Neurodevelopmental and Body Composition Outcomes in Children With Congenital Hypothyroidism Treated With High-Dose Initial Replacement and Close Monitoring

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Background: Despite newborn screening and early levothyroxine replacement, there are continued reports of mild neurocognitive impairment in children with congenital hypothyroidism (CHT). In Auckland, New Zealand, cases are identified by a neonatal screening program with rapid institution of high-dose levothyroxine replacement (10–15 μg/kg-d), producing prompt normalization of thyroid function. Subsequently, frequent monitoring and dose alterations are performed for 2 years. We aimed to assess whether the Auckland treatment strategy prevents impairment of intellectual and motor development.

Methods: This study encompassed all children with CHT born in 1993–2006 in Auckland and their siblings. Neurocognitive assessments included the following: 1) intelligence quotient via Weschler Preschool and Primary Scale of Intelligence III or Weschler Intelligence Scale for Children IV; 2) Movement Assessment Battery for Children; and 3) Beery Developmental Test of Visual-Motor Integration. Body composition was assessed by dual-energy x-ray absorptiometry.

Results: Forty-four CHT cases and 53 sibling controls aged 9.6 ± 3.9 years were studied. Overall intelligence quotient was similar among CHT cases and controls (95.2 vs 98.6; \( P = .20 \)), and there were also no differences in motor function. Severity of CHT did not influence outcome, but greater time to normalize free \( T_4 \) was associated with worse motor balance. There were no differences in anthropometry or body composition between groups.

Conclusions: These findings suggest that a strategy of rapidly identifying and treating infants with CHT using high-dose levothyroxine replacement is associated with normal intellectual and motor development. The subtle negative impact on motor function associated with time to normalize free \( T_4 \) levels is consistent with benefit from rapid initial correction. (J Clin Endocrinol Metab 98: 3663–3670, 2013)
When untreated, congenital hypothyroidism (CHT) leads to marked intellectual, motor (1), and growth retardation (2). The introduction of newborn screening programs and early levothyroxine replacement has markedly reduced the prevalence of intellectual disability in children with CHT from 8%–28% to 1% or less (3). However, there are continued reports of persisting mild neurocognitive impairment in children identified by neonatal screening programs, including reduced intelligence quotient (IQ) and problems with behavior and attention, as well as subtle fine motor, language, and visuospatial impairment (4–8). These impairments reflect borderline T₄ availability before birth or postnatal factors, such as late diagnosis, late initiation of treatment, and both under- and overtreatment.

Although some authors suggest that there are unavoidable effects of prenatal hypothyroidism (9), its role in later neurocognitive impairment remains unclear. The fetus is relatively protected by maternal T₄ transferred by the placenta; however, cord T₄ in CHT neonates is still lower on average than normal controls (10). Neurocognitive deficit in childhood has been associated with markers of CHT severity including initial T₄ (5, 6, 9) and TSH (9, 11), bone immaturity (9, 12), and etiology (thyroid agenesis) (9, 13) as well as sociodemographic factors such as parental education and rural setting (14).

Modifiable treatment factors are also associated with worse outcome, including later age at initiation of replacement (13, 15), low-dose initial levothyroxine replacement (4, 16–18), later time to normalize thyroid function (19), and fewer clinic attendances in the first year of life (14). These studies suggest that better outcomes may be achieved with earlier treatment and an initial high-dose of levothyroxine to more rapidly normalize thyroid function (20) as well as closer ongoing monitoring. These studies suggest that late treatment or undertreatment of CHT after birth is likely to be a major contributor to persistent neurocognitive deficits. If optimal early treatment can prevent neurocognitive deficits, then it would seem improbable that there is a permanent prenatal effect. Nonetheless, high-dose levothyroxine treatment is associated with an increased risk of supraphysiological free T₄ (FT₄) levels (21), which may lead to difficult temperament in infancy (22) and more frequent attention, behavioral, and psychiatric problems in childhood (17). Furthermore, the optimal testing frequency for infants with CHT is still unclear, and it is possible that better outcomes may be achieved with more frequent tests to prevent hyperthyroidism (23, 24) than recommended in currently endorsed guidelines (25).

In the 1990s, major CHT treatment guidelines were revised to recommend higher initial levothyroxine dosing, increasing the recommended starting dose from 6–8 µg/kg/d to 10–15 µg/kg/d (26, 27). Since 1993, our institution (Starship Children’s Hospital, Auckland, New Zealand) has based the initial levothyroxine replacement dose on CHT etiology as a proxy for severity: 15 µg/kg is the starting dose for athyreosis, 12 µg/kg for ectopia, and 10 µg/kg for dysshormonogenesis (24). Thyroid function tests are performed frequently: weekly over the first 4 weeks, monthly until 12 months of age, bimonthly until 24 months of age, and every 3 months thereafter. The dose of levothyroxine is reduced as soon as initial normalization occurs. This strategy results in rapid normalization of FT₄ concentration without persisting hyperthyroxinemia (24).

In addition to effects on neurodevelopment, body composition is altered in hypo- and hyperthyroidism postnataally, and there are reports of increased rates of obesity in children with congenital hypothyroidism (28, 29).

The aim of the present study was to investigate long-term neurocognitive and body composition outcome in children with CHT managed by this strategy. We hypothesized CHT subjects would be no different to their sibling controls.

### Materials and Methods

#### Ethics approval

Ethics approval for this study was provided by the Northern Y Regional Ethics Committee, Ministry of Health, New Zealand (NTY/10/03/018). Written informed consent was obtained from parents or guardians as well as verbal or written consent from each child as was appropriate to their age.

#### Participants

In New Zealand, the newborn screening for CHT is based on measurement of whole-blood TSH, and all children with CHT are recorded in a National Newborn Screening Unit database. Heel-prick samples are collected on filter paper from all newborn babies 48–72 hours after birth and immediately sent for testing by immunofluorescence (Delfia PerkinElmer Inc). Infants with TSH values greater than 50 mIU/L are referred directly to a pediatric endocrinologist. For borderline abnormal TSH values of 15–49 mIU/L, repeat samples are collected within 2 weeks. If the TSH values are persistently greater than 15 mIU/L, the infant is referred to pediatric endocrinology services for definitive evaluation. CHT was defined as a positive screen, followed by a confirmatory serum TSH of 15 mIU/L or greater. CHT etiology was classified based on thyroid scintiscan as athyreosis, ectopia, or dysshormonogenesis (a normally sited gland with normal or increased size and technetium uptake). This study encompassed all children with CHT born between May 1993 and May 2008 in the Auckland region. Auckland has a population of approximately 1.5 million, and all infants diagnosed with CHT in this region are treated by the pediatric endocrine team at Starship Children’s Hospital using the standardized approach previously described. Children were included in this study if they had a neonatal diagnosis of primary CHT and...
were treated in the first 3 years of life by the Starship’s Endocrine Service. Importantly, over the study period, there was no change to the assay or the cutoff values for repeating tests or case referral. Siblings of CHT children of the same age group were recruited as controls. Exclusion criteria for both groups included a severe developmental delay unexplained by the congenital hypothyroidism, chronic or current illness, syndromes or genetic conditions, and recreational drug use including tobacco.

**Study parameters**

All clinical and neurocognitive assessments were carried out by trained examiners at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Examiners were blinded to group designation (CHT or control). Assessments were booked within a week of normal FT4 and TSH levels.

Children’s heights were measured to the nearest 0.1 cm using a Harpender stadiometer. Body composition data were obtained using whole-body dual-energy x-ray absorptiometry (Lunar Prodigy 2000; General Electric). The parameters of interest were weight, total body fat percentage, and abdominal adiposity (expressed as the android fat to gynoid fat ratio). Parental heights and weights were also measured at the time of assessment whenever possible or else reported by a caregiver. Children’s heights, body mass index (BMI), and parental heights were transformed into SD scores (SDS) (30). Midparental height SDS was calculated for each child (31), as was the mean parental BMI SDS.

Pubertal staging was assessed by a pediatric endocrinologist. Pubertal onset was defined as Tanner stage 2 breast development in girls and testicular volume greater than 3 mL in boys. Ethnicity was identified by self-report using a prioritized system, such that if multiple ethnicities were selected, the subject was assigned to a single ethnicity, following a hierarchical classification (32). Socioeconomic status was determined using the New Zealand Index of Deprivation 2006 (NZDep2006), a geocoded deprivation score derived from current residential address (33).

**Neurocognitive assessments**

**General intelligence**

IQ in children aged younger than 7 years was measured with the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) (34), whereas subjects aged 7 years and older were assessed with the Wechsler Intelligence Scale for Children (WISC-R) IV (35). The core subtests from these scales were used to obtain composite scores on verbal, performance, and full-scale IQ. Both WPPSI-III and WISC-R IV are age-standardized tests, with a mean of 100 and a SD of 15.

**Other neurodevelopmental assessments**

Visual motor integration, visual perception, and motor coordination were measured with the Beery Developmental Test of Visual-Motor Integration, fifth edition (Beery VMI) (36). Motor development was further assessed using the Movement Assessment Battery for Children, second edition (MABC-2) (37). The performance test of the MABC-2 identifies impairments in gross and fine-motor function. The MABC-2 is composed of 8 fine- and gross-motor tasks grouped into 3 subscales: 1) manual dexterity, 2) aiming and catching, and 3) balance. In addition to the subscale scores, a total impairment score was obtained. All scores were standardized with a mean of 10 and SD of 3 (37).

Unlike other neurodevelopmental tests used in the assessments, higher MABC-2 scores reflect poorer function.

**Parental verbal ability and scholastic aptitude**

Estimates of parental intelligence were obtained with the Peabody Picture Vocabulary Test 4 (PPVT-4), which measures verbal ability and scholastic aptitude. The test was administered to the primary caregiver of study participants (38). Standardized scores have a mean of 100 and SD of 15 (38).

**Thyroid function**

Electrochemiluminescence immunoassays of serum TSH and FT4 were performed using Roche Elecsus and Modular Analytics analyzers (Roche). The intra- and interassay coefficients of variation were, respectively, 8.6% and 8.7% for TSH, and 1.6% and 3.5% for FT4. The reference range for FT4 is 10.6–39.8 pmol/L for those aged 4–30 days, 10.6–30.1 for age 2–12 months, and 11.2–22.5 for age 2–6 years. For TSH, the reference range is 0.43–16.1 mIU/L from 4 to 30 days, 0.62–8.05 from 2 to 12 months, and 0.54–4.53 from 2 to 6 years of age.

For the purposes of this study, we defined initial normalization as the first blood test with a FT4 greater than 10.5 pmol/L (the lower limit of the reference range in the first month of life). In the ongoing management of CHT replacement, levothyroxine dose adjustments were made to keep the FT4 in the upper half of the normal range. After the first month of therapy, TSH levels were also used to guide dose adjustment. We defined undertreatment as episodes in which TSH was greater than 15 mIU/L (39) and overtreatment as TSH less than 0.5 mIU/L. To allow for nonuniform time intervals and frequency of blood tests, we assessed the proportion of blood tests that showed under- or overtreatment in 2 broad time frames, less than 2 years of age and 2 years old and older.

**Statistical analyses**

Baseline comparisons were made using 1-way ANOVA between children with CHT and their sibling controls. Sex ratio, ethnic composition, and the proportion of children in puberty were compared with Fisher’s exact tests. These analyses were carried out in Minitab version 16 (Pennsylvania State University). Possible differences in neurocognitive outcomes or body composition were assessed using linear mixed models in SAS version 9.3 (SAS Institute). All models accounted for gender and socioeconomic status (NZDep2006). All models included family identification number as a random factor to identify sibling clusters. Other factors were controlled for as required, depending on the outcome response of interest: for anthropometry, pubertal status and the respective parental factor (mean parental BMI SDS or midparental height SDS); and for cognitive parameters, parental PPVT-4 score. Descriptive and demographic data are provided as means ± SD, whereas data from multivariate models are provided as means and 95% confidence intervals adjusted for confounding factors.

**Results**

**Study cohort**

A total of 83 children with CHT were identified in Auckland who were born during the 15-year period cove-
erred by the study (Figure 1). Eighteen children could not be located or were no longer living within the Auckland region. Of the remaining 65 potential participants, 6 declined to take part (Figure 1). All 59 volunteers were screened, and 11 participants failed to meet the inclusion criteria: 2 had trisomy 21, 3 had developmental delay unrelated to CHT, 2 had autism and sensorineural deafness, 1 had choreoathetosis associated with a known thyroid transcription factor-1 mutation (n = 1), and having developmental delay and absence seizures after severe noncompliance in the first 2 years of life (n = 1).

Of the 48 children enrolled into the study, 4 did not attend assessments. As a result, 44 CHT participants were included in this study, with all sibling controls matching in inclusion criteria also enrolled (n = 53) (Figure 1). Subjects were aged 9.6 years (range 4.0–18.6 years). Among CHT children, 9 had athyreosis (20%), 27 thyroid ectopia (61%), and 8 dyshormonogenesis (18%). Forty children (90%) had a screening whole-blood TSH of 50 mIU/L or greater (equivalent to a serum TSH >100 mIU/L).

### Power analysis

A post hoc power calculation was carried out based on our 44 cases and 53 controls (1.2 ratio of controls to cases). With an SD of 12 [reflecting the variation in IQ between siblings (40)], power of 80%, and α = .05, our study was sufficiently powered to detect a statistically significant difference between groups of approximately 5.2 IQ points.

### CHT children vs sibling controls

Children in the CHT group were younger (P < .001) and included a greater proportion of females (P = .004) than the control group. There were no differences in socioeconomic status, the proportion of children in puberty, or the ethnic distribution of participants (Table 1). Children in both groups were anthropometrically similar (Table 1).

IQ scores were similar among children with CHT and their siblings (Table 2). Only one child in each group had an IQ less than 70, and the proportion of children with an IQ less than 1 SD below the mean (<85) was similar in the CHT and control groups (27% vs 26%, respectively; P = .99). The overall Beery VMI score and the visual perception and motor coordination components were similar between groups (Table 2). MABC-2 scores were mostly similar, except that CHT children had lower manual dexterity scores, indicating better function (P = .009; Table 2).

### CHT group: time to diagnosis, normalization, and subtype comparison

CHT diagnosis occurred at a median age of 9 days (range 2–33 days). FT4 normalized within 7 days of diagnosis (range 0–16 days), at a median of 16 days of age (range 6–34 days). TSH normalized within a median of 14 days of diagnosis (range 1–111 days), at 25 days of age (range 8–119 days).

FT4 levels in children with athyreosis took longer to normalize than other children with CHT (8.1 ± 1.6 vs...
6.2 ± 3.5 days; \( P = .036 \), but TSH normalized within a similar period of time in both groups (20.3 ± 20.6 vs 19.9 ± 20.5 days; \( P = .86 \)). Mean FT4 and TSH were similar throughout the study period in both groups. Importantly, there were no differences in anthropometry or any of the psychological parameters among children with athyreosis compared with those with ectopia and dyshor- monogenesis (data not shown).

### Effects of clinical parameters

Exploratory analyses were carried out on the potential effects of clinical parameters associated with CHT and its treatment. Age at diagnosis appeared to have no effect on any outcome measures. Higher TSH levels at diagnosis were associated with lower MABC-2 total (\( P = .021 \)) and manual dexterity scores (\( P = .032 \)), indicating better function. Age at normalization of FT4 or TSH did not appear to affect any neurocognitive outcomes. However, a longer period of time taken to normalize FT4 (but not TSH) was associated with an increase in MABC-2 balance scores (\( P = .012 \)), indicating worse function.

Only 5.5% of children with CHT had an episode of undertreatment in the first 2 years of life; the rate was similar after 2 years of age (5.3%). Overtreatment was more common before and after 2 years of age (11% and 9%, respectively). There was no observed effect of the frequency of under- or overtreatment episodes.

### Discussion

This study showed that CHT children managed with rapid postnatal normalization of thyroid function had similar IQ scores to their sibling controls. This is consistent with 2 previous reports on high-dose initial replacement (13, 16), although contrasting findings were obtained in a recent Swiss study, in which CHT subjects at 14 years of age were 9.7 IQ points below controls (6). However, the sig-

### Table 1. Demographic and Anthropometric Data for Participants With CHT and Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>CHT</th>
<th>Controls</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>8.3 ± 3.7</td>
<td>10.7 ± 3.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex ratio (females)</td>
<td>73%</td>
<td>43%</td>
<td>.004</td>
</tr>
<tr>
<td>Pubertal</td>
<td>23%</td>
<td>35%</td>
<td>.18</td>
</tr>
<tr>
<td>Socioeconomic status (NZDep2006)</td>
<td>5.1 ± 3.1</td>
<td>5.8 ± 3.4</td>
<td>.33</td>
</tr>
<tr>
<td>Ethnicity (New Zealand European)</td>
<td>48%</td>
<td>36%</td>
<td>.30</td>
</tr>
<tr>
<td>Anthropometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height SDS (cm)</td>
<td>0.84 (0.50–1.18)</td>
<td>0.86 (0.54–1.19)</td>
<td>.90</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.00 (0.61–1.39)</td>
<td>0.81 (0.44–1.19)</td>
<td>.36</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>24.9 (21.4–28.4)</td>
<td>23.1 (19.7–26.5)</td>
<td>.35</td>
</tr>
</tbody>
</table>

Where applicable, demographic data are means ± SD; anthropometric data are means and 95% confidence intervals adjusted for other confounding factors in the multivariate models.

### Table 2. Psychological Data Comparing Patients With CHT and Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>CHT</th>
<th>Controls</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>WISC-IV/WPPSI-III, n/n</td>
<td>24/20</td>
<td>45/8</td>
<td></td>
</tr>
<tr>
<td>PPVT-4</td>
<td>99.6 ± 12.1</td>
<td>98.7 ± 11.2</td>
<td>.73</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>95.2 (90.8–99.6)</td>
<td>98.6 (94.4–102.8)</td>
<td>.20</td>
</tr>
<tr>
<td>Verbal</td>
<td>97.9 (93.5–102.2)</td>
<td>97.5 (93.3–101.7)</td>
<td>.90</td>
</tr>
<tr>
<td>Processing speed</td>
<td>94.0 (88.3–99.7)</td>
<td>98.3 (93.3–103.3)</td>
<td>.24</td>
</tr>
<tr>
<td>Beery VMI</td>
<td>10.9 (10.0–11.7)</td>
<td>11.6 (10.8–12.4)</td>
<td>.11</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>9.4 (8.4–10.3)</td>
<td>9.6 (9.0–10.8)</td>
<td>.38</td>
</tr>
<tr>
<td>Visual perception</td>
<td>10.6 (9.6–11.6)</td>
<td>10.1 (9.14–11.1)</td>
<td>.51</td>
</tr>
<tr>
<td>MABC-2 total</td>
<td>10.2 (9.0–11.3)</td>
<td>11.2 (10.2–12.3)</td>
<td>.10</td>
</tr>
<tr>
<td>MABC-2 balance</td>
<td>10.9 (9.8–12.0)</td>
<td>11.4 (10.4–12.4)</td>
<td>.50</td>
</tr>
<tr>
<td>MABC-2 catch</td>
<td>11.5 (10.4–12.6)</td>
<td>11.2 (10.2–12.3)</td>
<td>.68</td>
</tr>
<tr>
<td>MABC-2 manual dexterity</td>
<td>8.6 (7.4–9.7)</td>
<td>10.4 (9.4–11.5)</td>
<td>.009</td>
</tr>
</tbody>
</table>

PPVT-4 data are means ± SD; all other data are means and 95% confidence intervals adjusted for other confounding factors in the multivariate models. Unlike other parameters, higher MABC-2 scores indicate worse motor function.
significance of the latter finding is unclear because the control IQ was unusually high, control participants were unrelated, and there was no adjustment for parental intelligence. Thus, it seems that, unlike low-dose regimes (4, 7, 41), high-dose initial treatment can preserve intellectual development.

We observed no apparent defects in motor development, in contrast to a previous study that compared CHT children treated with high-dose initial replacement with a reference range (19). However, the importance of rapid normalization of thyroid function was underscored by the association between time to normalize FT4 and motor balance (MABC-2 balance). These findings suggest either that intellectual and motor impairment develop postnatally or that if they do develop prenatally, they can be reversed by brisk and sufficient levothyroxine replacement after birth.

An important difference in this study is that we have actively excluded children who had high risk of developmental problems or had neurodevelopmental delay unrelated to hypothyroidism. Our study demonstrated up to 14% of children with CHT had another environmental, syndromal, or genetic factor that could potentially affect neurodevelopment. A negative bias could exist in other outcome studies that have not made these exclusions. This is especially important because we have selected controls who were healthy and had no identified neurodevelopmental problems or risks.

This study was unique not only because of the use of sibling controls and early high-dose treatment but also because of frequent biochemical testing. Frequent testing allows earlier identification and correction of hypo- and hyperthyroidism so that when these do occur, they are brief. Overtreatment was common, occurring in 9% of tests in the first 2 years and 11% thereafter. It is possible that the avoidance of prolonged periods of hyperthyroidism, using this testing regimen, has prevented the worse neurodevelopmental outcome found in a previous high-dose initial replacement study that used less frequent testing (6).

The effect of severity of CHT on neurodevelopmental outcome was assessed by relating outcome measures to etiology and TSH at diagnosis. Initial FT4 was not included in the analysis because it was frequently below the limit of detection. In contrast to other studies that compared outcome according with severity (5, 6, 12, 13), in this study children with athyreosis did not have worse neurodevelopmental outcomes than those with ectopia and dyshormonogenesis. It is possible that a difference was undetected due to limited power in the subgroup analysis. Nevertheless, the CHT cohort as a whole had predominantly severe hypothyroidism at presentation and was not different from sibling controls. Furthermore, the only association between initial TSH and neurodevelopmental outcome was better motor function with higher initial TSH. This suggests the Auckland treatment program with dosing based on etiology and early initiation of treatment ameliorates the risk of intellectual impairment in all subjects, even those with severe congenital hypothyroidism. This strongly supports the use of high initial replacement doses with frequent monitoring and dose adjustment.

The WISC-R IV and WPSSI-III tools were recently referenced to an Australian population. The mean IQ in the CHT group was 95.2, a third of a SD below the expected mean. This small difference does not reflect lost intellectual function because it is not different from the sibling controls (98.6; P = .20); rather it may be a random sampling effect or it may reflect the high proportion of non-European ethnicity in our sample. The WISC-R IV reference population was 10% non-European (35), whereas our CHT participants were 53% non-European (P < .0001). Non-European ethnicities have generally lower socioeconomic status (42), which has been associated with lower IQ (43), and were more likely to have English as a second language, which may have affected performance during testing.

The lack of association between age at initiation of treatment and neurodevelopmental outcome in this study is not evidence that early treatment is unimportant. In our cohort, treatment was initiated within a narrow age range, predominantly in the first week. The subjects with later initiation of treatment were those with mild hypothyroidism confirmed on repeat testing. These factors and our relatively small cohort limit the study’s power to detect an effect of age at initiation on neurodevelopmental outcome. However, the overall lack of difference in neurodevelopmental outcomes between cases and controls in this study is consistent with a beneficial effect of early treatment.

There were no differences in height, BMI or adiposity between the CHT and control groups. This contrasts with Chinese (28) and Swiss (29) studies, which showed an increased rate of obesity compared with population norms, but is consistent with the low rate of undertreatment in the CHT subjects.

The major strengths of this study include the use of sibling controls, controlling for both genetic and environmental factors including socioeconomic status and parental intelligence, and the use of a program able to provide rapid diagnosis, treatment, and careful monitoring to quickly normalize thyroid function and maintain it within the normal range. Many studies have compared CHT subjects with population norms or unrelated controls. Comparison with population norms may not be appropriate if
there is a strong secular trend, which is the case for both body composition (increasing adiposity) and IQ (increasing scores), or if the group under investigation differs from the reference population (as our group does in regard to ethnic composition). Although nonrelated controls may circumvent the secular trend, they do not control for the genetic influences and would unlikely account for important environmental factors.

A limitation of this study is the relatively small sample size, spread over a relatively wide age range. This may have reduced the ability to detect differences between subgroups; however, this sample size is sufficient to detect clinically significant differences of the magnitude seen in previous controlled studies (6). Also, we used 2 different IQ tests to assess children younger than 7 years old and 7 years of age and older, meaning some sibling pairs were assessed with different tools. However, these tests are both produced by the Wechsler group, use similar subscales, and have the same population means and SD, meaning that they are comparable.

In conclusion, these data suggest that there is no evidence of intellectual or motor impairment in children with CHT identified on newborn screening and treated with high initial doses and frequent biochemical monitoring. The time to normalize thyroid function was the only apparent disease related factor contributing to any neurodevelopmental outcome (balance), underscoring the importance of early detection and initiation of sufficient T₄ replacement. This emphasizes the need to strive for efficiencies in neonatal screening programs and subsequent initiation of therapy and provides strong support for the adoption of an aggressive high initial replacement dose with close monitoring in early childhood.

Acknowledgments

We thank the many children who volunteered to participate and their families, who have made this study possible. We are grateful to the staff of the National Screening Unit (in particular Diane Casey and Kathy Bendikson) and to Catrin Roberts and Heather Stewart, who performed the psychological assessments. We acknowledge the Paykel Trust for long-term funding of the Maurice and Agnes Paykel Clinical Research Unit at the Liggins Institute (University of Auckland) and the New Zealand Ministry of Health for an unrestricted grant.

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This work was supported by a grant from the New Zealand Ministry of Health.

All authors have no financial or nonfinancial interests to declare that may be relevant to this work. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of this manuscript.

P.L.H., W.S.C., D.W., and T.W. conceived and designed the study; S.T. recruited; B.B.A., N.H., and S.M. collected and compiled the data; J.G.B.D. carried out the statistical analyses; B.B.A., N.H., J.G.B.D., D.W., and P.L.H. wrote the manuscript with input from A.J.G. and C.J. All authors have approved the submission of the final version of this manuscript.

Disclosure Summary: The authors have nothing to disclose.

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