Predictors of Autoimmune Hyperthyroidism Relapse in Children after Discontinuation of Antithyroid Drug Treatment

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Context: There is debate about how Graves' disease (GD) should be treated in children.

Objective: The aim of this study was to identify predictors of relapse after antithyroid drug (ATD) treatment in children with GD.

Study Design and Setting: We conducted a prospective, multicenter cohort study of children (n = 154) with GD treated with carbimazole for an intended duration of 24 ± 3 months. After the end of treatment, patients were followed up for at least 2 yr. The primary outcome was hyperthyroidism relapse. Cox's regression analysis was used and a prognostic score was constructed.

Results: The overall estimated relapse rate for hyperthyroidism was 59% (95% confidence interval 52–67%) at 1 yr and 68% (95% confidence interval 60–76%) at 2 yr after the end of treatment. Multivariate survival analysis showed that the risk of relapse was higher for patients of non-Caucasian origin [hazard ratio (HR) = 2.54, $P < 0.001$], with high serum thyroid-stimulating hormone receptor antibodies (HR = 1.21 by 10 U, $P = 0.03$) and free T_4 (HR = 1.18 by 10 pmol/liter, $P = 0.001$) levels at diagnosis. Conversely, relapse risk decreased with increasing age at onset (HR = 0.74 per 5 yr, $P = 0.03$) and duration of first course of ATD (HR = 0.57 per 12 months, $P = 0.005$). A prognostic score was constructed, allowing the identification of three different risk groups, with 2-yr relapse rates of 46, 77, and 98%.

Conclusions: A longer initial duration of euthyroid state with ATD seems to be the only variable related to the risk of hyperthyroidism relapse in children that can be manipulated. Ethnic origin, age, and severity of the disease at diagnosis may guide long-term disease management decisions. (***J Clin Endocrinol Metab*** **93: 3817–3826, 2008)**

Hyperthyroidism is less frequent in children (1) than in adults, and is mainly caused by Graves' disease (GD). GD is believed to result from a complex interaction between genetic background, environmental factors, and the immune system. For unknown reasons, the immune system produces autoantibodies, thyroid-stimulating hormone receptor antibodies (TRAb), that stimulate the thyroid gland to produce excess thyroid hormones (2).

Remission is achieved in less than 30% of children treated with antithyroid drugs (ATD) (3–8) *vs.* 40–60% of adult patients (9–11). When relapse occurs, thyroidectomy or radioactive iodine treatment is considered, although the use of these two therapeutic options in children remains controversial (12, 13). Reliable predictors of relapse after ATD treatment would greatly improve patient management, by facilitating the identification of children requiring long-term ATD or early surgery or radioiodine therapy.

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Abbreviations: ATD, Antithyroid drug; BMI, body mass index; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HR, hazard ratio; TPOAb, thyroid peroxidase autoantibodies; TRAb, thyroid-stimulating hormone receptor antibodies.

Several studies in adults have tried to identify factors, at disease onset or during follow-up, potentially predictive of the outcome of medical treatment. Being young (<40 yr) or male, having severe biochemical hyperthyroidism at onset, high TRAb levels at onset and at the end of treatment, and having a large goiter are associated with a poor prognosis of GD (14–17). Other factors, such as genetic background, iodine intake, and smoking, are thought to modulate individual responsiveness (10, 16, 18). There is also no clear evidence to suggest that extending treatment beyond 18 months in adult GD patients is of benefit (10, 19).

Such prognostic studies are limited in children (5, 7, 8, 20, 21) although age, initial hormone levels, goiter size, body mass index (BMI), and duration of drug treatment have been associated with the risk of GD relapse in childhood (5, 7, 20–23). As a result, children undergo longer periods of drug treatment than adults, despite the absence of an evidence-based strategy for disease management in these patients.

Unfortunately, all but one (8) of the pediatric studies published to date were retrospective, and none of these studies has led to widespread changes in clinical practice. Thus, in this prospective observational study, we aimed to identify predictors of thyrotoxicosis relapse within 2 yr of the end of primary ATD treatment in children with GD.

Patients and Methods

Patients

All consecutive patients (n = 154) aged up to 18 yr with GD seen at the centers of a French nationwide network between 1997 and 2002 were included. GD diagnosis was based on clinical signs of hyperthyroidism, combined with TSH concentrations below the detection threshold (TSH <0.05 μU/ml) and high serum free T_4 (FT4 >21 pmol/liter, normal range 8–21 pmol/liter) and/or free T_3 (FT3 >11 pmol/liter, normal range 4.4–11 pmol/liter) concentrations, together with the presence of significant titers of TRAb and/or thyroid peroxidase autoantibodies (TPOAb). Neonatal hyperthyroidism was excluded.

Study protocol

The intention was to treat all patients with one or two daily doses of carbimazole for a total of 24 ± 3 months. The initial starting dose was 0.7 mg/kg·d if FT4 serum concentration was 50 pmol/liter or greater at diagnosis or 0.5 mg/kg·d if FT4 concentration was less than 50 pmol/liter. This dose was subsequently reduced by 20 to 40% and adjusted to maintain euthyroidism, based on the results of serum thyroid hormone testing during follow-up. No additional benefit accrues from the maintenance of high doses of ATD combined with replacement doses of L-thyroxine (19, 24), so all decisions concerning the management of L-thyroxine treatment were made on an individual basis. All children followed similar timetables of predefined medical visits, which included clinical evaluation and the measurement of TSH and FT4 levels at 1, 2, 3, 6, 9, 12, 18, and 24 months of treatment and during post-treatment follow-up.

The following information was recorded at disease onset: age; sex; ethnicity; weight and initial weight loss, if any; height; pubertal status; goiter size; presence of tachycardia (pulse rate >100/min); presence of an increase in blood pressure (25); presence of ophthalmic abnormalities (exophthalmos and/or upper lid retraction); thyroid hormone levels; and presence of TRAb and TPOAb. TRAb titer was also determined at the end of ATD treatment. The presence of associated autoimmune disease and a family history of hyperthyroidism (first and second degree relatives) if any, were recorded.

The study protocol was reviewed and approved by the faculty ethics committee. It was explained to all subjects and their parents, who signed a written consent form for participation.

Clinical assessment at diagnosis

Height, weight, and BMI [weight/(height)^2 in kilograms per square meter] were expressed in SD scores to normalize for age and sex (26, 27). Pubertal development was assessed by determining Tanner stage. Children were classified as Caucasian or non-Caucasian (African, Asian, Caribbean), based on the geographic origin of their parents. Initial clinical presentation was described as severe if at least two of the following features were present: tachycardia, hypertension, weight loss (≥1 kg) and/or ophthalmic abnormalities.

The size of the thyroid gland was estimated on clinical examination at diagnosis and measured on thyroid ultrasonography in all but two cases. All thyroid ultrasonographies were reviewed by the same pediatric radiologist, blind to the biological data. We corrected for age-related differences in the volume of the normal thyroid by classification into four categories: no goiter, small (<1.5 times normal size), moderate (1.5–2.5 times normal size), or large (>2.5 times normal size) goiter (5).

Laboratory tests

Serum TSH, FT4, and FT3 concentrations were determined by competitive immunoassay, using either direct chemiluminescence technology or fluorescence depolarization. TPOAb levels were determined by hemagglutination or radioimmune assays. TRAb levels were determined by radioreceptor assays (competitive inhibition assays) based on a preparation of porcine thyroid membranes (TRAK assay; BRAHMS Diagnostica, Berlin, Germany; normal upper limit 14 IU/liter) or human recombinant TSH receptors (DYNOtest-Trak human; BRAHMS Diagnostica; normal upper limit 1.5 IU/liter) and I^{125}-labeled TSH. We corrected for interlaboratory variations in the use of these two assays over time by expressing TRAb titers as a multiple of the normal upper limit of each radioreceptor assay used (*e.g.* 30 U/liter TRAb in a human DYNOtest-Trak test corresponds to 20 times the upper limit of the normal range of this assay).

Outcome

The ATD medication and dose prescribed, total ATD treatment duration, and reasons for discontinuing ATD treatment were recorded. Compliance with treatment was assessed by questioning patients about irregularities in their use of medication or clinically identifying relapses of thyrotoxicosis after discontinuation of treatment at the patient's own initiative.

Relapse was defined as the presence of suppressed levels of TSH (TSH <0.05 mIU/liter) combined with serum FT4 concentrations greater than 21 pmol/liter or FT3 concentrations greater than 11 pmol/liter. However, relapse is unlikely to occur under ATD treatment. We therefore considered the risk of relapse to exist from the first day of complete cessation or the first day of a progressive decrease in ATD dose. For patients who stopped the treatment at their own initiative, the period of risk was considered to begin at the medical visit at which treatment discontinuation or thyrotoxicosis relapse was acknowledged. In this last case, time to relapse was considered to be null.

Statistical analysis

Results are expressed as numerical values (percentages) for categorical variables and as medians (25th-75th percentiles) for continuous variables. Comparisons of the characteristics of different groups of patients at onset were based on χ^2 or Fisher's exact tests for categorical variables and Wilcoxon test for continuous variables. Correlations between continuous variables were evaluated, by calculating Spearman's rank correlation coefficient. Time from the discontinuation of ATD treatment to relapse was analyzed for up to 2 yr of follow-up, by plotting Kaplan-Meier curves.

Cox's regression analysis was performed to evaluate the significance of different factors for prediction of the risk of relapse. Variables in-

cluded in the multivariate regression analysis fulfilled the following criteria: 1) bivariate association with relapse, with $P \leq 0.20$; 2) 10% or less missing data; and 3) absence of colinearity with other explanatory variables. Goiter size was analyzed as a dichotomous variable because of the small numbers of patients in some categories.

Multivariate model selection was based on a stepwise procedure. The presence of a center effect was explored. Results are expressed as hazard ratios with 95% confidence intervals (CIs). All tests were two sided, and a significance level of 5% was considered for multivariate analysis. The selection of variables in the final model was validated by applying a Cox multivariate model to identify predictive factors in a large number of patients' subsamples. These subsamples were created by resampling, with replacement, from the original sample of patients by a bootstrapping procedure (28). A prognostic score was constructed by identifying cutoff points defining severity levels for each continuous predictive variable, using the classification and regression tree method (29) and ensuring clinical relevance. The prognostic score was thus the weighted sum of the independent predictors, with the weighting defined by the estimated Cox regression coefficient. Based on score distribution, three risk groups with different mean predicted relapse probabilities were defined. For the simplification of routine use by practitioners trying to assign future patients to the appropriate group, score was modified by linear transformation of the regression estimates (divided by 0.25) and rounding to the closest integer. Statistical analysis was performed using SAS 9.1 (SAS Inc., Cary, NC) and S-Plus 6.2 (MathSoft Inc., Seattle, WA).

Results

Patients' characteristics at diagnosis

The characteristics of the 154 children initially included are summarized in Table 1 and Fig. 1. Serum TRAb levels were significantly higher in young (≤5 yr of age) patients than in older (>5 yr of age) patients ($P < 0.001$) and in patients with a severe initial clinical presentation than in those without clinical severity ($P = 0.03$) (Fig. 2). There was a positive correlation between serum TRAb and FT4 levels (Spearman's coefficient 0.38, $P < 0.0001$) and between serum TRAb and FT3 levels (Spearman's coefficient 0.25, $P = 0.005$). No significant relationship was found between serum TRAb levels and either goiter size or sex. Moreover, statistically significant differences were found between ethnic groups: non-Caucasian patients were younger ($P = 0.001$) and had higher serum FT4 ($P < 0.0001$), FT3 ($P = 0.001$), and TRAb levels ($P < 0.001$) than Caucasian patients (Fig. 3). Finally, the proportion of young patients (≤5 yr) was higher for boys than for girls (22 *vs.* 7%, $P = 0.01$).

Patients' characteristics at the end of treatment

Most patients (n = 147, 95%) completed one course of ATD (Fig. 4). The remaining seven patients were excluded from the outcome analysis because they were lost to follow-up shortly after inclusion in the study (n = 4), treated with ^{131}I 2 months after inclusion due to serious adverse effects (allergic reactions) of ATD (n = 1) or were still on ATD treatment at their last medical visit (n = 2).

Overall, the median duration of ATD treatment was 25 (23–28) months. Eighty-three patients (56%) received ATD according to the protocol for 21–27 months, whereas deviations from the study protocol for ATD treatment duration were observed in 64 children (44%) (20 patients received ATD for 12–20 months because of noncompliance with long-term treatment and 44 pa-

TABLE 1. Characteristics of children with Graves' disease at presentation (n = 154)

	n	Median (25th-75th percentiles or %)	N
Age (yr)		11.9 (9.4–13.9)	154
5 or younger	17	(11)	
Older than 5 yr	137	(89)	
Sex			154
Female	118	(77)	
Male	36	(23)	
Ethnicity			154
Caucasian	123	(80)	
Non-Caucasian			
African	19	(12)	
Asian/Caribbean	12	(8)	
$Weight_{SD}$ score		0.38 (−0.44–1.57)	153
$Height_{SD}$ score		1.45 (0.37–2.35)	152
BMI_{SD} score		−0.50 (−1.20–0.30)	152
Pubertal development			154
Prepubertal (Tanner 1)	65	(42)	
Pubertal (Tanner 2–4)	58	(38)	
Postpubertal (Tanner 5)	31	(20)	
Personal history of autoimmunity and susceptibility factors	22[b]	(14)	154
Family history of hyperthyroidism	37[c]	(24)	151
Severe initial clinical presentation[d]	109	(78)	140
Ophthalmic abnormalities	88	(59)	148
Tachycardia	122	(83)	147
Hypertension	24	(17)	140
Loss of weight	85	(59)	145
Goiter			145
Absent	15	(10)	
Small	52	(36)	
Moderate	48	(33)	
Large	30	(21)	
FT4 (pmol/liter)		52 (40.2–70.5)	152
FT3 (pmol/liter)		26 (17–31)	128
TRAb[e] positivity	129[f]	(88)	147
Multiple of normal upper limit for TRAb		4 (1.5–8.6)	146
TPOAb[a] positivity	99	(70)	141

n, Absolute number per category; N, number of available data for each variable.

[a] Thyroid peroxidase autoantibodies.

[b] Diabetes (n = 9), idiopathic thrombocytopenic purpura (n = 1), trisomy 21 (n = 7), trisomy 18 (n = 1), DiGeorge syndrome (n = 3), diabetes + trisomy 21 (n = 1).

[c] First-degree relative(s), n = 18; second-degree relative(s), n = 17; both first- and second-degree relatives, n = 2.

[d] Severe initial clinical presentation is defined by the presence of at least two of the following features: tachycardia, hypertension, initial weight loss, ophthalmic abnormalities.

[e] TSH receptor autoantibodies.

[f] During follow-up, serum assays for TRAb were positive in 145 patients, negative in eight, and no measurement had ever been undertaken in one patient. This last patient and all patients with negative TRAb results tested positive for TROAb.

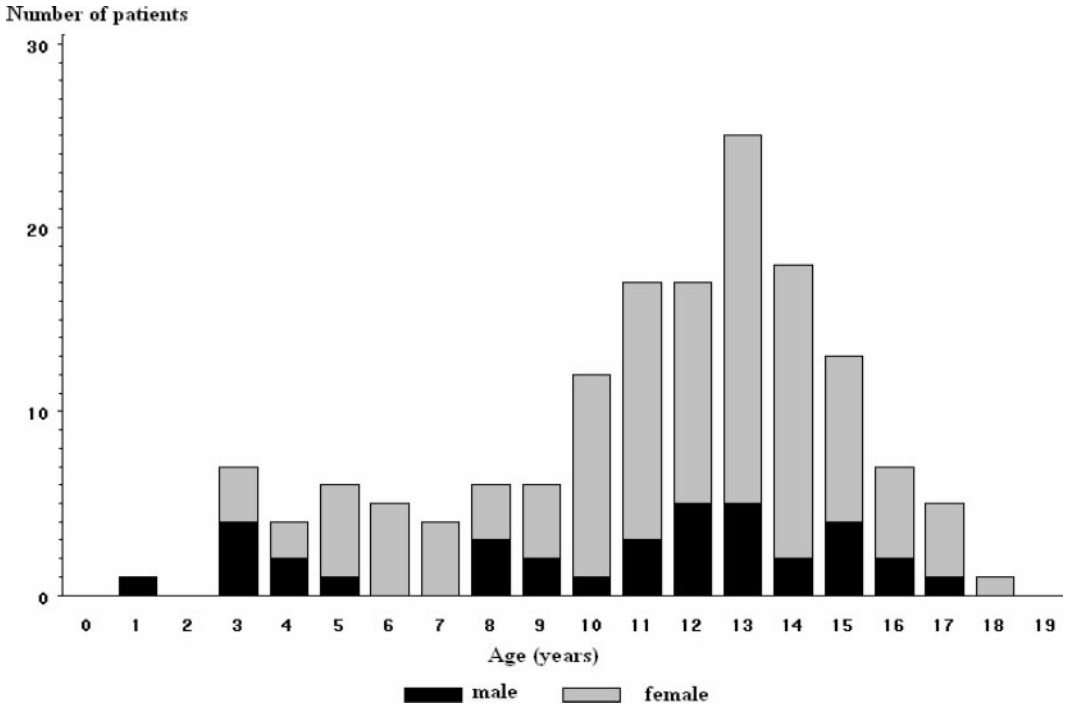


FIG. 1. Age and sex distribution of the children and adolescents population at GD diagnosis.

tients received ATD for more than 27 months). However, no differences were found in the clinical presentation of patients completing 21–27 months of ATD treatment and patients not treated according to the study protocol (data not shown). Forty-seven (32%) patients found it difficult to comply with treatment, and nine patients (6%) presented adverse reactions on ATD (urticaria: n = 6; arthralgia: n = 2; leukoneutropenia: n = 1; thrombopenia: n = 1), with a change of drug treatment being necessary for five patients and radioactive iodine being administered to one patient. L-thyroxine treatment was administered temporarily in 84 children (43%) for a median time of 17 months.

During the treatment period, serum FT4, FT3, and TSH levels remained within the normal range, and the median dose of carbimazole administered was 0.34 and 0.27 mg/kg·d after 12 and 24 months of treatment, respectively. At the end of ATD treatment, TRAb was detected in only 31 (36%) of the 87 patients for whom TRAb levels were determined.

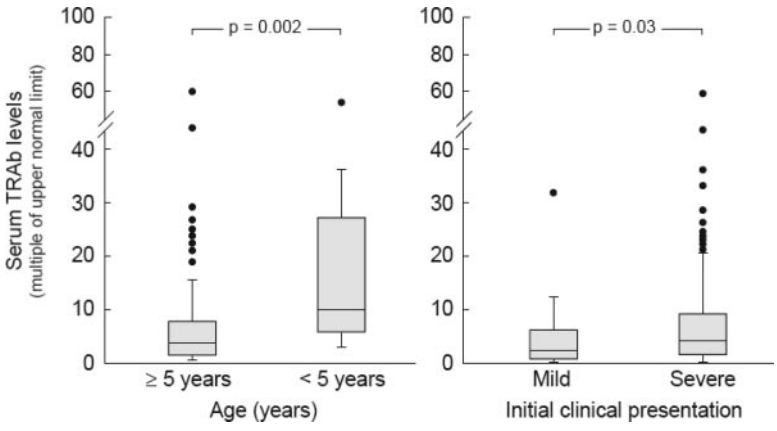


FIG. 2. Relationship between serum TRAb levels and age at GD diagnosis and initial clinical presentation. *Box plots* show the median values and the first and third quartiles in each group. *T bars* represent the rest of the data with a maximum of 1.5 times the interquartile range. *Dots* represent outliers.

Hyperthyroidism relapse rate

Hyperthyroidism relapse was observed after ATD treatment was stopped on the doctor's advice (n = 67), after ATD dose was gradually decreased on the doctor's advice (n = 5), or after treatment was stopped at the patient's initiative (n = 27).

Figure 5 shows the cumulative percentage of patients presenting relapses. The overall estimated relapse rate for hyperthyroidism was 59% (95% CI 52–67%) at 1 yr and 68% (95% CI 60–76%) at 2 yr after the end of ATD treatment. Median time to relapse was 8 months (95% CI 5.4–11.4 months). In total, 87 of the 99 relapses occurred in the first year, principally in the first 6 months (n = 64).

Furthermore, the estimated relapse rate 2 yr after the end of treatment was 83% (95% CI 71–92%) in patients treated for no more than 24 months, and 60% (95% CI 50–70%) in patients treated for more than 24 months.

Predictive factors for relapse

The variables found to be independently associated with relapse within 2 yr of the end of treatment are shown in Table 2. However, based on predefined criteria, we retained only seven variables for multivariate analysis because pubertal stage was collinear with age, and more than 10% of the values were missing for serum FT3 levels at diagnosis and serum TRAb levels at the end of ATD treatment.

Five variables were identified as independent predictors of relapse in a multivariate Cox model: age, serum FT4 and TRAb levels at presentation and du-

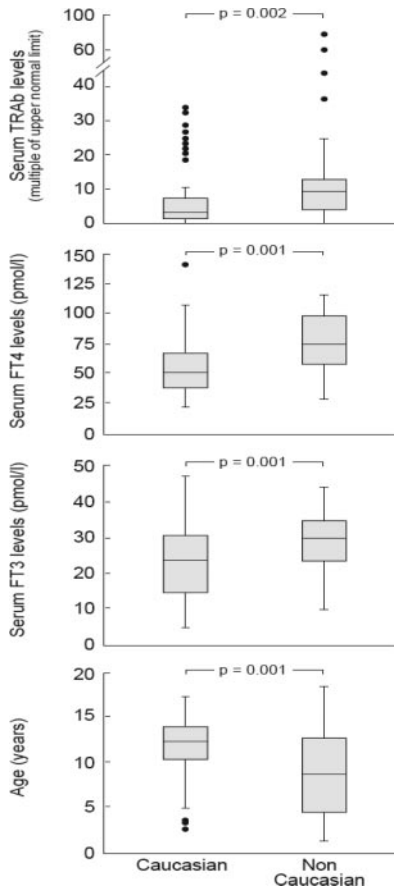


FIG. 3. Relationship between ethnicity and serum TRAb, FT4 levels, FT3 levels, and age at GD diagnosis. *Box plots* show the median values and the first and third quartiles in each group. *T bars* represent the rest of the data with a maximum of 1.5 times the interquartile range. *Dots* represent outliers.

ration of ATD treatment. Non-Caucasian patients were found to be 2.5 times more likely to suffer a relapse than Caucasian patients. Similarly, a 10-point increase in serum FT4 levels and a 10-unit increase in the multiple of upper normal limit for serum TRAb levels at diagnosis resulted in an 18 and 21% increase of the risk of relapse, respectively. Older children were less likely to relapse, with a decrease in risk of 26% for every 5-yr increase in age. Moreover, children who had received longer courses of ATD therapy were less likely to relapse, with a 43% decrease in relapse risk for every additional 12 months of treatment. No center effect was identified in the analysis (data not shown).

A Cox multivariate model was applied to 3000 subsamples of 147 patients created by bootstrapping for internal validation of the final predictive model. The variables most frequently selected as predictive of relapse in the 3000 analyses were then compared with those retained in the final predictive model. Ethnicity was selected as a predictive factor for relapse in 91% of all subsamples, age was selected in 48%, serum FT4 levels in 93%, serum TRAb levels in 45%, and duration of ATD therapy in 58% of subsamples. All other variables were selected in less than 30% of subsamples.

Prognostic score

The prognostic score derived from the regression coefficient of each variable retained in the final model is shown in Table 3. It made it possible to classify patients into three risk groups: group A (low risk group, score from 0 to 3, n = 52; 38%); group B (intermediate risk group, score from 4 to 7, n = 65; 47%); and group C (high risk group, score from 8 to 11, n = 21; 15%). The median score in our population was 4 (3–6) points. Overall, marked differences in the observed and predicted relapse rates were found among the three risk groups (Fig. 6). The patients in risk group A had a predicted 2-yr relapse rate of 46%, whereas those in group C had relapse rates as high as 98% 2 yr after the end of ATD treatment.

Discussion

In this study, we demonstrated differences in the presentation and outcome of GD during childhood and identified several independent predictive factors of relapse for children with GD. The combination of these factors into a prognostic score should help to guide disease management because the probability of a positive long-term therapeutic response varies widely, from 2 to 54%, as a function of risk group. As in other autoimmune conditions, such as insulin-dependent diabetes mellitus (30), levels of autoimmune stimulation, as assessed by determining TRAb titers, were highest for the youngest patients. Severity of hyperthyroidism at presentation, as evaluated by high serum levels of FT4, FT3, and TRAb, and young age were also found to be independently and significantly associated with a higher probability of hyperthyroidism relapse. These findings are consistent with the findings of some previous studies in children (8, 20–23) and adults (14, 15, 31), although they conflict with the results of others (11, 16, 17, 32). Nevertheless, the most controversial prognostic factor is serum TRAb levels, even though these antibodies are considered highly pathogenic in GD. A meta-analysis by Feldt-Rasmussen *et al.* (33) suggested that TRAb is not sufficiently predictive of

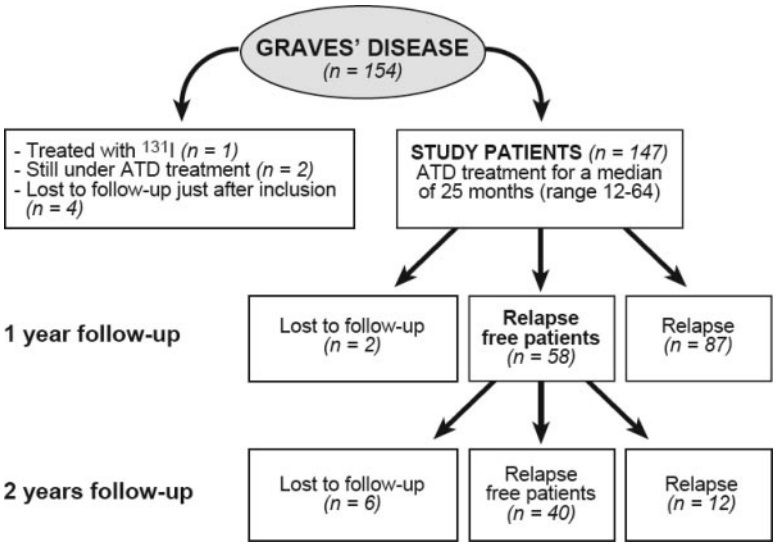
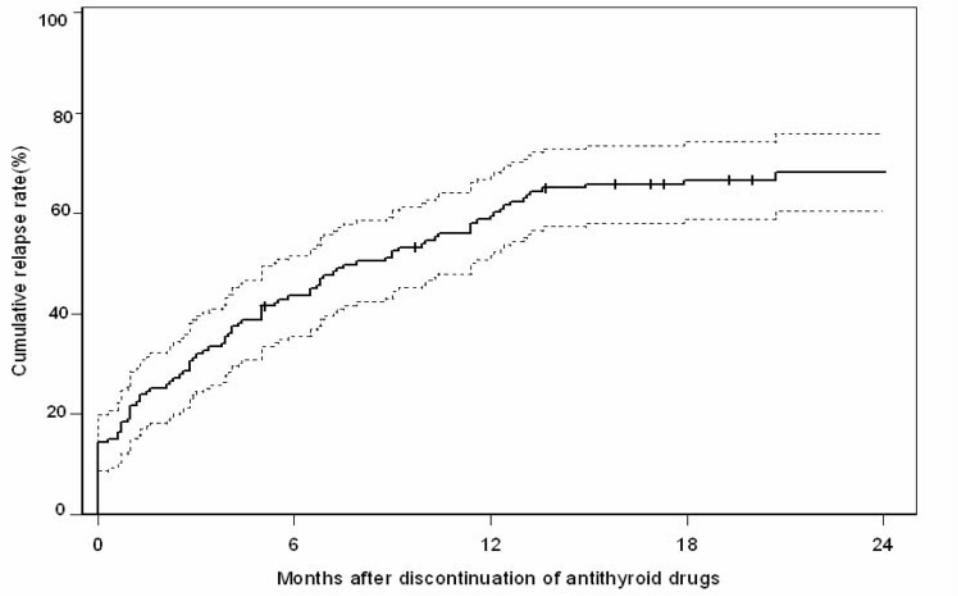


FIG. 4. Outcome of the study population after primary ATD treatment.



Months after discontinuation of antithyroid drugs	0	6	12	18	24
N patients at risk	126	82	58	44	40
Cumulative N of relapses	21*	64	87	97	99

FIG. 5. Cumulative incidence of relapse estimated by a Kaplan-Meier curve. Data are plotted from the end of antithyroid drug treatment and are limited to the 2-yr period of follow-up. *Tick marks on curves* indicate censored observation times. *, Twenty-one of the patients who stopped ATD treatment at their own initiative (n = 27) rapidly relapsed. For these patients, the end of treatment (time = 0) corresponds to the medical visit at which GD relapse was acknowledged and thus time to relapse is considered to be null.

relapse after ATD in adults, whereas most recent studies have clearly demonstrated that TRAb levels at the onset and end of ATD treatment are of prognostic value (11, 15–18, 34, 35). Shibayama *et al.* (36) concluded that TRAb determination is useful for GD management in affected children, but most studies have failed to assess this factor either at diagnosis or during follow-up because of missing data.

Differences in age, biochemical severity, and autoimmune stimulation at presentation and in the risk of relapse of hyperthyroidism after the end of medical treatment were found between ethnic groups in our series. Non-Caucasian patients were younger, presented higher free thyroid hormone levels and TRAb titers at presentation, and were more likely to experience a recurrence of hyperthyroidism than Caucasian patients. The ethnicity of patients has rarely been considered in pediatric and adult studies, although GD incidence is higher in certain parts of the world, and this increase in incidence has been shown not to be due to iodine nutritional status (37, 38). However, it has clearly been suggested that genetic, environmental and immunological background may affect outcome (18, 39).

In contrast to previous studies (14, 15), this study found no effect of sex and positive family history of hyperthyroidism on long-term outcome. An effect of TRAb levels on goiter size at disease onset and an effect of goiter size on remission rate have been reported in some studies (5, 40) but not others (8). Differences in goiter size assessment and laboratory methods for determining TRAb levels may account for such discrepancies. In particular, the manual assessment of goiter size used in most of these studies may be biased by the clinician's knowledge of the patient's biochemical condition (FT4, FT3, TRAb levels), with a tendency to overestimate goiter volume in patients with high hormone and antibody concentrations. Thus, we are aware of possible limitations in the assessment of TRAb levels in our study, but goiter size was carefully assessed by ultrasound evaluation, carried out by an investigator blind to the results of biological tests. Also, our pediatric series was larger than those evaluated in previous studies (7, 8, 21, 32, 41), making it possible to obtain more precise estimates of the effects of initial characteristics on relapse risk, although the patients' genetic background was not considered in our study.

Treatments limiting TRAb production have undergone preliminary trials in adult patients, but there are currently no recommendations for their use (39, 42). There is currently no specific, effective drug treatment for the disease and potential complications are associated with each of the three available therapeutic options (ATD, thyroidectomy, radioactive iodine) (9, 12, 13, 43, 44). Drug therapy is still the first-line treatment for GD in children in many countries. However, the long-term results of ATD treatment remain generally unsatisfactory, as shown by the results of our study, with a remission rate of about 30% after an average of 2 yr of ATD treatment followed by a 2 yr period off treatment, consistent with previous reports in pediatric patients (3, 6, 8, 20, 41). We cannot exclude the possibility that some patients experience a relapse of hyperthyroidism

TABLE 2. Bivariate and multivariate Cox proportional hazards models for relapse predictors within 2 yr of the discontinuation of primary ATD treatment in children with Graves' disease (n = 147)

	Bivariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	***p***	**Hazard ratio (95% CI)**	***p***
Sex				
Male		1		
Female	1.02 (0.65–1.62)	0.92		
Age	0.77 (0.59–1.00)	**0.05**	0.74[a] (0.56–0.97)	**0.03**
Ethnicity				
Caucasian	1			
Non-Caucasian[b]	2.35 (1.48–3.70)	**0.0003**	2.54 (1.50–4.3)	**0.0005**
Initial clinical presentation				
Not severe	1			
Severe	2.14 (1.23–3.73)	**0.007**	[c]	
BMI_{SD} score	0.96 (0.83–1.10)	0.54		
Pubertal development				
Prepubertal	1			
Pubertal	0.72 (0.47–1.12)	**0.15**	[c]	
Postpubertal	0.71 (0.41–1.24)	0.23		
Family history of hyperthyroidism				
Negative	1			
Positive	0.97 (0.62–1.53)	0.90		
Personal history of autoimmunity and susceptibility factors				
Negative	1			
Positive	0.68 (0.37–1.24)	**0.20**	[c]	
Goiter				
Absent/small	1			
Moderate/large	1.00 (0.67–1.51)	0.98		
Serum FT4 concentration	1.20 (1.10–1.30)	**<0.0001**	1.18[d] (1.07–1.30)	**0.001**
Serum FT3 concentration	1.04 (1.02–1.07)	**0.0005**	[c]	
Duration of ATD treatment	0.61 (0.42–0.88)	**0.007**	0.57[e] (0.39–0.84)	**0.005**
Multiple of upper normal limit for TRAb concentration at onset	1.43 (1.21–1.68)	**<0.0001**	1.21[f] (1.02–1.45)	**0.03**
TPOAb				
Negative	1			
Positive	0.87 (0.56–1.36)	0.55		
TRAb at the end of ATD treatment				
Negative	1			
Positive	2.77 (1.65–4.65)	**0.0001**	[c]	

[a] HR related to a 5-yr increase in age.

[b] African, Asian, Caribbean.

[c] Variable not retained in the final model.

[d] HR related to a 10-pmol/liter increase in serum FT4 concentration.

[e] HR related to a 12-month increase in duration of ATD treatment.

[f] HR related to a 10-unit increase in multiple of upper normal limit.

P values in bold indicate statistical significance as defined in the bivariate and multivariate analysis.

more than 2 yr after the end of ATD treatment, as reported in adult studies, in which relapses may occur even 5 yr after the end of ATD treatment (15, 45). Clinical decisions concerning the long-term treatment of patients with GD are difficult, and the identification of treatment regimens lowering relapse rates is therefore of value. There have been few studies of the relationship between ATD treatment duration and relapse risk in pediatric patients. However, the need to prescribe longer treatment courses than in adult patients is widely accepted (19). In a retrospective analysis, Lippe *et al.* (20) demonstrated that remission rates in 63 children and adolescents treated with ATD increased by 25% for every additional 2 yr of treatment. Although, our study was not designed to establish the optimal duration of treatment in children, our results highlight the positive impact of a long period of primary ATD treatment on outcome. Moreover, they are consistent with recently proposed hypotheses concerning GD physiopathology, stressing the importance of rendering and maintaining patients euthyroid for a long period, to minimize thyroid autoimmunity and GD recurrence (46, 47). Poor compliance with treatment, as often reported in long courses of treatment, particularly in adolescents (3, 48), may compromise GD remission. This is currently the main argument put forward for considering early ^{131}I treatment or surgical thyroid ablation earlier in children with GD (12, 13).

The combination of identified independent predictors of hyperthyroidism relapse provided an easily obtainable and clini-

TABLE 3. Prognostic score for relapse in children with GD[a]

Weight	0	1	2	3
Ethnicity	Caucasian		Non-Caucasian	
Age, yr	>12 years	5-12 years	<5 years	
FT4 serum concentration	<50 pmol/liter			≥50 pmol/liter
Multiple of upper normal limit for TRAb concentration	≤ × 4(N)[b]	> × 4(N)[b]		
Duration of ATD treatment	>24 months			≤24 months

For each patient, score may range from 0 to 11.

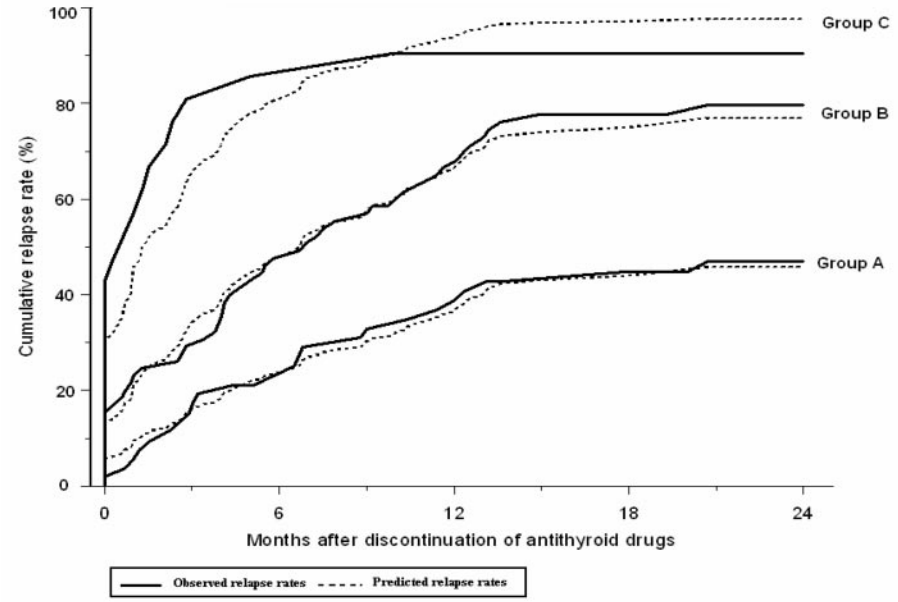
[a] The prognostic score was calculated from the data of 138 of 147 patients because of missing data (n = 9).

[b] Upper normal limit of the assay used at onset.

cally meaningful scoring system for practitioners. Although external validation is still necessary, this classification system could help clinicians in making individual treatment decisions. It also made it possible to identify a small group of children at a very high risk of relapse, essentially young (<5 yr) non-Caucasian children with severe initial hyperthyroidism. Nonetheless, alternative therapeutic options are still a concern at this young age, and initial ATD treatment should be proposed for such patients before considering surgery or radioactive iodine treatment.

In this study, we were able to follow 95% of a well-defined population of patients with GD, taking into account a large number of clinical and biological variables for analysis, rendering this pediatric study the most comprehensive to date. However, this study is limited by the observational nature of data collection. Indeed, 44% of the patients deviated from the study protocol and were not treated for the defined period of 24 ± 3 months but were nonetheless retained for the analysis. This deviation does not bias the study conclusions further because all analyses were adjusted for the duration of medical treatment.

In conclusion, this study, which is, to our knowledge, the largest prospective study in children with GD, provides strong evidence that there is an association between ethnicity, age, and disease severity at diagnosis and the risk of relapse 2 yr after the end of the initial course of ATD treatment. Our results suggest that the use of long courses of ATD treatment is associated with a better outcome. Indeed, the duration of medical treatment seems to be the only variable related to risk of relapse that can be manipulated, as every additional year of treatment was associated with a decrease in relapse rate, independently of the patient's age, ethnicity, and initial severity of disease. However, the optimal duration of medical treatment should be evaluated in large prospective, randomized trials. The use of a predictive score, with treatment duration adjusted as a function of the patient's characteristics, to improve the prognosis could have important implications in daily practice and should be validated by application to another population of children with GD. Whether patients can respond further to therapy or whether they have an



Risk group	Relapse rates			
	1-year		2-year	
	Observed (95% CI)	Mean predicted	Observed (95% CI)	Mean predicted
Group A (0 ≤score≤ 3)	39% (27-54%)	37%	47% (34-62%)	46%
Group B (4 ≤score≤ 7)	66% (55-78%)	66%	80% (69-89%)	77%
Group C (score ≥ 8)	91% (74-98%)	94%	91% (74-98%)	98%

FIG. 6. Observed and mean predicted relapse rates 1 and 2 yr after end of ATD treatment, according to the three-group prognostic classification (groups A, B, and C, corresponding to low, intermediate, and high risk groups, respectively). Observed relapse rates were recorded when applying the prognostic score to our population of patients (n = 138). Mean predicted relapse rates were calculated for each risk group as a function of score values.

intrinsic pathological endocrine condition resulting in an unsatisfactory response to drug treatment remains to be determined. Finally, compliance is an important issue in the management of these children and should be improved by educational strategies.

Appendix

The following persons participated in the French Childhood Graves' Disease Study Group: R. Coutant, N. Montaud-Raguideau (Angers); H. Bony-Trifunovic (Amiens); A. M. Bertrand (Besançon); N. Lucidarme, S. Sauvion (Bondy); P. Barat, V. Bex-Bachellerie, M. Colle, O. Puel (Bordeaux); C. Metz (Brest); S. Nivot (Caen); G. A. Loeuille (Dunkerque); F. Kurtz (St. Avold); M. Bost (Grenoble); J. P. Charvet (Hyeres); J. Nsota, C. Pelatan (Le Mans); C. Stuckens (Lille); C. Naud-Saudreau (Lorient); M. Nicolino, F. Tixier (Lyon); M. Arzim, C. Raybaud (Montelimar); S. Gallet, R. Goddon (Montluçon); S. Baron (Nantes); E. Baechler-Sadoul, K. Wagner (Nice); S. Cabrol, B. Esteva, M. Houang, M. C. Raux-Demay, G. Pinto, M. Polak, D. Zenaty (Paris); P. Blanc (Poissy); K. Boulkessaim, S. Louf (Rang du Fliers); C. Lecointre (Rouen); C. Raynaud-Ravni (St. Etienne); H. Crosnier (St Germain en Laye); S. Feki, S. Soskin (Strasbourg); M. Jesuran-Perelroizen, I. Oliver, C. Pienkowski, M. Tauber (Toulouse); F. Despert (Tours); V. Degros (Valenciennes); M. Taghian, P. Thierry (Vesoul).

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