

younger age, and girls were more affected than boys. The authors pointed out that the limitations of the study included the use of self or proxy reported height data, lack of longitudinal growth information, and the specific time of documentation of pubertal status. However, the large size of the study and the use of sibling controls helped to validate the significance of the differences found. Finally, the authors stated that most patients with ALL were currently treated with chemotherapy alone. Therefore the relationship between chemotherapy agents and linear growth velocity should be available in the future.

Chow E, Friedman D, Yasui Y, et al. Decreased adult height in survivors of childhood acute lymphoblastic leukemia (ALL): A report from the Childhood Cancer Survivor Study. *J Pediatr.* 2007;150:370-5.

**Editor's Comment:** This paper is accompanied by a thoughtful editorial by Oberfield.<sup>1</sup> Her comments included a discussion of previous reports from the CCSS regarding morbidity among childhood cancer survivors

and specifically those who were survivors of childhood brain cancers and were subsequently treated with growth hormone. Oberfield points out shortcomings with regard to self reported or proxy reported height and the definition of prepubertal and pubertal based on age, but affirms the uniqueness of the study because of its large size and the fact that even with chemotherapy alone there was a greater than threefold increased risk of decreased stature.

The data in this study involved survivors of ALL who were treated with a treatment regimen which differs from that currently in use. It clearly demonstrated that previous treatment regimens were associated with reduced adult height. It is hoped that oncologists will continue to carefully record auxologic and pubertal data on their patients so that similar long-term outcomes can be examined from a different therapeutic era in the future.

William L. Clarke, MD

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## Congenital Hypothyroidism—Outcome of Early Treatment

Previous research conducted by Kempers and colleagues, in a cohort born and screened in 1981-1982, demonstrated persistent cognitive and motor deficits associated with congenital hypothyroidism despite initiating T<sub>4</sub> replacement at a median age of 28 days after birth. In the present study, the same investigators examined potential benefits of commencing T<sub>4</sub> replacement at an earlier age (median = 20 days) for a cohort born in 1992 and 1993. During this time, Dutch pediatricians were advised to start with 6-8µg T<sub>4</sub>/kg/day with T<sub>4</sub> dose adjustments based on thyroid function labs obtained at regular outpatient follow-up visits.

Participants included 82 Dutch children (mean age 10.5 years, range 9.6 to 11.4 years) diagnosed with thyroidal congenital hypothyroidism (CH-T). An additional 5 participants were diagnosed with central congenital hypothyroidism (CH-C); results were

analyzed separately for these due to differing etiology, treatment regimen, and sequelae.

Intelligence was assessed with the Dutch version of the Wechsler Intelligence Scale for Children, third edition (WISC-III), except for the first 10 patients for whom the WISC-R was used (and recalculated into WISC-III scores according to recommended guidelines). Three IQ scores were derived for each participant: full-scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ). General population IQ scores for each domain have a mean of 100 (±15). Motor skills were assessed with the Movement Assessment Battery for Children (MABC), designed to identify motor function impairments in children aged 4-12 years, including subscales for manual dexterity, ball skills, and balance; higher scores indicating more motor problems. For the 1981-1982 cohort, motor skills were assessed using a

#### IQ scores of the CH-T group

	FSIQ	P (t)	Verbal IQ	P (t)	Performance	P (t)
<b>Severe CH-T</b> (n=41)	93.7(89.5-97.9) <sup>1,3</sup>	0.004(-3.0)	94.9(90.1-99.7) <sup>2</sup>	0.039(-2.1)	93.9(90.9-97.8) <sup>1,3</sup>	0.003(-3.1)
<b>Moderate CH-T</b> (n=19)	96.2(88.9-103.5)	0.290(-1.1)	95.4(87.9-102.9)	0.210(-1.3)	98.0(91.1-104.9)	0.550(-0.6)
<b>Mild CH-T</b> (n=22)	105.0(99.5-110.4)	0.73(1.9)	103.6(98.2-109.1)	0.182(1.4)	105.3(99.3-111.3)	0.082(1.8)
<b>Total</b> (n=82)	97.3(94.2-100.4)	0.088(-1.7)	97.4(94.1-100.6)	0.113(-1.6)	97.9(94.8-100.9)	0.172(-1.4)
<b>Range</b>	57-129		65-138		58-134	

IQ scores, expressed as mean (confidence interval), are presented for the total CH-T group and the three severity subgroups.

P values (with t value in parentheses) refer to the comparison with the normative population.

<sup>1</sup> P < 0.01 compared to the population mean

<sup>2</sup> P < 0.05 compared to the population mean

<sup>3</sup> P < 0.01 compared to mild CH-T

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forerunner of the MABC: the Test of Motor Impairment (TOMI). IQ and motor scores were compared among the following subgroups: severe vs. moderate vs. mild CH-T (based on pretreatment free  $T_4$  concentration) and early-treated vs. late-treated patients (ie, before or after the mean starting day of treatment) with severe, moderate, or mild CH-T.

Although mean FSIQ, VIQ, and PIQ scores for the total 1992-1993 cohort were not significantly different from population norms, those in the severe CH-T subgroup received lower scores in all 3 areas (Table). In contrast, IQ scores were not significantly different from the population means for the moderate or mild CH-T subgroups. With regard to motor development, the mean total MABC was significantly poorer than that of the normative population; and a significantly higher proportion of all CH-T severity subgroups received "subnormal" scores. Patients with severe CH-T had significantly worse total MABC and manual dexterity scores than patients with moderate CH-T.

In the severe CH-T group, IQ and motor scores did not differ in patients treated before or later than 19 days after birth. Moreover, IQ and motor scores were not different in the moderate and mild CH-T group when treatment was initiated either before or after 19 and 31 days, respectively. Only the severity of CH-T appeared to be a significant predictor of FSIQ when a multiple regression analysis was conducted using severity of CH-T and starting day of treatment as predictor variables.

Compared to patients from the earlier cohort, those from the 1992-1993 cohort with mild or severe CH-T had initiated  $T_4$  supplementation at a significantly younger age (days 31 and 19 vs. days 68 and 29, respectively). The initial  $T_4$  dose and the FSIQ scores of the subgroups were not significantly different between the 2 cohorts. In patients with mild CH-T, the percentage of patients with a subnormal total motor score was significantly higher in the 1992-1993 cohort; differences were not significant for severe and moderate CH-T. The authors speculated the reason for the increased motor problems scores in the latter cohort may be a result of selecting a measurement tool (the MABC vs. TOMI) exhibiting enhanced sensitivity.

In summary, patients with severe CH-T, whose treatment with  $T_4$  was initiated at a mean age of 19 days after birth, exhibit significant cognitive and motor deficits. Those with mild or moderate CH-T (initiated at a mean age of 31 and 19 days, respectively) had a better

prognosis for IQ, but still showed substantial motor deficits. Based on the observed deficits, despite earlier initiation of  $T_4$  treatment, the authors speculated that intellectual and motor development deficits may be the consequence of the hypothyroid prenatal state.

Kempers MJE, van der Sluijs Veer L, Nijhuis-van der Sanden R, et al. Neonatal screening for congenital hypothyroidism in the Netherlands: cognitive and motor outcome at 10 years of age. *J Clin Endocrinol Metab.* 2007;92:919-24.

**Editor's Comment:** In a review of the earlier paper by Kempers and colleagues in *GGH*,<sup>1</sup> Lanes noted 2 other recent reports of cognitive deficits among those born with severe CH.<sup>2,3</sup> In the current report, IQ deficits were evident among those with severe CH and motor deficits were discernable across all 3 severity subgroups. The American Academy of Pediatrics and other professional societies recently published a clinical report "Update of Newborn Screening and Therapy for Congenital Hypothyroidism,"<sup>4</sup> in which it was acknowledged that those showing signs of prenatal hypothyroidism may evidence more marked cognitive and other impairments; whether these differences, which were characterized as "minor" are preventable by further optimizing postnatal therapy was considered an open question.

In consideration of the potentially increased vulnerability of children with severe CH despite early and adequate  $T_4$  supplementation, this subgroup should receive particular scrutiny with regard to neurocognitive function. Parental reports of adequate school performance in early years obviously do not rule out specific learning disabilities that, if left undetected, could result in suboptimal academic achievement misattributed to other factors. Finally, when neurocognitive capacity is the clinical outcome of interest, do not assume good adherence to

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### GGH Contact Information

Phone: 805-682-7640 x 249  
Fax: 805-456-0111  
Editor@GGHjournal.com  
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recommended  $T_4$  supplementation; in a psychometric and school achievement study of 14-year-olds with CH, identified by newborn screen, approximately 45% had poorly controlled hypothyroidism.<sup>5</sup> Of particular relevance to the issue of cognitive function in these youths, improved hormonal values were accompanied by significant improvements in test results.

David E. Sandberg, PhD

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## Failure to Thrive: Terminology and Anthropometry

In the February 2007 issue of the *Archives of Diseases in Childhood*, there are 6 articles or perspectives pertaining to one form of aberrant infant growth termed “failure to thrive” (FTT). As Hughes<sup>1</sup> commented—except for infants with obvious disease (eg, cystic fibrosis, celiac disease), the operative definition of “non-organic” FTT in developed societies is not agreed upon, resulting in difficulty in establishing a clear diagnosis and in blurring the divide between a normal extreme and clinical illness; the latter perhaps associated with impaired development. However, a suboptimal nutritional state is usually recognized as one of the hallmarks of this entity.<sup>2</sup> Olsen et al evaluated growth data from 6090 Danish children examined between 1 to 5 weeks of age, 2 to 6 months of age, and 6 to 11 months of age in an effort to establish the prevalence of this growth pattern. Utilizing 7 anthropometric criteria of FTT (Table), they examined the concurrence of these criteria in establishing its presence. In this population of infants, 27% met one or more of the anthropometric criteria at either the earlier (3-6 months) or later (6-11 months) examinations. Only 1.3% of infants met the criterion “weight <80% of median weight for length,” and they were a good deal longer than other infants. Twenty-two percent of infants crossed 2 major weight percentiles downward, but they were substantially heavier at birth and

throughout the study than were other children with FTT. None of the infants in this study were concordant for all 7 criteria, and approximately 70% of subjects with FTT met only one criterion. Significant under-nutrition, defined as BMI <5th percentile for chronological age, was present in only 2% of children screened. Olsen et al concluded that “... no single measurement ... is adequate to identify nutritional growth delay ... (or) to predict outcomes such as neurodevelopmental or behavioral outcomes.” Spencer reached the same conclusion; indeed this investigator stated unequivocally “weight monitoring is not a good screening test for FTT.”<sup>2</sup>

Emond and co-workers previously examined family, socioeconomic, and prenatal factors that were epidemiologically related to FTT and found that only higher parity (infants born in a 4th or subsequent pregnancy) and small maternal stature (<160 cm) were associated with poor infantile weight gain during the first 9 months of life.<sup>3</sup> They reported that parental postnatal factors associated with FTT as assessed by conditional weight gain of the offspring are maternal age >32 years, height <160 cm, and parity >3; infant characteristics are prolonged breast feeding (>7 months), slow feeding, and ingesting only small amounts of solid food after 6 months of age.

Lucas et al reviewed the literature reporting lay (primarily maternal) views on infant growth and well being. In this population, infant size was primarily utilized as an index of the health and the quality of care provided by the parent(s). While supranormal growth is not of concern, subnormal growth evokes anxiety and fear about the infant and self-recrimination. Wright and Weaver<sup>4</sup> commented that it is essential to differentiate between size (a static measurement) and growth (a dynamic change) when assessing the likelihood of underlying illness in an infant with FTT and that aggressive intervention in the short, thin, normally growing and developing infant is unnecessary.

Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Arch Dis Child*. 2007;92:109-14.

Emond A, Drewett R, Blair P, Emmett P. Post natal factors associated with failure to thrive in term infants in the Avon Longitudinal Study of Parents and Children. *Arch Dis Child*. 2007;92:115-9.

### Anthropometric Criteria of Failure to Thrive

- Weight <75% of median weight for chronological age (Gomez criterion)
- Weight <80% of median weight for length (Waterlow criterion)
- Body mass index for chronological age <5th centile
- Weight for chronological age <5th centile
- Length for chronological age <5th centile
- Weight deceleration crossing more than two centile lines; centile lines used: 5, 10, 25, 50, 75, 90, 95, from birth until weight within the given age group
- Conditional weight gain=lowest 5%, adjusted for regression towards the mean from birth until weight within the given age group\*

\* Conditional weight gain was determined by the “thrive index”—the change in weight z-scores between 2 points, from birth to the later age, adjusted for regression to the mean.

Adapted from Olsen EM, et al. *Arch Dis Child*. 2007;92:109-14.