Free Thyroxine Levels After Very Preterm Birth and Neurodevelopmental Outcomes at Age 7 Years

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Abstract

BACKGROUND AND OBJECTIVES: Preterm infants commonly have transient hypothyroxinemia of prematurity after birth, which has been associated with deficits in general intellectual functioning, memory, attention, and academic achievement. However, research has predominantly focused on thyroxine levels in the first 2 weeks of life and outcomes are limited to the preschool period. Our objective was to evaluate the relationships between free thyroxine (fT4) levels over the first 6 weeks after very preterm (VPT) birth with cognitive functioning and brain development at age 7 years.

METHODS: A total of 83 infants born VPT (<30 weeks' gestation) had fT4 concentrations measured postnatally and 2- and 6-week area under the curve (AUC) summary measures were calculated. Follow-up at age 7 years included a neuropsychological assessment and brain MRI. Univariable and multivariable regression modeling was used where AUC for fT4 was the main predictor of neurodevelopmental outcome at age 7 years.

RESULTS: Multivariable modeling revealed that higher, not lower, postnatal fT4 levels (2-week AUC) were associated with poorer cognitive performances at age 7 years on tasks of verbal learning (P = .02), verbal memory (P = .03), and simple reaction time (P < .001). A similar pattern of results was found when the 6-week AUC was examined. No significant associations between postnatal fT4 levels and brain volumes at age 7 years were identified.

CONCLUSIONS: Results are contradictory to previous observations and suggest that after adjustment for confounders, higher postnatal fT4 levels in VPT infants, rather than lower levels, may be a marker of adverse neuropsychological development in childhood. Pediatrics 2014;133:e955–e963

WHAT'S KNOWN ON THIS SUBJECT: Preterm infants have transiently lowered thyroid hormone levels during the early postnatal period. Past research suggests that low thyroid hormone levels are related to cognitive and developmental deficits in children born preterm.

WHAT THIS STUDY ADDS: Contrary to expectations, in this study of children born <30 weeks’ gestation, higher concentrations of free thyroxine over the first 6 weeks of life were associated with poorer cognitive function at 7 years of age.
Very preterm (VPT, <32 weeks’ gestation) children are at increased risk for a range of neuropsychological deficits, including impairments in general intellect, language, visuoperceptual reasoning, learning and memory, attention, and executive functioning. Furthermore, neuroimaging studies of preterm infants and children have reported volumetric reductions in gray and white matter tissue, as well as specific brain regions (cerebellum, basal ganglia, amygdala, hippocampi, and corpus callosum). Identifying mechanisms underpinning these negative outcomes is critical to improve the management and outcomes of these infants.

Transient hypothyroxinemia of prematurity (THOP) is a condition that primarily affects preterm infants born <30 weeks’ gestation and is characterized by low levels of circulating thyroid hormones (THs), despite normal levels of the pituitary hormone, thyroid stimulating hormone (TSH). This condition usually resolves within 3 to 4 weeks with progressive maturation of the hypothalamic-pituitary-thyroid axis. As no consensus exists for THOP reference ranges, prevalence rates vary by study definition, with 35% to 85% of VPT infants reported to be affected.

THs are critical for normal central nervous system (CNS) development, including cerebral neurogenesis (during early prenatal life), neural migration and differentiation, axonal and dendritic growth, and synaptogenesis; gliogenesis (late fetal life until 6 months postnatally); dendritic arborization; and myelogenesis (second trimester to 2 years postnataally). Consistent with this literature, the low levels of T4 associated with THOP have been found to be related to neurodevelopmental deficits in children born preterm, such as delayed development of motor, cognitive, language, and educational skills.

Research to date has predominantly focused on TH levels in the first 2 weeks of life, and in most studies outcome assessments have been limited to infancy and the preschool period. The current study aimed to examine the relationship between fT4 over the first 6 weeks after VPT birth and cognitive functioning and brain development at age 7 years. Based on previous research it was hypothesized that low fT4 levels would be negatively associated with cognitive performance and brain volumes at age 7 years in a group of children born VPT.

METHOD

Study Design

Participants (n = 99) were born <30 weeks’ GA between June 2002 and December 2003 at the Royal Women’s Hospital (Melbourne, Victoria, Australia). Infants who had significant genetic or congenital abnormalities likely to affect brain growth or development were excluded. At age 7 years, 83 were assessed (the “assessed group”). Approval for the study was obtained from the Human Research Ethics Committees of the Royal Women’s Hospital and the Royal Children’s Hospital. Written consent was obtained from parents.

Procedure and Measures

Whole blood (0.5 mL) was collected from the cord at delivery; then on days 1, 4, 7, 14, 21, 28, and 42. Specimen collection was timed with routine morning blood sampling (7 to 9 AM). Whole blood was centrifuged at 3000 rpm for 5 minutes. Plasma was collected and stored at −70°C; hormone assays were performed in batches. Free T4 was measured directly by competitive analog immunoassay using a chemiluminescent substrate on the Immulite 2000 (Siemens AG, Healthcare Sector, Erlangen, Federal Republic of Germany). The level of fT4 was interpolated from a stored standard curve calibrated for fT4 concentrations.25 The intra- and inter-assay coefficients of variation were acceptable (intra-assay = 5.1%; inter-assay range = 7.5% to 5.7%). Neonatal fT4 data were expressed as area under the curve (AUC) values as a summary measure of hormone exposure over 2 designated time periods: (1) birth to day 14, and (2) birth to day 42.

Additional perinatal variables of interest included GA (weeks), sex, and duration of intermittent positive pressure ventilation (IPPV), which was used as a general marker of illness. At term equivalent age, T1 and T2 images were acquired with a 1.5 Tesla MRI scanner at the Royal Children’s Hospital (Signa LX Echospeed System; General Electric, Milwaukee, WI). A validated global cerebral abnormality scoring system was rated by a neonatal neurologist who was blinded to TH status, with higher values reflecting more severe pathology.

The 7-year follow-up included a detailed neuropsychological assessment and neuroimaging. Neuropsychological measures for the current study were selected to represent a broad range of cognitive domains (Table 1). Children who attempted a task but were too impaired to perform or had difficulty comprehending task instructions were assigned the lowest possible raw score for a subtest, or in the case of reaction time measures, the highest score recorded to signify a longer reaction time. The Social Risk Index parent questionnaire was also administered with higher scores representing greater social disadvantage.
TABLE 1 Neuropsychological Measures

<table>
<thead>
<tr>
<th>Test Battery</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASI</td>
<td>The 4-subtest version of the WASI was administered to estimate general intellectual functioning (FSIQ); Normative mean = 100, SD = 15.</td>
</tr>
<tr>
<td>CELF-IV</td>
<td>The Core Language Index from the CELF-IV was administered and used as a measure of general language ability. Normative mean = 100, SD = 15.</td>
</tr>
<tr>
<td>WMTBC</td>
<td>Three subtests from the WMTBC were administered to assess elements of immediate and working memory: (1) Digit Recall involves the child repeating a sequence of numbers, assessing immediate verbal memory; (2) Backward Digit Recall involves the child repeating a presented sequence of numbers in reverse order, assessing verbal working memory; and (3) Block Recall requires the child to recall a sequence of blocks that the examiner taps on a standardized board, assessing spatial immediate memory. Raw scores for each task were used in the analyses.</td>
</tr>
<tr>
<td>CVLT-C</td>
<td>The CVLT-C is a verbal learning and memory task in which the child is required to recall a list of 15 words, which is presented 5 times. Raw total learning score (total words recalled from trial 1 to 5) and long delay recall score were used as measures of verbal learning and verbal memory, respectively.</td>
</tr>
<tr>
<td>CMS</td>
<td>Dot Locations subtest from the CMS was administered to assess spatial learning and memory. The child is required to learn and remember the spatial location of an array of dots, which is presented 3 times. Raw total learning score (total score from trials 1 to 3) and long delay recall score were used as measures of spatial learning and spatial memory, respectively.</td>
</tr>
<tr>
<td>TEA-Ch</td>
<td>Raw scores for 4 selected subtests were used to assess different attention domains: (1) Sky Search (number of correct targets) assesses selective attention; (2) Score! (number of correct trials) assesses sustained attention; (3) Creature Counting (number of correct trials) assesses shifting attention; and (4) Sky Search Dual Task (proportion of correct counting games and identified targets) assesses divided attention.</td>
</tr>
<tr>
<td>TOL</td>
<td>The TOL is a measure of planning, organization, and problem solving. The total raw score was used, which is a summary score for the 12 items where higher points are awarded for quicker completion times and points subtracted for planning errors.</td>
</tr>
<tr>
<td>CogState Research&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Two subtests from the CogState Research battery were selected to assess processing speed: (1) Detection assesses simple reaction time; and (2) Identification assesses choice reaction time. The variable of interest for these 2 tasks was the mean of the log10 transformed reaction times for correct responses where lower scores indicated a better performance.</td>
</tr>
</tbody>
</table>

Whole brain images were acquired at age 7 years on a 3 Tesla Siemens Magnetom Trio (Tim system) scanner, at the Royal Children’s Hospital, Melbourne, Australia (n = 65). Reasons for drop-out included: failing the mock scan (n = 7), being too impaired to participate (n = 4), parents not consenting to MRI (n = 3), failing to attend (n = 1), refusal by the child (n = 1), cochlear implant (n = 1), and extreme movement artifact (n = 1). Structural T1-weighted images were used for the purpose of the current study (flip angle = 90, repetition time = 2.27 ms, echo time = 2.27 ms, field of view = 210 × 210 mm, matrix = 256 × 256, 0.8 mm<sup>3</sup> isotropic voxels). Images were visually inspected and those that were considered of unacceptably poor quality due to artifact were excluded (n = 13). Data were processed by a single operator on Linux workstations using the automated FreeSurfer imaging processing suite (stable release version 4.4.0, http://surfer.nmr.mgh.harvard.edu). FreeSurfer output was inspected and manually edited as required. Cortical and cerebellar gray and white matter, thalamus, caudate, putamen, pallidum, hippocampus, and amygdala volumes were estimated for each hemisphere, and volumes from both hemispheres combined. The total volumes for the caudate, putamen, and pallidum were combined to represent basal ganglia volume. Cerebellar volume was the sum of cerebellar white and gray matter. Total brain tissue was the combined volumes of all brain structures, excluding cerebrospinal fluid.

**Data Analysis**

Data were analyzed by using Stata 12 (StataCorp, College Station, TX). Lost to follow-up analyses used t tests or Mann-Whitney U (continuous data) and χ² (categorical data). Regression models were employed by using AUC for fT4 as the main predictor of outcome with models fitted in 2 ways: (1) cord to day 14 levels (14-day AUC), and (2) cord to day 42 (42-day AUC). Cognitive models were fitted controlling for GA, sex, social risk, duration of IPPV, and global neonatal brain abnormality score. Imaging model covariates included GA, sex, duration of IPPV, and global neonatal brain abnormality.

To account for the non-independent effect of twins/triplets, robust standard errors using the Huber/White/sandwich method were used for all analyses. Standardized β coefficients (β) (cut-points: 0.10 = weak, 0.30 = moderate, 0.50 = strong) were used as measures of the magnitude of effect. Also, the proportion of variance explained by an independent predictor (R² for unadjusted analyses; sr² for adjusted analyses) was investigated and expressed as a percentage, where larger values were more desirable.

**RESULTS**

**Sample and Hormone Characteristics**

Table 2 outlines the sample characteristics of the assessed and imaged groups. The mean age of the assessed group was 7.5 years (range, 6.8–8.3 years). There were no characteristic

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**TABLE 2** Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.5</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>55%</td>
</tr>
<tr>
<td>Social risk</td>
<td>Low</td>
</tr>
<tr>
<td>Duration of IPPV</td>
<td>High</td>
</tr>
<tr>
<td>Global neonatal brain abnormality score</td>
<td>High</td>
</tr>
</tbody>
</table>

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**ARTICLE**

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differences between those who did and did not attend (data not shown). Sample characteristics for those children who had a useable MRI scan at age 7 years are also presented in Table 2; those in the imaged group had higher Full Scale IQ (FSIQ) scores than the non-imaged group (mean difference = 10.8; 95% confidence interval (CI) = 3.0 to 18.6; \( P = .007 \)).

Importantly, there were no differences in \( \text{fT}_4 \) levels between the assessed group and those lost to follow-up. The \( \text{fT}_4 \) profile of the assessed cohort included a slight elevation in mean concentration over the first 24 hours of life, followed by a decrease to a nadir at day 4 to 7. Recovery from this transient state was noted over the next 2 to 3 weeks with concentrations rising slightly above cord concentrations by day 42 (see Fig 1). Those born less mature and sicker in infancy (with longer durations of assisted ventilation) were exposed to lower levels of \( \text{fT}_4 \) over both the first 2 (GA: \( b \)-coefficient [95% CI] = 21.9 [17.9 to 25.4], \( P < .001 \); duration of IPPV: \( b \)-coefficient [95% CI] = −0.05 [−0.07 to −0.04], \( P < .001 \)) and 6 (GA: \( b \)-coefficient [95% CI] = 47.0 [36.7 to 57.4], \( P < .001 \); duration of IPPV: \( b \)-coefficient [95% CI] = −0.11 [−0.15 to −0.07], \( P < .001 \)) weeks of life.

**Cognitive Results**

No relationships between \( \text{fT}_4 \) and cognitive performance were observed at a univariable level. On multivariable analysis, higher levels of \( \text{fT}_4 \) were associated with poorer performances on verbal learning, verbal memory, and simple reaction time tasks (Table 3). The 14-day AUC independently accounted for between 6.5% and 13% of the variance for these outcomes, with moderate to strong effect sizes observed.

As expected, the pattern of results obtained when the 42-day AUC was examined was less profound than the 14-day AUC analyses. However, a similar profile was observed with higher levels of \( \text{fT}_4 \) over the first 6 weeks of life related to poorer cognitive performance (Table 3).

### TABLE 2 Perinatal, Demographic, and Hormone Characteristics

<table>
<thead>
<tr>
<th></th>
<th>7-Year Cognitive Group (n = 83)*</th>
<th>7-Year Imaging Group (n = 52)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA (wk), M (SD)</td>
<td>27.3 (1.7)</td>
<td>27.4 (1.6)</td>
</tr>
<tr>
<td>Birth weight (g), M (SD)</td>
<td>975 (235)</td>
<td>982 (216)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>35 (42.2)</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Singleton, n (%)</td>
<td>49 (59.0)</td>
<td>27 (51.9)</td>
</tr>
<tr>
<td><strong>Perinatal medical factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for GA, n (%)</td>
<td>2 (2.4)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>34 (41.0)</td>
<td>21 (40.4)</td>
</tr>
<tr>
<td>Patent ductus arteriosus, n (%)</td>
<td>40 (48.2)</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, n (%)</td>
<td>9 (10.8)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia, n (%)</td>
<td>26 (31.7)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>Antenatal corticosteroids, n (%)</td>
<td>76 (91.6)</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td>Postnatal corticosteroids, n (%)</td>
<td>10 (12.0)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>IPPV (hours), median (25th and 75th percentile)</td>
<td>98 (7, 431)</td>
<td>88 (8, 376.5)</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia, n (%)</td>
<td>1 (1.2)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Grade III/IV intracerebral hemorrhage, n (%)</td>
<td>3 (3.6)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>MRI brain injury, median (25th and 75th percentile)</td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td><strong>Neonatal free thyroxine characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-day AUC (pmol)</td>
<td>154.1 (47.7)</td>
<td>159.9 (46.8)</td>
</tr>
<tr>
<td>42-day AUC (pmol)</td>
<td>525.4 (114.4)</td>
<td>535.0 (117.0)</td>
</tr>
<tr>
<td><strong>7-year measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social risk score at age 7 years, median (25th and 75th percentile)</td>
<td>2 (1.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>FSIQ, M (SD)</td>
<td>95.5 (17.8)</td>
<td>99.5 (12.7)*</td>
</tr>
</tbody>
</table>

* Some sample sizes are less than the total sample owing to missing data.

* Those in the image analysis group had higher FSIQs at age 7 years than those without imaging data (\( P = .007 \)).

![Figure 1](http://pediatrics.aappublications.org/)

**FIGURE 1**

Boxplot of the \( \text{fT}_4 \) profile from cord to day 42 for the assessed group. Values depicted as the median (solid line within box), 25th to 75th percentiles (margins of the box), and range of the data. Outliers were removed.
TABLE 3  Relationship Between Free Thyroxine 14-Day AUC/42-Day AUC and 7-Year Cognitive Outcomes

<table>
<thead>
<tr>
<th>Cognitive outcomes</th>
<th>14-Day AUC (unadjusted; n = 83)</th>
<th>14-day auct</th>
<th>42-day AUC (unadjusted; n = 83)</th>
<th>42-day AUC (adjusted; n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>R² (%)</td>
<td>p</td>
<td>β</td>
</tr>
<tr>
<td>General intellectual ability</td>
<td>FSIQ</td>
<td>0.17</td>
<td>2.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Language</td>
<td>General language ability</td>
<td>0.02</td>
<td>0.03</td>
<td>0.90</td>
</tr>
<tr>
<td>Verbal working memory, learning, and memory</td>
<td>Immediate verbal memory</td>
<td>−0.03</td>
<td>0.08</td>
<td>0.83</td>
</tr>
<tr>
<td>Working memory</td>
<td>−0.003</td>
<td>&lt;0.001</td>
<td>0.98</td>
<td>−0.15</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>−0.04</td>
<td>0.2</td>
<td>0.72</td>
<td>−0.42</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>−0.06</td>
<td>0.4</td>
<td>0.61</td>
<td>−0.40</td>
</tr>
<tr>
<td>Spatial working memory, learning, and memory</td>
<td>Immediate spatial memory</td>
<td>−0.07</td>
<td>0.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Spatial learning</td>
<td>−0.09</td>
<td>0.9</td>
<td>0.51</td>
<td>−0.26</td>
</tr>
<tr>
<td>Spatial memory</td>
<td>−0.11</td>
<td>1.3</td>
<td>0.44</td>
<td>−0.21</td>
</tr>
<tr>
<td>Attention and executive functioning</td>
<td>Selective attention</td>
<td>−0.03</td>
<td>0.1</td>
<td>0.80</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>0.97</td>
<td>−0.15</td>
</tr>
<tr>
<td>Shifting attention</td>
<td>0.19</td>
<td>3.7</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>Divided attention</td>
<td>0.06</td>
<td>0.4</td>
<td>0.58</td>
<td>−0.07</td>
</tr>
<tr>
<td>Planning</td>
<td>0.008</td>
<td>0.01</td>
<td>0.95</td>
<td>−0.19</td>
</tr>
<tr>
<td>Speed of information processing and reaction time</td>
<td>Simple reaction timeb</td>
<td>0.19</td>
<td>3.66</td>
<td>0.13</td>
</tr>
<tr>
<td>Complex reaction timeb</td>
<td>−0.0003</td>
<td>&lt;0.001</td>
<td>0.99</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Covariates for adjusted analyses included GA, gender, social risk, duration of IPPV, and neonatal brain injury.

a Some sample sizes are less than the total sample owing to missing data.
b Task is reverse-scored, where higher scores signify a slower reaction time.

Brain Volume Results

Despite a consistent pattern of results from the cognitive models, no unadjusted or adjusted associations were found between early postnatal fT4 levels and measures of 7-year brain volume (Table 4). Consequently, fT4 levels only explained a limited percentage of variance within the models (14-day AUC, 0.01%–1.7%; 42-day AUC, 0.1%–4.0%).

DISCUSSION

In the current study the concentrations of fT4 over the first 6 weeks of life in infants <30 weeks’ GA were similar to previous reports, but the surprising finding was that higher concentrations rather than lower concentrations of fT4 were associated with poorer cognitive function at age 7 years. The association between fT4 and cognitive outcome was not explained by effects on brain volumes at age 7 years.

Free Thyroxine Concentrations Over the First 6 Weeks of Life

The daily mean (SD) of fT4 ranged from 9.9 (4.1) to 14.0 (3.0) pmol/L over the 8 sampling days, with the lowest levels observed on day 7, consistent with other reports and with the phenomenon of THOP.28,29 For example, 1 study investigated a group of 128 infants born 23 to 29 weeks’ gestation whose fT4 profile included a gradual decrease from 15 pmol/L at <5 hours of age, reached a nadir of 9.7 pmol/L on day 7, and then increased to 11.0 pmol/L on day 14.29 Both GA and increased duration of IPPV (marker of illness) affected fT4 levels in the current study, consistent with past reports.11,29 Of note, 2 more recent studies observed this GA/illness trend only when total T4, not fT4 levels, were considered.28,30

Free Thyroxine and Cognition

There was little evidence that low postnatal fT4 levels over different periods of exposure were associated with cognitive deficits at age 7 years across a broad range of neuro-psychological domains in children born VPT. Contrary to expectations, higher fT4 levels were related to adverse cognitive performances on tasks of verbal learning, verbal memory, and simple reaction time, after adjustment for confounding variables. Given the sparse nature of the literature, the best support for the aforementioned findings rests in studies of neonatal thyrotoxicosis and results from TH supplementation trials. Neonatal thyrotoxicosis is rare, usually arising in mothers who have Graves’ disease in which the exposure to elevated levels of THs appears to be detrimental.31 Although long-term outcome studies following this condition are limited and mixed, elevated rates of intellectual and psychological impairment32,33 have been reported. Furthermore, in a model using rats made hyperthyroid during the first 24 days of life, the
animals performed less well on a learning task as adults compared with controls. It is important to note that the levels of $fT_4$ observed in our study did not approach levels consistent with those seen in children who have neonatal thyrotoxicosis. In the same way as causation for deficit following THOP has been extrapolated from understanding mechanisms in congenital hypothyroidism, relative elevation of $fT_4$ may be on the spectrum of maldevelopment linked to neonatal thyrotoxicosis.

With regard to TH supplementation trials, 1 study included a randomized, placebo-controlled, double-blind trial of $T_4$ supplementation that involved 200 infants born <30 weeks’ gestation and 3 follow-up investigations. At age 2 years, $T_4$-treated infants born <27 weeks’ gestation scored 18 points higher on a general development examination than those in the placebo group. However, for those in the $T_4$-treated group born at 27 weeks’ gestation or later, a detrimental effect of the supplementation was found, with the $T_4$-treated group scoring 10 points lower than their placebo counterparts. At the 5.7- and 10.5-year follow-ups a similar gestational difference was noted. In another study $T_4$ supplementation was positively associated with outcome in children born <29 weeks’ gestation (especially in the 25/26-week GA group), but more developmental problems were observed in those $T_4$-treated children born >29 weeks’ gestation. Although these findings support the notion that elevated $T_4$ levels may be problematic for later outcome in VPT subgroups, it is important to note that conclusions were based largely on a set of posteriori analyses, which have innate limitations.

Further support for the finding that elevated $fT_4$ levels may be of concern rests in an endocrine model of critical illness. This model outlines the hypothetical response of the endocrine system to both acute and chronic illness phases. In summary, the acute phase is considered transient, adaptive, and beneficial, and hormone variations during this time are thought to promote the redirection of energy to vital organs such as the brain. The chronic phase is a harmful, maladaptive response of the body’s natural defense mechanisms. Thyroid hormones have been monitored over these phases and have been noted to drop significantly in the first hours after illness onset with the magnitude of the drop reflecting the severity of illness. Moreover, TSH concentrations remain unchanged, suggesting that the feedback mechanisms are altered at the hypothalamic-pituitary level. If illness remains prolonged, THs continue to be reduced, but are then accompanied by diminished TSH secretion.

The application of this model to the preterm population is interesting. It suggests that the low levels of THs, without a reduction in TSH, may be a protective reaction to illness, with the body potentially treating preterm birth itself as an acute illness state. Findings from the current study further support this premise in that low $fT_4$ levels in our group of VPT infants were not associated with adverse later childhood outcomes. In contrast, higher $fT_4$ levels fall outside the expected endocrine response to acute illness.

It is possible that our cohort of VPT infants may have been healthier than groups examined in past studies. Many of the published studies began before the late 1990s when advances in perinatal, neonatal, and obstetric care, such as increased use of antenatal corticosteroids and surfactant therapy, were not regularly used. It is therefore possible that experiencing chronic illness endocrine patterns during early postnatal life may affect later outcome.

### Free Thyroxine and Brain Volumes

In the current study, there was little evidence of an association between $fT_4$ exposure over the first weeks of life and brain volumes at age 7 years in children born VPT. This was unexpected, especially for white matter volume. THs are important for (1) the maturation of oligodendrocytes; (2) the accumulation of oligodendrocytes...
within white matter tracts; (3) the regulation and production of components of myelin such as basic myelin protein; and (4) the compaction of myelin within the axonal sheath. The role of THs in myelination also appears to be time-dependent, with different brain regions affected at different developmental stages.

There are limited MRI studies investigating the impact of TH status on brain morphology. In one study, MRI and a subjective rating system were used to investigate myelination and CNS morphology in infants who had congenital hypothyroidism before TH replacement therapy. No differences in myelination patterns were found between those who had congenital hypothyroidism and control subjects; both groups also had normal MRI examinations. In another study of very low birth weight infants, cerebral white matter damage diagnosed by cranial ultrasound was twice as common in infants exposed to low total T4 levels compared with peers exposed to higher total T4 levels. A limitation of our study was use of a direct immunoassay to measure fT4 levels; immunoassays can produce variable results, with a tendency to overestimate fT4 at high protein concentrations and underestimate fT4 at low protein concentrations, which tend to be found in sick infants. Therefore, direct dialysis methods are now considered to be the “gold standard” for measuring TH levels.

The current study is the first of its kind to comprehensively examine the association of postnatal fT4 and brain volumetrics in childhood. Myelination in the human brain is largely complete by 2 years of postnatal age. It is possible that an early delay in myelination did occur as a result of disturbed thyroid levels, but that imaging at 7 years of age missed the window in which to detect this delay. If there was any scope for catch-up in myelination, then this may well have occurred by 7 years of age, explaining the absence of association between fT4 levels and global white matter volumes. Therefore, more research is needed to truly understand this relationship, especially given the findings from the cognitive models detailed above. Finally it must be noted that our imaged group had higher FS IQ scores than those who attended 7-year follow-up and did not have a usable MRI scan. This bias may have skewed our imaging data by not allowing examination of those children who had more severe cognitive difficulties who were unable to participate in scanning procedures.

CONCLUSIONS

The fT4 profile observed in our group of VPT infants was consistent with the transiently altered levels commonly reported within the literature. However, novel elements of our study included the use of brain volumetrics and the unexpected relationship between higher postnatal fT4 levels and reduced cognitive performances at age 7 years. Conclusions supported an endocrine model of critical illness and suggest that future investigations should potentially be directed toward those infants exhibiting unexpected endocrine patterns after VPT birth.

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