

address transitional strategies to avoid dropout and improve the overall outcome of childhood cancer treatment and survivors. Also it is necessary for physicians, as well as patients and family members, to know that late-onset complications of a cancer survivor can occur even after many years following cancer treatment.<sup>3</sup>

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## References

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## Renal and Urinary Tract Anomalies in Congenital Hypothyroidism

Newborn screening for congenital hypothyroidism (CH) is one of the major achievements of preventive medicine, as the condition occurs frequently (1/3000-4000 newborns). An early diagnosis and treatment prevents brain damage and the ensuing mental retardation. It is well known that CH has increased incidence of congenital malformations of heart, gastrointestinal, and skeletal systems. However, the prevalence of congenital renal and urologic anomalies on CH has not been well established.

Kumar et al reported that children with CH have significantly increased risk of congenital renal and urological anomalies. They investigated the prevalence of congenital renal and urologic anomalies in children with CH as compared to children without CH. Analysis of Congenital Malformation Registry data showed 980 children with CH and 3,661,585 children without CH born in New York State (1992-2005). Children with CH had a significantly increased risk of congenital renal and urological anomalies with the odds ratio (OR) of 13.2 (10.6-16.5). The other significantly increased defects and prevalence rates in patients with CH were cardiac, gastrointestinal, and skeletal (Table). Analysis of matched data (CH data from New York State newborn screening; 1,538 children with CH and 3,654,033 children without CH) also confirmed an increase of congenital renal and urologic anomalies with an OR of 4.8 (3.7-6.3). There are limitations of their study; the Congenital Malformation Registry is compiled on the basis of hospital-generated data and is limited to children under 2 years of age. Therefore, there may be an underestimating of the true prevalence of congenital renal and urologic anomalies.

Hydronephrosis, UPJ obstruction, hypospadias, renal dysplasia, and renal agenesis were especially significant. Therefore, they suggested that CH children should be evaluated for the presence of congenital renal and urologic anomalies by a renal ultrasound examination.

Kumar J, Gordili R, Kaskel FJ, Druschel CM, Wordniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. *J Pediatr*. 2009;154:263-266.

**Editor's Comment:** This is a very interesting article; it provides important information for physicians who care for patients with CH and elucidates the high incidence of

### Prevalence rates of congenital anomalies in hypothyroidism (CH) and in general population (non CH)

Congenital anomalies	CH (RATE/10 000)	Non-CH (RATE/10 000)
<b>Renal</b>		
Dysplastic kidney	30.6	1.7
Renal agenesis	102.0	4.3
Ectopic kidney	30.6	1.7
Hydronephrosis	346.9	21.1
Hydroureter	20.4	1.5
UPJ obstruction	30.6	1.9
Reflux	20.4	0.4
Hypospadias	275.5	39.6
Obstruction meatus	20.4	0.3
Posterior urethral valves	10.2	0.7
<b>Cardiovascular</b>		
Atrial septal defect	622.4	29.0
Ventricular septal defect	602.0	36.6
Coartation of aorta	81.6	4.1
Tetralogy of Fallot	183.7	4.6
Endocardial cushion defect	275.5	3.1
<b>Gastrointestinal</b>		
Duodenal atresia/stenosis	51.0	1.6
Gastroschisis	10.2	1.4
Omphalocele	40.8	1.3
Oral clefts	91.3	12.9
Pyloric stenosis	40.8	17.1
Tracheoesophageal fistula	61.2	2.4
<b>Skeletal</b>		
Craniosynostosis	50.0	4.0
Congenital hip dysplasia	30.6	1.7
Limb reduction	40.8	3.3

Modified from Kumar J, et al. *J Pediatr*. 2009;154:263-266. Copyright © Elsevier 2009. All rights reserved.

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-*