

congenital renal and urologic anomalies. Early detection of these anomalies may prevent or delay the risk of renal damage and developing end-stage kidney disease. The paper also provides data regarding the prevalence and odd risk ratios of cardiovascular, gastrointestinal, and skeletal anomalies in CH.

The causes of CH are: thyroid agenesis or hypoplasia, which accounts for 20% to 40% of the cases; ectopic thyroid, which accounts for 45% to 60%; and dysmorphogenesis, which accounts for the remaining 10% to 15% of cases. However, Kumar's observation did not discern the association differences of congenital renal and urologic anomalies among these types of CH; they reported that mutations in PAX8, TITF1, and FOXE1

genes have been associated with CH in patients with either isolated thyroid dysplasia or thyroid dysplasia with associated malformations involving kidney, lung, forebrain, and palate.

Hydronephrosis was the major defect in CH while hypospadias was most seen in the general population. The renal and urologic anomalies except hypospadias are not found on a routine physical examination, but can be easily detected by a renal ultrasound examination. Hypospadias can be easily diagnosed on a routine physical examination. Therefore, they recommended a routine renal ultrasound examination in CH.

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## Corticotropin-Releasing Hormone Testing in Assessment of Hypothalamic-Pituitary-Adrenal Axis Function in Infants with Congenital Central Hypothyroidism

The ACTH deficiency in neonates with multiple pituitary hormone deficiencies (MPHDs) results in sustained hypoglycemia and neuroglycopenia and is a major cause of morbidity and mortality. Under basal conditions, clinical signs of hypothalamus-pituitary-adrenocortex (HPA) axis dysfunction are usually absent and the HPA axis is probably the most difficult to assess in the neonate. For the assessment of HPA axis function in the neonate the corticotropin-releasing hormone (CRH) test (in which both the ACTH secretion by the pituitary gland and the subsequent cortisol secretion by the adrenal cortex can be evaluated) was considered as the most relevant choice. The overall aim of the study by van Tijn and colleagues was to develop a diagnostic workup for fast and reliable assessment of HPA axis function in neonates with congenital hypothyroidism of central origin (CH-C), detected by neonatal screening.

This was a Dutch nationwide prospective study (enrollment 1994–1996). Patients were included if neonatal CH screening results were indicative of CH-C and HPA axis function could be tested within 6 months of birth. Nine male and 3 female infants with CH-C and 4 infants with false-positive screening results or transient hypothyroidism were included in the study.

The assessment of HPA axis function was based on CRH and ACTH tests, multiple random plasma cortisol samples taken in the 24-hour period between thyrotropin-releasing hormone (TRH) and CRH tests, determination of cortisol excretion in 24-hour urine samples collected during this same interval, and long-term follow-up. For each patient the results of all endocrine examinations, including the other hypothalamic-pituitary axes, in combination with the results of cerebral MRI, added up to profiles on which overall diagnoses of HPA function were based. Diagnoses were reevaluated after 5 and 10 year follow-up (false positives, 3 to 5 year follow-up).

Of the 12 CH-C patients included in the overall

analysis, 3 showed diminished peak responses to CRH of both ACTH and cortisol (subjects 1–3). In addition, their highest measured random plasma cortisol concentrations and 24-hour urine cortisol excretions were below the predefined cutoffs. Another 4 infants (subjects 4–6 and 12) showed adequate ACTH peak response, but diminished cortisol peak response. This discordant response was considered abnormal. All 4 subjects with false-positive screening results included in the overall analysis were diagnosed as having sufficient HPA axis.

The CRH test proved to be a fast and reliable tool in the assessment of HPA axis dysfunction in asymptomatic neonates at risk for serious morbidity and mortality when congenital hypothyroidism had been detected. The discordant response type with normal ACTH, but low cortisol response, which has not been described before, may be an early phase of HPA axis dysfunction. A prolonged follow-up until the age of 10 years in some patients confirmed the neonatal diagnosis and the choice of early hydrocortisone replacement therapy.

van Tijn DA, de Vijlder JJ, Vulsma T. Role of corticotropin-releasing hormone testing in assessment of hypothalamic-pituitary-adrenal axis function in infants with congenital central hypothyroidism. *J Clin Endocrinol Metab.* 2008;93:3794-3803.

**Editor's Comment:** *The cortisol peak response to CRH is the most valuable marker of HPA axis function. Ten years of follow-up have shown that it has the highest predictive value of all criteria evaluated in this study. In neonates with hypoglycemia and/or persistent jaundice, HPA deficiency can be suspected. However in the most cases there is no clinical indicator to avoid the high risk of death in early MPH deficiency. With the background provided by neonatal screening for hypothyroidism as suggested by the Dutch set-up<sup>1</sup> the CRH test appears to be the most valuable tool for early diagnosis of HPA axis dysfunction and for hydrocortisone treatment. As already known, hypothalamic-*

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

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## 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 T<sub>4</sub> 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 GD<sup>1</sup>**

Weight	0	1	2	3
Ethnicity	Caucasian		Non-Caucasian	
Age	>12 years	1-12 years	<5 years	
Free T <sub>4</sub> 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.

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

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