

pituitary MRI would show in a large proportion of these cases; the most significant developmental abnormalities would be an ectopic posterior pituitary.

Raphaël Rappaport, MD

Reference

- van Tijn DA, De Vijlder JJ, Vulsma T. Role of the thyrotropin-releasing hormone stimulation test in diagnosis of congenital central hypothyroidism in infants. *J Clin Endocrinol Metab.* 2008;93:410-419.

Predictors of Relapse of Hyperthyroidism

There is debate about how Graves' disease (GD) should be treated in children. Remission is achieved in less than 30% of children treated with antithyroid drugs (ATD) vs 40% – 60% in adult patients. When relapse occurs, thyroidectomy or radioactive iodine treatment is considered, although the use of these therapeutic options in children remains controversial. Reliable predictors of relapse after ATD treatment would greatly improve patient management, by facilitating the identification of children requiring long-term ATD or needing early surgery or radioiodine therapy.

The aim of this study was to identify predictors of relapse after ATD treatment in children with GD. This was a prospective, multicenter cohort study of children (n=154) with GD treated with carbimazole for an intended duration of 24 ± 3 months. Most patients (n=147, 95%) completed 1 course of ATD. After the end of treatment, patients were followed up for at least 2 years. The primary outcome was hyperthyroidism relapse. Cox's regression analysis was used and a prognostic score was constructed.

Hyperthyroidism relapse was frequently observed after ATD treatment was stopped. The overall estimated relapse rate for hyperthyroidism was 59% (95% CI, 52% – 67%) at 1 year and 68% (95% CI, 60% – 76%) at 2 years after the end of ATD treatment. Median time to relapse was 8 months (95% CI, 5.4 to 11.4 months). In total, 87

of the 99 relapses occurred in the first year, principally in the first 6 months (n=64). Five variables were identified as independent predictors of relapse in a multivariate Cox model: age, serum free T₄ and TRAb levels at the time of diagnosis and duration of ATD treatment. Non-Caucasian patients were found to be 2.5 times more likely to suffer a relapse than Caucasian patients. Relapse risk decreased with increasing age at onset (hazard ratio [HR] = 0.74 per 5 year increase in age, 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 3 different risk groups, with 2-year relapse rates of 46%, 77%, and 98% (Table). Overall, marked differences in the observed and predicted relapse rates were found among the 3 identified risk groups. The patients in risk group A had a predicted 2-year relapse rate of 46%, whereas those in group C had relapse rates as high as 98% at 2 years after the end of ATD treatment.

In conclusion, this study, which is, to our knowledge, the largest prospective study in children with GD, provided strong evidence that there is an association between ethnicity, age, and disease severity at diagnosis and the risk of relapse 2 years after the end of the initial course of ATD treatment. Results suggested that the use of prolonged 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. 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.

Kaguelidou F, Alberti C, Castanet M, Guittény M-A, Czernichow P, Léger J for the French Childhood Graves' Disease Study Group. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab.* 2008;93:3817-3826.

First Editor's Comment: Although radioiodine or surgery have been advocated as the first choice of therapy in children with autoimmune hyperthyroidism, ATD therapy remains the first choice in most clinics. Therefore, this prospective paper deserves much attention. The study was carefully managed and most of its methodological limitations were taken into account. Because it is everyone's experience that the outcome is rather unpredictable, these data with a practical scoring may turn out to be quite

Prognostic score for relapse in children with GD¹

Weight	0	1	2	3
Ethnicity	Caucasian		Non-Caucasian	
Age	>12 years	1-12 years	<5 years	
Free T ₄ serum concentration	<50 pmol/L			≥50 pmol/L
Multiple of upper normal limit for TRAb concentration	≤x4(N)2	>x4(N)2		
Duration of ATD treatment	>24 months			≤24 months

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

¹ The prognostic score was calculated from the data of 138 of 147 patients because of missing data (n=9).

Reprinted with permission Kaguelidou F, et al. *J Clin Endocrinol Metab.* 2008;93:3817-3826. Copyright © The Endocrine Society 2008. All rights reserved.

useful in the management of individual cases and with the difficult task of maintaining compliance. It also made it possible to identify a small group of children at a very high risk of relapse, essentially young (<5 years of age) non-Caucasian children with severe initial hyperthyroidism. In conclusion, a longer initial duration of a euthyroid state with ATD treatment is the most significant prognostic variable. However, the optimal duration remains to be evaluated in further studies.

Raphaël Rappaport, MD

Second Editor's Comment: Hyperthyroidism is believed to result from a complex interaction between the autoimmune system, environmental factors, and genetic background; it is mainly due to Graves' disease and is less frequently seen in children than in adults. ATD treatment is the initial form of therapy for all hyperthyroid children in an attempt to normalize thyroid function tests. Whether this form of treatment is continued long-term or whether other therapeutic options, such as surgery or radioactive iodine treatment, are considered is often dependant on the rate of relapse after ATD treatment. Reliable predictors of relapse after ATD treatment would facilitate the management of these children by allowing for the identification of those requiring long-term ATD, or alternatively thyroidectomy or radioiodine therapy.¹ In this study, Kaguelidou et al were able to find the 5 variables most predictive of relapse following ATD. At diagnosis the key factors to consider when evaluating the risk of relapse of a patient are: ethnicity (higher risk for children of Non-Caucasian origin), age (the younger the patients the higher the risk for relapse), severity of the disease as manifested by elevated serum free T_4 and TRAb levels (the higher these concentrations, the higher the risk of relapse) and duration of the disease. It is interesting to note that children receiving longer ATD treatment were less likely to relapse, with a 43% decrease in relapse risk for each additional 12 months of treatment. While it is clear that there is no ideal form of therapy for this disease as the 3 available therapeutical options (ATD, thyroidectomy, and radioactive iodine) are associated with potential complications, drug therapy remains the first line of treatment in many countries. The remission rate after 2 years of ATD treatment (about 30%) observed in this study is in agreement with a 1987 report.² This study also demonstrated that the remission rate increases significantly in children and adolescents with every additional year of

treatment. The need for prescribing longer treatment courses in children than in adults is now widely accepted and the duration of medical treatment seems to be the only variable, independent of ethnicity, age and severity of disease, that can be manipulated.

Roberto Lanes, MD

Third Editor's Comment: The value of predictors to determine the relapse risk of patients with hyperthyroidism following ATD therapy has long been studied in children and adults. The most controversial factor is the serum TRAb level which may not be sufficiently sensitive to predict a relapse after ATD treatment³ even though others have considered them useful in children.⁴ TRAb data are often lacking at diagnosis and/or during follow-up of these patients with Graves' disease, as was the case in this study of Kaguelidou et al. However, the long-term results of ATD treatment remain generally unsatisfactory in most studies. Poor compliance with medical therapy is often the most important factor that determines the therapeutic outcome, particularly in adolescents. Yet long-term treatment seems to be the only variable that is at the clinician's control to reduce the risk of relapse of the disease. Thus, important arguments have been put forward for considering ¹³¹Iodine therapy or surgical ablation in the treatment of children with hyperthyroidism.^{5,6}

Fima Lifshitz, MD

References

1. Nedrebo BG, Holm PI, Uhlving S, et al. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. *Eur J Endocrinol.* 2002;147:583-589.
2. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. *J Clin Endocrinol Metab.* 1987;64:1241-1245.
3. Feldt-Rasmussen U, Schlensener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. *J Clin Endo Metab.* 1994;78:98-102.
4. Shiyayama K, Ohya Y, Yokota Y, Ohtsu S, Takubo N, Matsuura N. Assays for thyroid-stimulating antibodies and thyrotropin-binding inhibitory immunoglobulins in children with Graves' disease. *Endocr J.* 2005;52:505-550.
5. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. *J Clin Endo Metab.* 2007;92:797-800.
6. Lee JA, Grumbach MM, Clark OH. The optimal treatment for pediatric Graves' disease is surgery. *J Clin Endo Metab.* 2007;92:801-803.

Treatment Guidelines for Children with Disorders of Sex Development

Disorders of sex development (DSD) is the umbrella term replacing intersexuality to cover congenital conditions characterized by atypical chromosomal, gonadal, or anatomic sex.¹ This article was published in a special issue of a journal focusing on gender identity disorders (GID). However, Meyer-Bahlburg

sees sufficient differences between gender-variant persons, with and without a DSD, to urge distinct evaluation and treatment approaches.

GID is characterized by discomfort or distress with one's apparent or assigned gender accompanied by a persistent identification with the opposite sex. In