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# Impaired Neuromotor Outcome in School-Age Children With Congenital Hypothyroidism Receiving Early High-Dose Substitution Treatment

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**ABSTRACT:** Congenital hypothyroidism (CH) can lead to intellectual deficits despite early high-dose treatment. Our study aimed to determine whether motor impairments can occur despite early high-dose treatment. Sixty-three children with CH and early (median age of onset of treatment 9 d), high-dose treatment (median starting dose of levothyroxine 14.7 μg/kg/d) were tested with the Zurich Neuromotor Assessment (ZNA) at a median age of 13.8 y (range 7.0–14.2 y). Median *z*-scores in the children with CH were −0.95 in the pure and −0.56 in the adaptive fine motor component, significantly lower than in the ZNA test norms ($p < 0.001$ and $p = 0.01$, respectively). The 26 children with athyreosis were more affected than the 33 children with dysgenesis, particularly in the pure motor (−1.55 *versus* −0.76, $p = 0.03$), adaptive fine motor (−1.31 *versus* 0.13, $p < 0.01$), and static balance task (−0.47 *versus* 0.67, $p = 0.01$). Boys performed worse than girls. Older age at onset of treatment was related to poorer adaptive fine motor performance. Movement quality (assessed by associated movements) was not affected. We conclude that severe CH can cause neuromotor deficits persisting into adolescence. These deficits cannot completely be reversed by postnatal treatment, but earlier age at treatment may reduce the degree of impairment. **(*Pediatr Res* 70: 614–618, 2011)**

Children with congenital hypothyroidism (CH) may develop a variety of long-term neurobehavioral and developmental abnormalities despite early detection and treatment. Intellectual deficits have been described by several studies (1–3) and often persist into adolescence (4). New guidelines for the optimal treatment of children with CH have been published in the 90s. They include early treatment initiation (within 14 d) and high initial doses (10–15 μg/kg/d) of thyroxine (T4) (5). The question arises whether this early high-dose substitution can eliminate negative long-term effects of CH or whether brain injury already occurs prenatally and therefore does not completely resolve. Dimitropoulos *et al.* (4) demonstrated that children with athyreosis as the severest form of CH manifest intellectual deficits at 14 y of age despite early high-dose substitution. These findings support the concept that in children with CH, prenatal brain injury may occur and could also affect the neuromotor functioning of these children. However, studies on motor outcome in children with CH are scarce and only available until the age of 10 y (2,6–8). Motor deficits have been described for adults with CH (2,3). Notably, the mean age at start of treatment in these studies was later than 20 d of age and the initial dose was less than proposed in the new guidelines. Thus, little is known regarding the long-term effects of CH on motor functioning and whether early high-dose treatment may improve potential adverse effects in older children. At the University Children's Hospital Zurich in Switzerland, this treatment regime had been initiated already in the early 1970s. Therefore, we aimed to determine whether early high-dose treatment has an effect on long-term motor functioning and whether treatment throughout childhood modifies outcome.

## METHODS

Screening for CH was introduced in Switzerland in the mid-1970s (9,10). Since then, the standard therapy has been early high-dose substitution with levothyroxine (L-T4). A regional cohort of children diagnosed with CH living in the greater area of Zurich was prospectively enrolled and followed until adolescence. Informed consent was obtained at birth from the parents who were also present during the time of all examinations. The ethics committee of the University Children's Hospital Zurich and the Canton Zurich confirmed that the study was performed according to the Declaration of Helsinki, and conformed to legal and ethical norms.

***Neonatal screening and therapy.*** Thyroid-stimulating hormone (TSH) was measured in blood spots dried on filter paper taken by heel puncture 72–96 h postnatally. If the TSH value was higher than 50 mU/L, therapy was started immediately after taking a second venous blood sample of both child and mother for confirmation of the diagnosis. Substitution usually consisted of an oral dose of 50 μg LT-4 per day irrespective of weight (equivalent to an initial dose of 10–15 μg/kg/d). The therapeutic regimen was regularly monitored by pediatricians in private practice initially every 2–4 wk, then every 3–6 mo, and after the age of 2 y every 6–12 mo by capillary blood on filter paper. The children were followed up at the Division of Endocrinology and Diabetology of the University Children's Hospital at 1, 2, 4, 7, 10, 12, 14, and 18 y of age. Venous TSH and free T4 levels were used to adjust dosage and to evaluate compliance and adequate treatment regimen. Venous TSH and free T4 were measured the same day when the neurodevelopmental assessment was performed. Detailed information on the study population regarding screening and therapy has been published previously (4).

***Population.*** Eighty-nine children were diagnosed with CH by neonatal screening from January 1978 to January 1991 and prospectively enrolled into

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**Abbreviations: ANCOVA,** analysis of covariance; **CH,** congenital hypothyroidism; **fT4,** free thyroxine; **L-T4,** levothyroxine; **T4,** thyroxine; **ZNA,** Zurich Neuromotor Assessment

**Table 1.** *Demographic, neonatal, and pretreatment endocrinological variables of children with CH grouped according to etiology*

| | Total ($n$ = 63) | Athyreosis ($n$ = 26) | Dysgenesis ($n$ = 33)* | Dyshormonogenesis ($n$ = 4)† |
|---|---|---|---|---|
| Gender (female/male), $n$ | 49/14 | 18/8 | 28/5 | 3/1 |
| Birth weight (g) | 3400 (2120–5040) | 3325 (2290–5040) | 3450 (2120–4090) | 3060 (2840–3740) |
| Gestational age (wk) | 41 (36–44.7) | 40.7 (36–44.7) | 41.3 (37.6–43.3) | 40 (39.9–40.4) |
| Pretreatment T4 (nmol/L)‡ | 45 (1.9–164) | 37§ (6.4–148) | 71 (1.9–164) | 29 (24.0–30) |
| Pretreatment TSH (mU/L)‡ | 399 (50–1250) | 462¶ (131–1035) | 321 (50–1250) | 207 (72–531) |
| Age at onset of treatment (days after birth) | 9 (5–18) | 9 (6–13) | 9 (5–18) | 8 (6–9) |
| Initial dose of L-T4 ($\mu$g/kg/day) | 14.7 (9.9–23.6) | 15.0 (9.9–21.8) | 14.3 (12.2–23.6) | 16.3 (13.4–17.6) |

Values are expressed as median (range).

* Ectopia (31) and Hypoplasia (2).

† Excluded from subgroup analysis.

‡ Venous pretreatment TSH and T4 levels taken for confirmation of screening result before start of therapy.

§ $p \leq 0.01$ between children with athyreosis and with dysgenesis (Mann-Whitney $U$ test, level of significance).

¶ $p \leq 0.05$ between children with athyreosis and with dysgenesis (Mann-Whitney $U$ test, level of significance).

our study. The families lived in the Zurich area. All children were term born babies except for one individual with athyreosis, born at 36 wk of gestation. One child died at the age of 3 mo due to congenital echovirus infection. Five families declined participation and one child was excluded due to pseudohypoparathyroidism and additional dysmorphic features, suggesting fetal alcohol syndrome. Eleven children did not return for neurodevelopmental assessment after the age of 7 y. They did not differ in IQ at 7 y, birth weight, pretreatment T4 and TSH, age at onset of treatment, and initial dose of L-T4 compared with those who were followed up. Seven children were excluded because therapy was started later than 20 d after birth. One child could not complete the neurodevelopmental testing because of language difficulties. Thus, 63 children (49 girls and 14 boys) were included in the analysis. In one child, treatment was discontinued at the age of 10 y for unknown reasons. At 14 y, TSH level was 197 and fT4 level was 6.3 (Ref. 10.3–29.7). Neuromotor testing was within normal range. This child was excluded for the analysis between pretreatment endocrinological variables, treatment course, and neuromotor performance.

***Neuromotor assessment.*** Children were examined by one developmental pediatrician who was aware of the severity of CH but not of the endocrinological levels at the time of examination as the results were only available after neuromotor testing was performed. One blinded trained research assistant (N.D.) rated all associated movements from the video recordings.

Children underwent repeated neurodevelopmental assessments. For this analysis, we used the motor assessment that was at the same time or closest to the intellectual assessment at 14 y to be in accordance with the reported intellectual outcome (4). In 83% of the cohort ($n$ = 52), the neuromotor performance of 12–14 y was used. For the 11 remaining children, motor outcome at 7–10 y was used. The median age of Zurich Neuromotor Assessment (ZNA) was 13.8 y (range 7.0–14.2 y). During the examination, some children did not complete all neuromotor tasks due to noncompliance or difficulties performing the neuromotor tasks. Thus, the number of children varied per component. To correlate endocrinological parameters with neuromotor performance, TSH and free T4 levels were measured on the day of neuromotor testing.

Motor outcome was assessed with the ZNA. The ZNA is a standardized procedure for assessing specific motor tasks in regard to speed (timed performance) and quality of movements [intensity of associated movements (associated movements)] (11,12). Test-retest, interobserver and intraobserver reliability (13), and the validity of the ZNA (14,15) have been established, and gender- and age-related normative values (percentiles) (11,12) are available. The battery includes the assessment of pure motor tasks (repetitive, alternating and sequential movements), adaptive fine (pegboard) and adaptive gross motor tasks (dynamic balance), static balance, and stress gaits. Some motor tasks (static and dynamic balance) are performed with increasing difficulty and depend on the child's age. The following descriptions are given for the age of 10 to 16 y. The pure motor tasks consist of repetitive foot (20 per foot), hand (20 per hand) and finger movements (20 per hand), alternating foot (10 per foot) and hand movements (10 per hand), and sequential movements of the fingers (five sequences of finger-thumb opposition per hand). In the adaptive fine motor task "pegboard," 12 brass pins are removed from a pegboard, inverted in the same hand, and then replaced in the pegboard, first with the dominant and then with the nondominant hand. The passive hand is placed in a relaxed position beside the pegboard. The "pegboard" is performed twice. The adaptive gross motor task "dynamic balance" consists of 15 sideways jumps over a rope placed at a height of 20 cm and of three lengths forward jumps within two lines. The "static balance" task involves standing on one foot while holding the ends of a stick lifted over the head with closed eyes.

The child's performance is videotaped. Motor performance is timed with a stopwatch. Movement quality is scored by classifying the duration (score 0–10) and degree (score 0–3) of associated movements. To combine duration and degree of associated movements into an intensity measure, their product was calculated by a square root transformation (for statistical details, see Ref. 16). Timed performance and associated movements of the motor tasks are summarized into standard components (for statistical details, see Ref. 17): pure motor tasks, adaptive fine motor, adaptive gross motor, and static balance component. The intensity measures of associated movements for all motor tasks are summarized in the associated movements component.

***Etiology, neonatal, and pretreatment endocrinological variables.*** Children with CH were grouped into three categories based on the scintigraphic and sonographic findings: dysgenesis ($n$ = 33; ectopy $n$ = 31 and hypoplasia $n$ = 2), athyreosis ($n$ = 26), and dyshormonogenesis ($n$ = 4). Because of the small number of children with dyshormogenesis, this subgroup was excluded from the comparison between CH severity, but not from overall analysis. Detailed demographic, neonatal, and pretreatment endocrinological variables can be seen in Table 1.

***Statistics.*** Data were analyzed with S-PLUS 8 for Windows (Insightful Corporation Seattle, WA). Significance level was defined as $p \leq 0.05$. Because most variables were nonnormally distributed, nonparametric descriptive analysis was performed. Differences between groups were analyzed with the Mann-Whitney $U$ test or with $\chi^2$ analysis. Comparison to ZNA test norms were performed using the Wilcoxon signed-rank test. To determine the independent effect of CH on neuromotor outcome, an analysis of covariance (ANCOVA) was performed including the variables "group" (CH compared with age and sex standardized norms) and "gender." As socioeconomic status was not related to motor performance in our sample and in the normative sample (unpublished data), socioeconomic status was not included in the multivariate analysis. The evaluation of the association between neonatal as well as postneonatal endocrinological parameters and later neuromotor dysfunction was only performed for the impaired neuromotor components to reduce the number of statistical tests. Subgroup analysis for etiology (dysgenesis and athyreosis) compared with the norm was carried out with multiple comparisons after Tukey. Because the number of children with a dyshormonogenesis was small ($n$ = 4), they were excluded from this subgroup analysis. Potential interactions were explored. The influence of pretreatment and treatment variables on neuromotor outcome was analyzed using ANCOVA.

## RESULTS

***Neuromotor outcome.*** Median $z$-scores in the pure motor and the adaptive fine motor components of the ZNA were lower in children with CH compared with the ZNA test norms (Table 2; Fig. 1). The total of children achieving results below the 10th percentile in a component was the following: 39.7% ($n$ = 23) for the pure motor, 32.1% ($n$ = 18) for the adaptive fine motor, 26.9% ($n$ = 14) for the adaptive gross motor,

**Table 2.** *Neuromotor performance in the Zurich Neuromotor Assessment expressed as z-scores in relation to the norm*

| | Total group* ($n = 63$) | | Athyreosis ($n = 26$) | | Dysgenesis ($n = 33$) | |
|---|---|---|---|---|---|---|
| | Median (range) | $p$† | Median (range) | $p$† | Median (range) | $p$† |
| Timed motor performance | | | | | | |
| Pure motor | −0.95 (−2.9 to 2.9) | <0.001 | −1.55 (−2.9 to 0.6) | <0.001 | −0.76 (−2.5 to 2.9) | 0.001 |
| Adaptive fine motor | −0.56 (−4.5 to 2.2) | 0.001 | −1.31 (−4.5 to 0.5) | <0.001 | 0.13 (−4.0 to 2.2) | 0.4 |
| Adaptive gross motor | −0.04 (−7.5 to 5.4) | 0.4 | −0.14 (−5.8 to 2.1) | 0.3 | 0.23 (−3.4 to 5.4) | 0.4 |
| Static balance | 0.01 (−3.4 to 2.1) | 0.6 | −0.47 (−3.4 to 1.0) | 0.02 | 0.67 (−2.5 to 2.1) | 0.07 |
| Associated movements | −0.03 (−1.8 to 1.1) | 0.8 | −0.05 (−1.1 to 1.1) | 1 | 0.04 (−1.8 to 0.9) | 1 |

* Because the number of children in the dyshormonogenesis group was small ($n = 4$), they were excluded from subgroup analysis.

† Comparison of $z$-score values to the norm (one sample Wilcoxon signed-rank test).

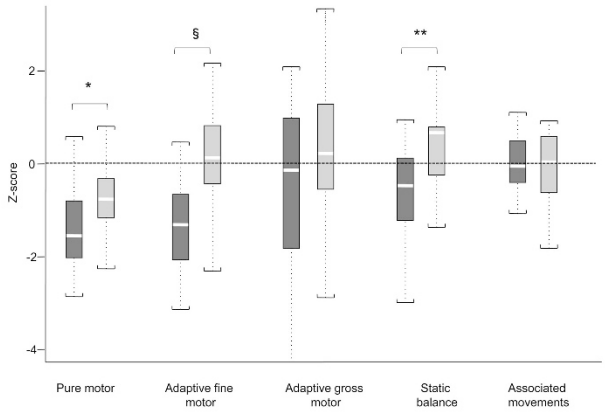


**Figure 1.** Boxplots for neuromotor performance stratified for disease severity. Boxes: *dark gray*, athyreosis; *light gray*, dysgenesis. Box length: interquartile range; *white line* in box: median; upper/lower extreme: 1.5 × interquartile range; discontinuous *horizontal line* indicates normal value of 0 for all neuromotor components. *$p = 0.03$; **$p = 0.01$; §$p < 0.001$.

14.5% ($n = 8$) for the static balance, and 4.8% ($n = 2$) for the associated movements component. This proportion was significantly higher than the expected 10% for pure motor ($p < 0.001$), adaptive fine ($p < 0.001$), and gross motor performance ($p = 0.001$).

Neuromotor performance was poorer in children with athyreosis than in those with dysgenesis for all timed motor components (pure motor: $p = 0.03$, adaptive fine motor: $p < 0.01$, and static balance tasks: $p = 0.01$), except for the adaptive gross motor component. Associated movements did not differ. When comparing to the norm, children in the athyreosis group performed poorer in all components except for the adaptive gross motor component and associated movements. Children with dysgenesis were poorer than the norm only in the pure motor component.

Compared with girls, male children achieved poorer results in the pure motor component (mean −1.53 *versus* −0.87, Wilcoxon signed-rank test $p = 0.03$), the adaptive fine (mean −1.17 *versus* −0.57, $p = 0.12$), the adaptive gross motor component (mean −0.68 *versus* −0.29, $p = 0.18$), and the balance component (mean −0.56 *versus* 0.01, $p = 0.11$). There was no gender difference for the associated movement component (mean −0.07 *versus* −0.08, $p = 0.98$).

***Pretreatment and treatment endocrinological variables and neuromotor outcome.*** We related pretreatment variables (pretreatment T4, TSH, age at onset of treatment, and initial dose of L-T4) and treatment levels at the time of the ZNA with neuromotor performance. After adjusting for gender and CH severity, only older age at onset of treatment was significantly related to poorer adaptive fine motor performance (regression coefficient −0.24, $p = 0.05$). Older age at onset of treatment was associated with better adaptive gross motor performance (regression coefficient 0.35, $p = 0.02$). We did not find a threshold effect of age at onset of treatment on motor outcome. All other endocrinological variables were not related to motor outcome. This was also true for the analysis within the subgroups of children with athyreosis or dysgenesis and for the analysis without adjustment for severity. A threshold effect of free T4, as suggested by Tillotson *et al.* (18), could not be detected.

***Treatment course over time and neuromotor outcome.*** As can be seen in detail in the publication of Dimitropoulos *et al.* (4), the majority of endocrinological T4 and TSH values were within the recommended range. At the time of testing, the majority of children had T4 values within the reference values for free T4 of 10.3–29.7 pmol/L; only one child had a free T4 value below 10.3 pmol/ and three children had values above 29.7 pmol/L. Free T4 did not correlate with the ZNA at time of testing. Endocrinological variables at defined age intervals (4) were related to neuromotor outcome, adjusted for gender and CH severity. Treatment TSH at an age older than 1 y was negatively related to static balance (1–4 y: regression coefficient −0.31, $p = 0.02$; 4–7 y: −0.49, $p < 0.001$, 7–14 y: −0.33, $p = 0.01$). Treatment T4 levels at 1–4 y were positively related to adaptive fine motor performance (regression coefficient 0.26, $p = 0.04$) and levels at 4–7 y to adaptive gross motor performance (regression coefficient 0.32, $p = 0.04$). L-T4 at ages 1–4 y was positively related to adaptive gross motor performance (regression coefficient 0.31, $p = 0.03$). We also looked at the age interval of 0–2 mo. Endocrinological values during that interval were not related to neuromotor performance except for a negative correlation between TSH values and static balance (regression coefficient −0.33, $p = 0.01$). No threshold effect could be detected at any age interval.

## DISCUSSION

In this study on long-term neuromotor outcome of school-age children between 7 and 14 y of age with CH receiving early high-dose substitution treatment, neuromotor performance was significantly poorer in pure motor, adaptive fine, and gross motor functioning. Children with athyreosis were

more affected than children with dysgenesis. The movement quality assessed by the associated movements was unaffected.

Kooistra *et al.* (8) showed that Dutch children with CH tested at the ages 7.5 and 9.5 y demonstrated neuromotor impairments (examined with the test of motor impairment) in the areas of fine motor and balance functions. Children with agenesis were particularly affected. These findings are in line with our results. However, children in the study of Kooistra *et al.* were treated at a later age than in our study (range 5–293 d) and the dosage of L-T4 treatment was not mentioned. Kempers *et al.* studied the motor skills of children with CH at the age of 10 y using the Movement Assessment Battery for Children. Overall motor performance was most affected in those with severe CH. Again, fine motor functioning was impaired most (19). In that study, the treatment started at an age between 2 and 73 d and consisted of a lower L-T4 dosage (mean 5–7 $\mu$g/kg/d) than in our population. Here, we could demonstrate that neuromotor functioning was also impaired in older children and adolescents, even when they were treated earlier and with higher dosages. However, we may speculate that the higher initial dosages of L-T4 and the earlier start of treatment are beneficial, because children with dysgenesis in our study were only impaired in the pure motor tasks. This idea is supported by the finding that later onset of treatment has a negative effect on adaptive fine motor even after adjusting for gender and severity. One study demonstrated persisting motor deficits in adult CH patients (3). Treatment, however, was started at a later age (mean 28 d) and with a lower thyroxine dosage than in our population.

One recent study by Arenz *et al.* examined a small group of children with CH with an early (range 4–15 d) high-dose treatment (range 7.2–17 $\mu$g/kg/d). Motor skills were tested at an age of 5.5 y with a German motor test (MOT 4–6) (7). They showed that children had an impaired motor development, especially those with pretreatment TSH-values of $>$200 mU/L. No information is given on performance in specific motor areas and thus comparability to our study is limited. In our study population, there was no significant relationship between pretreatment TSH and neuromotor outcome.

Our findings on neuromotor functioning relate to those of Dimitropoulos *et al.* who studied the intellectual outcome of the same population. Children with CH had a significant lower mean IQ than the normal population. Children with athyreosis were more affected than children with dysgenesis. Combining these two studies, neuromotor as well as intellectual outcome in children with CH is lower compared with the normal population.

The clinical significance of motor impairments depends on the severity of impairment and the degree to which other neurodevelopmental areas are also affected. It has been shown that motor problems in childhood can be associated with visuomotor and visuoperceptual impairments (15) as well as with attention and memory problems (20). Children with fine motor problems may face significant problems in writing, performing crafts, and drawing. Gross motor problem may impair social participation in class and during leisure time. This may lead to secondary behavioral problems and impaired quality of life.

***Endocrinological parameters and neuromotor outcome.*** Of all neonatal and postnatal endocrinological parameters, only older age at onset of treatment had an impact on later neuromotor dysfunction. Older age at treatment onset was significantly related to poorer adaptive fine motor performance. This finding supports the notion that earlier high-dose substitution has a favorable effect on neuromotor function. We also found an unexpected correlation where older age at onset of treatment was associated with a better adaptive gross motor performance. It is conceivable that children with milder forms of CH were treated at a later age. Then, pretreatment TSH values should have correlated with neuromotor outcome, which was not the case in our sample. It is also possible that this association was a random finding. Socioeconomic status was not related to neuromotor functioning (data not shown). This is in line with the findings of the original description of the ZNA (11,12) in the normative sample.

***Treatment course of time and neuromotor outcome.*** Treatment course and neuromotor performance were only poorly linked. A consistent negative relationship was found between TSH levels for children older than 1 y and static balance: higher TSH levels were associated with poorer static balance performance. Thus, static balance may be an indicator for poorer substitution and/or compliance. The mechanism involved in this association remains unclear. Interestingly, static balance performance declined between 7 and 9 y of age in the study by Kooistra *et al.* (8). We did not find a free T4 threshold effect of as suggested by Tillotson *et al.* (18).

Potentially, a transient hyperthyroidism associated with early high-dose treatment might have occurred in the first few days or weeks of life and may have contributed to adverse outcome. We could not find such an association. In addition, it is unlikely that a significant hyperthyroidism occurred as rapid infant weight gain led to a decrease of dose per weight.

***Gender.*** The distribution between the sexes in our study population was 49 girls to 14 boys. It reflects female gender as a known risk factor for CH (21). Nevertheless, male gender was associated with a poorer performance on all motor components except of associated movements. This was the case despite that the normative data for the ZNA are gender-specific and that there were more female children in the study cohort. The male disadvantage in neuromotor outcome has been described for other populations at risk such as children born prematurely (22) but not for children with CH.

***Mechanism of brain injury.*** The study of Dimitropoulos *et al.* and our study demonstrate that intellectual and neuromotor performance remains impaired in children with early high-dose treatment for CH and that children with athyreosis are more affected than those with dysgenesis. Our findings raise the question whether irreversible brain damage occurs prenatally in children with CH. The thyroid gland develops very early in gestation and thyroxine synthesis of the fetus begins by mid-gestation. Before that time, the mother is the only source of free T4 (fT4) available for the fetal tissues. The fT4 deiodinases (D2) localized in the fetal brain with a temporal and local specificity. This is crucial because the brain is dependent on T3 for optimal development. The fetal contribution to fT4 and T4 increases until birth (23). However,

maternal transfer of T4 to the fetus continues until the umbilical cord is severed (24). Obregon *et al.* suggest that after mid-gestation, a normal supply of maternal thyroxine together with an increase in local D2 activity in the fetal brain are sufficient to protect the fetal brain from T3 activity and brain damage. This hypothesis stands in contrast to our findings as our children with an early high-dose treatment suffer from impairments of neuromotor and intellectual functioning, which indicates prenatal brain damage. In addition, despite early high-dose treatment, there is a lack of thyroid hormone in the first few days of life until normalization of thyroxine blood levels after treatment initiation. However, this time period is rather short and less likely responsible for the neuromotor and intellectual deficits of children with CH than prenatally occurring brain damage.

***Limitations.*** Neuromotor testing was performed at a rather large age interval ranging from 7 to 14 y. However, the majority (83%) of children were examined between 12 and 14 y. In addition, we did not have a control group for comparison. Results were compared with age- and sex-adjusted norms and expressed as *z*-values. Therefore, age at testing should not affect the analysis of the effect of CH on motor outcome. Furthermore, children who served as the normative group for the tested children were born between 1981 and 1988. This is comparable to the birth years of the CH patients (1978–1991) and thus motor performance of CH and controls can be compared.

In conclusion, our study demonstrates that adolescents with CH, and in particular those with athyreosis, are at increased risk for neuromotor deficits despite early high-dose treatment. We hypothesize that prenatal brain injury occurs and cannot be completely reversed by postnatal treatment. But earlier age at treatment may reduce the degree of impairment. Health professionals and parents should pay specific attention to neuromotor deficits in children with CH to facilitate early therapeutic inventions. Detailed neurodevelopmental assessments at school-age are needed to detect these deficits and potential associated neurobehavioral problems. Future studies should include neonatal brain imaging and measurement of connectivity and maturation such as diffusion tensor imaging or volumetric measures to better characterize the effect of prenatal thyroid hormone deficiency on the developing brain.

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