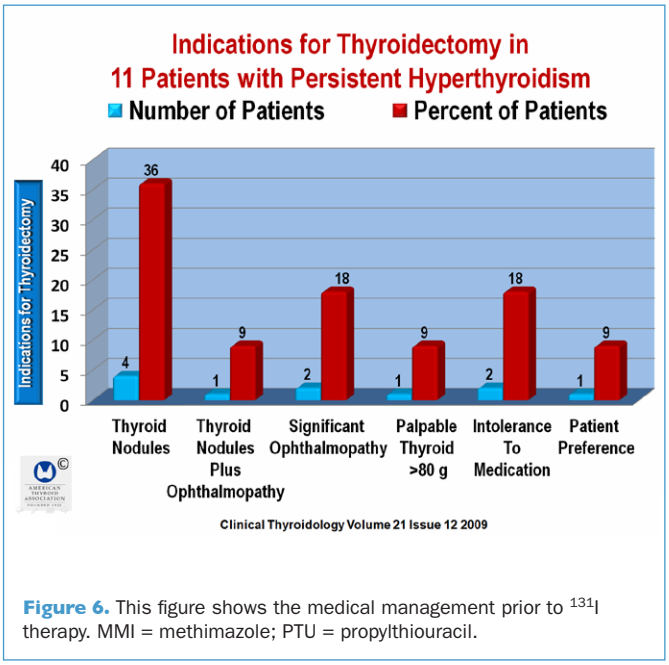

Figure 6. This figure shows the medical management prior to ^{131}I therapy. MMI = methimazole; PTU = propylthiouracil.

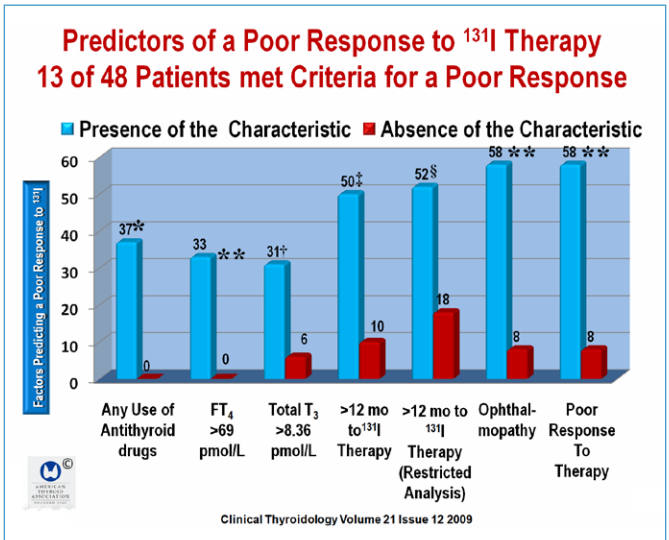

Figure 7. This figure shows the predictors of a poor response to ^{131}I therapy in 13 patients. The data in this figure are derived from Table 2 in McCormack et al. *P<0.02, **P = 0.002, †P = 0.01, ‡P = 0.003, §P = 0.04

COMMENTARY

Antithyroid medications, surgery, and ^{131}I have been widely used for more than five decades for the treatment of Graves' hyperthyroidism in children and adolescents, (1) yet children often require prolonged courses of antithyroid drugs to achieve remission, and long-term compliance is often challenging (2). For example, a study by Glaser et al. (2) of 191 patients with Graves' disease who were younger than 19 years old found that patients achieving early remission were older (mean, 12.5 vs. 10.9 years; P = 0.039) and had a higher BMI (19.0 vs. 16.6, P = 0.002), lower heart rates (110 vs. 121, P = 0.023), and smaller goiters (60% with moderate goiter versus 83%, with larger goiters; (P = 0.050), and lower serum T_4 and T_3 concentrations (18 vs 22.5 μ g/dL P = 0.008).

Controversy still exists concerning the merits of each of the three therapies in children, especially the use of ^{131}I. This is particularly important as long-term spontaneous remission of Graves' disease occurs in less than 30% of children (1), but may rise incrementally over the ensuing years (3). Still, most children with Graves' disease require definitive treatment, mainly because there is little evidence that the use of antithyroid drugs beyond 1 year enhances outcome. For example, Greer et al(4) found that the lasting remission rate in children is as good when antithyroid drugs are stopped as soon as the patient is euthyroid as when they are continued for 1 year or more. Nonetheless, Barrio et al.(5) found that the implementation of a long-term antithyroid drug protocol achieved 40% long-term remissions in pediatric patients with Graves' disease.

The goal of ^{131}I therapy in both children and adults is to induce hypothyroidism in order to prevent a recurrence of Graves' disease, which is achieved in approximately 80% of patients, regardless of the approach to ^{131}I dosing, although calculated dosimetry may have an efficacy similar to that of fixed dosing, but with less radiation exposure (1;6).

Graves' disease is associated with few acute side effects, and the potential long-term adverse side effects, including thyroid cancer and genetic damage, have yet to be observed in individuals treated with ^{131}I as children or adolescents (1). In support of this observation, a 36-year retrospective study by Read et al. (7) of the efficacy and safety of ^{131}I treatment of young patients with Graves' disease, including 6 who were younger than 6 years of age, 11 who were between 6 and 11, and 45 who were between 11 and 15, and 45 who were between 16 and 19 years of age at the time of ^{131}I treatment. After an average length of follow-up of 36 years in 2001 to 2002, none of the patients had cancer of the thyroid or leukemia. Early on in this study, when the objective of treatment was euthyroidism, the dose of ^{131}I was low, and retreatment was frequently needed, but the ^{131}I doses were subsequently increased. The authors concluded that treating young people with Graves' disease with ^{131}I is safe and effective over the long term.

Rivkees et al. (8), assessed the dose response of ^{131}I in children with hyperthyroidism treated with one of three doses: 80 to 120 μCi/g (72 to 108 Gy), 200 to 250 μCi/g (180 to 225 Gy), and 300 to 405 μCi/g (270 to 364 Gy), in 31 patients ranging in age from 7 to 18 years. When thyroid status was assessed >1 year after therapy, the ^{131}I doses of 110, 220, and 330 μCi/g resulted in hypothyroidism in 50%, 70%, and 95% of treated individuals, respectively. The authors concluded that 300 μCi/g of thyroid is needed for ^{131}I treatment of hyperthyroidism, especially when the thyroid is large.

A meta-analysis of randomized, controlled trials by Walter et al,(9) found that, antithyroid medication was associated with an increased risk of treatment failure (relative risk, 1.28; 95% CI, 1.07 to 1.52; P = 0.006) and a reduced risk for hypothyroidism (relative risk, 0.68; 95% CI, 0.53 to 0.87; P = 0.006) after ^{131}I treatment. The main conclusion was that antithyroid drugs increase the rates of ^{131}I failure and reduce rates of hypothyroidism if they are given in the week before or after radioiodine treatment, respectively. Similar observations were found by Tuttle et al. (10).

The main conclusions of the study by McCormack et al. were that high success rates of ^{131}I therapy are achievable in children and adolescents with hyperthyroidism but may be hindered by preexisting eye disease and a prolonged time from diagnosis to ^{131}I therapy and that pretreatment use of antithyroid drugs may confer resistance to ^{131}I therapy.

The authors mention several limitations of this study. The main problems are the limits in statistical power for subgroup analysis, which impaired the performance of multivariate analysis. Also, some patients did not have thyroid-function tests, and data were missing in the primary indications for ^{131}I. Lastly, the estimation of thyroid volume by palpation leaves some room for error that may have altered the amounts of ^{131}I chosen for therapy.

Nonetheless, there is robust information that ^{131}I is highly effective and safe for the treatment of children and young adults with Graves' hyperthyroidism, providing antithyroid drugs are not given prior to therapy and delay in ^{131}I therapy is minimized.

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