Thyroid problems in pediatric oncology: damage, prevention and consequences
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The changing thyroid hormone state in children receiving chemotherapy

HM van Santen, NM Thonissen, J de Kraker, T. Vulsma

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Abstract

OBJECTIVE: The concentrations of thyroid function determinants may change during severe illness. Our goal was to quantify their changes in children with cancer during chemotherapy, and to correlate them to clinical condition and type of drugs.

DESIGN During a 3-month period all patients admitted for chemotherapy to the paediatric oncology ward were evaluated for inclusion. Patients with brain tumours, neuroblastoma, (cranio) spinal irradiation and use of dexamethasone already before the first blood sample were excluded.

MEASUREMENTS Plasma concentrations of T₄, T₃, rT₃, thyroxine-binding globulin (TBG), thyroglobulin (Tg), TSH, IGF-1, cortisol, PRL, and physical well-being by means of questionnaires were measured before and during chemotherapy.

RESULTS Of 19 children, 46 courses of chemotherapy and 123 plasma samples were analysed. During chemotherapy, mean concentrations of TSH, T₃, Tg and cortisol decreased to 53, 67, 69 and 15 % of the baseline value respectively. Mean plasma rT₃ increased to 217 % of baseline. In 87 % of all courses, ≥ 1 thyroid parameter(s) was aberrant. Furthermore, in 23 samples (19 %) of 10 patients (53 %), the concentration of IGF-1 was below the reference value (adjusted for sex and age). Small changes were seen in scores for clinical condition and none were related to a change in thyroid function determinant. Most changes in thyroid hormones could be attributed to using dexamethasone.

CONCLUSIONS These results demonstrate that, in children, the thyroid hormone state changes significantly during chemotherapy, apparently not related to physical well-being but to the drugs administered. Future investigations should focus on the impact for patient care and possibilities of (preventive) intervention.
Introduction

During severe illness, caloric deprivation and psychological stress, changes in the thyroid hormone state are known to occur, often described as the euthyroid sick syndrome or the phenomenon of non-thyroidal illness (NTI) \(^1\). NTI comprises a variety of abnormalities in the thyroid state e.g. low plasma concentrations of \(T\_3\), low concentrations of \(T\_3\) and \(T\_4\), and high concentrations of \(T\_4\). \(^4\)

In children, NTI has been reported in cardiac surgery patients \(^7\), premature and sick neonates \(^8\), in poorly controlled diabetes mellitus (DM) type 1 \(^9\), and acute hepatitis A \(^10\). The sickest patients show the lowest \(T\_3\) concentrations, those with complications showing more prolonged depression and delayed recovery of thyroid function determinants \(^7\).

When children undergo treatment for a malignant disease, it may be expected that their endocrine state is or will become disturbed, either due to the tumour, chemotherapy, the distorted emotional state (fear, pain) or due to the impaired physical well-being (caused by the combination of the disease, chemotherapy and accompanying symptoms of vomiting and poor food intake). Also, drugs can influence the thyroid state, directly or indirectly by influencing the clinical condition of the patient \(^11\)-\(^13\).

Little studies have been performed on the changes in thyroid hormone state in children with cancer, though, and most of these studies report on adult cohorts with only some patients in the paediatric age group \(^14\)-\(^16\).

A fundamental explanation for NTI is still lacking \(^6\), and it is unclear whether these changes in thyroid hormone state should be considered to be an adaptive phenomenon to reduce metabolic rate during illness, a part of the disease process, or just an epiphenomenon that can be used as a marker of the severity of illness \(^7\). Even if NTI reflects an adaptive process, however, it can not be assumed that a reduced metabolic rate is beneficial, irrespective of the underlying illness. For children, the changes in thyroid hormone state could even be of more significance than for adults, considering the fact that at young age thyroid hormone is required for optimal (brain) development and growth into adulthood. For children with chronic diseases or those who receive treatment for a longer period of time, recurrent or long lasting endocrine disturbances may have negative effects on growth and development into adulthood. If changes in
the thyroid state can be used as marker for the negative effects of chemotherapy on the physical well-being of the child, this may be used to develop ways of intervention to improve their physical well-being and possibly their growth and development. For this, firstly the relations between the changes in thyroid state, the administered drugs and physical well-being must be determined.

An observational prospective evaluation was performed on the thyroid state, right before and during chemotherapy, and the physical well-being of children admitted to a paediatric oncology ward.

Patients and methods

From March to June 2003, all patients admitted to the paediatric oncology ward were evaluated for inclusion in the study. Of 51 patients, 32 were excluded; five because of a brain tumour (possible damage to the pituitary-hypothalamus region \(^{17-18}\)); three because of a neuroblastoma (chance of diagnostics or treatment with \(^{131}\)I-meta-iodobenzylguanidine (MIBG) that may damage the thyroid gland \(^{19}\)); three because of a history of radiotherapy in the head/neck region (possible damage to the hypothalamus, pituitary or thyroid gland \(^{20,21}\)); three because only one blood sample could be obtained (due to the short course of chemotherapy or lack of central venous catheter); two because they had used dexamethasone at home before the first blood withdrawal; two because they were admitted for other reasons than chemotherapy; 12 because no informed consent was obtained due to admission in the weekend or parents' refusal and two were initially included but later excluded from analysis because hormonal measurements were only performed after starting chemotherapy.

Nineteen patients were included. Their tumours were osteosarcoma (n=4), Ewing sarcoma (n=2), rhabdomyosarcoma (n=1), high risk Acute Lymphoblastic Leukaemia (ALL) (n=4), non-high risk ALL (n=2), T-cell ALL (n=3), acute non-lymphoblastic leukaemia (ANLL) (n=2) and a glioma of the spinal cord (n=1).

From all parents, written informed consent was obtained. The research protocol was approved by the medical ethical committee of the Academic Medical Centre. For ethical reasons, a blood sample for the study was only taken if, simultaneously, a sampling for clinical information was necessary. For analysis of changes in hormone
concentrations, only paired blood samples, before and after chemotherapy, were used. The drugs were grouped into 9 categories, according their mode of action. The data were grouped into day 0 (before chemotherapy) and day ≥ 1 (after chemotherapy). On day 0, chemotherapy had not been given for at least 7 days.

The following thyroid function determinants were tested: TSH, T₄, T₃, rT₃, thyroxine-binding globulin (TBG), thyroglobulin (Tg), IGF-1, PRL and cortisol. Pre-treatment levels of anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were measured. Plasma T₄, T₃, rT₃ and anti-TG were measured by in-house radio-immunoassays; TSH by a time resolved fluoro-immunoassay (Delfia® hTSH, Wallac Oy, Tuurku, Finland); Tg by an immuno-luminometric assay (ILMA, Brahms®: Germany); anti-TPO by a luminescence immunoassay (LIA, Brahms®: Germany); cortisol by a chemilumiscence immunoassay (DPC®); PRL by a fluoro-immuno assay (Perkin Elmer®) and TBG by a radio-immuno assay (Eikenchemical Co, Tokyo, Japan). Reference values are shown in table 1. Free T₄ measurements were not used, because of possible interaction with heparin used in central venous catheters.

Clinical data was collected on the days of blood sampling, with special attention to weight, food intake, vomiting, stools, vital parameters, temperature and actual medication. Questionnaires to measure the daily physical well-being of the patient on the days of blood withdrawal were taken from the parents and the patients older than 10 years. In the questionnaires, parents and patients were asked to rate several complaints (n=15). This was assessed on 10 cm visual analogue scales (VAS), that ranged from ‘very little’ to ‘very many’. The following complaints were scored: dyspnoea, pain, tiredness, diminished appetite, nausea, vomiting, diarrhoea, constipation, fever, painful mouth/mucositis, cough, headache, loss of energy, hair loss, and ‘any other complaint’. Also, the food and drink intake of that day was asked for. Finally, a ‘day’- mark was asked for by questioning “How are you (is your child) feeling today?”

Differences in mean absolute hormone concentrations for all patients were calculated (table 1).

Due to the fact that in 39 of 46 courses dexamethasone was administered, and the baseline characteristics between these groups differed as shown in figure 1, further analyses were done separately for courses with and courses without dexamethasone.
For evaluation of the effect of other cytotoxic agents, ANOVA linear regression was performed on the various agents and the difference between the geometric mean of the hormone concentration of day $\geq 1$ and the log of the concentration of day 0 within a course of chemotherapy.

For analysis of the complaints scored on the questionnaire, univariate tests (Mann Whitney U) were performed for all courses on the difference between the mean score on day $\geq 1$ and day 0. Subsequently, a multi-variate analysis was performed for all complaints that had significantly changed in the questionnaire as univariate on day $\geq 1$ and the different subgroups of chemotherapy on all courses, using ANOVA regression analysis.

To analyse the effect of the change in complaints on the endocrine determinants, regression analysis was performed on the difference of the geometric mean of the concentration on day $\geq 1$ and the log of the concentration of day 0 of the endocrine determinants for all significant changed complaints.

For the evaluation of the effect of tumour type on endocrine function determinants, tumours were divided in solid tumours versus leukaemia (high risk and non-high risk ALL, ANLL and T-cell ALL).

The data were analysed using SPSS 11.5 and MSO-XP Excel software. Descriptive statistics were calculated using the Independent Samples T-test, Mann-Whitney U tests and ANOVA regression analysis. P values of 0.05 or less were considered to indicate statistical significance.

### Table 1. Mean plasma concentrations of endocrine determinants in 19 patients measured before (day 0) and after starting chemotherapy (day $\geq 1$)

<table>
<thead>
<tr>
<th>Endocrine determinant (reference range)</th>
<th>Day 0</th>
<th>Day $\geq 1$</th>
<th>% of baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (0.4-4.0 mU/L)</td>
<td>1.45</td>
<td>0.77</td>
<td>53</td>
<td>n.s.</td>
</tr>
<tr>
<td>T3 (70-150 nmol/L)</td>
<td>115</td>
<td>111</td>
<td>97</td>
<td>n.s.</td>
</tr>
<tr>
<td>T4 (1.3-2.7 nmol/L)</td>
<td>2.4</td>
<td>1.6</td>
<td>0.7</td>
<td>0.000***</td>
</tr>
<tr>
<td>rT3 (0.1-0.44 nmol/L)</td>
<td>0.18</td>
<td>0.39</td>
<td>21</td>
<td>0.000***</td>
</tr>
<tr>
<td>TBG (200-650 nmol/L)</td>
<td>398</td>
<td>425</td>
<td>19</td>
<td>n.s.</td>
</tr>
<tr>
<td>T4 (1-45 pmol/L)</td>
<td>8.9</td>
<td>6.1</td>
<td>63</td>
<td>0.004**</td>
</tr>
<tr>
<td>PRL (0-15 µg/L)</td>
<td>9.8</td>
<td>10.5</td>
<td>0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cortisol (100-650 nmol/L)</td>
<td>168</td>
<td>25</td>
<td>15</td>
<td>0.000***</td>
</tr>
<tr>
<td>IGF-1 (nmol/L, age and sex specific)</td>
<td>31</td>
<td>28</td>
<td>90</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Statistical analysis is performed on the geometric mean of the concentration on day $\geq 1$ and the logarithm of the concentration on day 0. * = p < 0.05, ** = p < 0.03, *** = p < 0.001 (Mann-Whitney U tests).
Results

Patients
Nineteen patients (12 boys), with a median age of 11.0 years (range 2-16) were included. In total, 46 courses (123 sample moments) could be analysed with measurements both before and during chemotherapy.

Thyroid function determinants
At baseline, in 28 (61%) courses ≥ 1 thyroid function determinant was already aberrant. Seventeen patients (89.5%) developed changes in their thyroid function determinants after administration of chemotherapy. In 40 out of 46 courses (87%) at least one determinant became aberrant.

In table 1, mean plasma concentrations and percentage of change compared to baseline values are given. Significant decrease of mean plasma concentrations of TSH, T₄, and Tg was seen, while mean concentration of plasma rT₃ significantly increased. The T₄/T₃ ratio increased significantly from day 0 to day ≥ 1 (49.8 and 77.8 respectively; p < 0.000). No changes were found in the T₄/TBG-ratio. In none of the patients elevated anti-TPO concentrations or anti-TG concentrations were found.

Considering the different criteria used for the definition of NTI (low T₃ & low T₄ & low-normal TSH & high rT₃, low T₃ & low T₄, or a low T₃ only), this phenomenon occurred in 1 course before starting chemotherapy and in 5.0-42.0% of all patients and in 2.1-21.7% of all given courses after starting chemotherapy.

A significant decrease in the mean concentration of plasma cortisol was seen. The mean concentration of IGF-1 did not change after starting chemotherapy. In 23 samples (18.7%), however, of which 7 before starting chemotherapy, the concentration of IGF-1 was below the P₅-value, adjusted for age and sex.

Chemotherapy
In 85% of courses, dexamethasone was administered, 6-15 mg/m². NTI only occurred when dexamethasone had been administered during the course. However, in the courses without dexamethasone administration (n=7), in 4 courses (57.1%) also ≥ 1 thyroid function determinants became aberrant. In 3 courses (in 1 patient), an elevated concentration of plasma T₃ was found after vincristine and asparaginase administration
Figure 1. Differences in concentrations of endocrine determinants in courses with and without dexamethasone, before and after administration of chemotherapy.

Mean concentration and 95% Confidence Intervals of log TSH, T₃, T₄, rT₃, TBG, Cortisol, IGF-1 and PRL in patients with and without (no) dexamethasone, before (——) and after (-----) administration of chemotherapy. Dex = dexamethasone, *= p < 0.05, **= p < 0.03, ***= p ≤ 0.001 (Mann-Whitney U tests).
(range 3.35-3.95 nmol/L), in one course accompanied by an elevated TSH concentration and in another by a decreased level of rT₃.

The patient-characteristics during courses with dexamethasone differed significantly from those without dexamethasone, regarding age, sex, heart rate, diminished intake, and point for clinical condition and tumour-type. Due to these differences, further analysis was done separately for both groups as described in the methods section.

In figure 1, the effects of chemotherapy administration on plasma concentrations of TSH, T₃, T₄, rT₃, TBG, IGF-1, cortisol, and PRL are shown, during courses with and without dexamethasone. Of the courses with dexamethasone (n=39), baseline TSH and PRL were found to be significantly lower and the concentrations of rT₃ and T₄ were significantly higher. No differences were seen in baseline T₄, TBG, IGF-1, and cortisol. After administration of dexamethasone during the course of chemotherapy, significant lower concentrations of plasma TSH, T₃, Tg (not shown), and cortisol and an increase in plasma rT₃ were found. In patients, who did not receive dexamethasone during the course of chemotherapy, a significant increase was found in the concentration of plasma rT₃.

After multi-variate analysis on all groups of chemotherapy and endocrine determinants, additional significant negative influence in the courses with dexamethasone was found for alkylating agents, anti-neoplasics, anti-metabolites, cisplatin and the topo-isomerase inhibitors (table 2). In the 7 courses without dexamethasone, asparaginase significantly influenced rT₃ and Tg.

Because all results are presented in 'mean concentrations of groups of patients', figure 2 is added to illustrate the changes of thyroid function determinants within an individual patient. During treatment for a recurrent T-cell lymphoma, the plasma concentrations of TSH, TBG and T₄ decreased during the administration of multiple drugs from day 0 to day 20. After day 20, chemotherapy was continued once weekly and the determinants recovered. The increase of plasma concentration rT₃ was most obvious after the first day with the administration of mitoxantrone, vincristine, cytarabine, methotrexate and dexamethasone. Decrease of TBG was consistent with the administration of asparaginase (day 7, 13, 14, 16-20 and 27), as previously described by others.15.
Table 2. Significant changes in endocrine determinants after administration of chemotherapy

<table>
<thead>
<tr>
<th>Endocrine determinant</th>
<th>Group of drugs</th>
<th>( \beta )</th>
<th>p-value</th>
<th>95 % C-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Alkylation</td>
<td>-2.246</td>
<td>0.0001</td>
<td>-1.06 to -0.59</td>
</tr>
<tr>
<td></td>
<td>Anti-neopl.</td>
<td>-2.44*</td>
<td>0.02*</td>
<td>-0.29 to -0.02</td>
</tr>
<tr>
<td></td>
<td>Anti-metab.</td>
<td>-2.80*</td>
<td>0.0001</td>
<td>-1.26 to -0.08</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>-1.96*</td>
<td>0.0001</td>
<td>-1.15 to -0.54</td>
</tr>
<tr>
<td></td>
<td>Topoisom. inh.</td>
<td>-0.385</td>
<td>0.042</td>
<td>-0.22 to -0.05</td>
</tr>
<tr>
<td></td>
<td>Amsacrine</td>
<td>0.47*</td>
<td>0.006</td>
<td>0.13 to 0.74</td>
</tr>
<tr>
<td>Tg</td>
<td>Topoisom. inh.</td>
<td>-0.47*</td>
<td>0.012</td>
<td>-0.16 to -0.22</td>
</tr>
<tr>
<td>TBG</td>
<td>Topoisom. inh.</td>
<td>-0.45*</td>
<td>0.02*</td>
<td>-0.50 to -0.32</td>
</tr>
</tbody>
</table>

A: All courses in which dexamethasone was administered (n=39). B: All courses in which no dexamethasone was given (n=7). ANOVA linear regression is performed on the difference of the geometric mean of the concentration of day ≥ 1 and the log of the concentration of day 0 per course per patient and the different subgroups of chemotherapy. \( \beta \)=Standardized coefficient. 95 % C-I= 95 % Confidence Interval.

Questionnaires

Of the parents, 108 of 123 (88 %) questionnaires were obtained. Of the children older than 10 years of age, 69 of 79 (87 %) questionnaires were answered.

The mean day-mark for physical well-being in all patients, before starting chemotherapy, was 1.1 (scored by the children) and 1.6 (scored by the parents). After starting chemotherapy these scores changed to 2.4 (p= 0.054) and 2.7 (p=0.024), indicating, statistically (near) significant change but, clinically a fairly well condition. In the univariate analyses no significant changes were found in the clinical condition in the 7 courses without dexamethasone.

In the 39 courses with dexamethasone small, but significant changes were found for the following complaints before and after starting chemotherapy scored by the patient: stomach ache (p=0.029), loss of energy (p=0.028), nausea (p=0.032), tiredness (p=0.019) and diminished appetite (p=0.012). Also, the scores for loss of hair and occurrence of mucositis increased (p=0.022 and p=0.037). The parents scored significant changes in tiredness, nausea, coughing, energy and the day-mark (p= 0.017, 0.042, 0.015, 0.002 and 0.009 resp.). After multi-variate analysis, it was seen that cisplatin
Figure 2. Thyroid function determinants in a 16-year old boy receiving treatment for recurrent T-cell lymphoma

Table 3

<table>
<thead>
<tr>
<th>Day</th>
<th>Administered cytotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>mitoxantrone, vincristine, cytarabine, methotrexate and dexamethasone</td>
</tr>
<tr>
<td>Day 7</td>
<td>mitoxantrone, vincristine and asparaginase</td>
</tr>
<tr>
<td>Day 13</td>
<td>asparaginase</td>
</tr>
<tr>
<td>Day 14</td>
<td>mitoxantrone, vincristine, asparaginase and dexamethasone</td>
</tr>
<tr>
<td>Day 16-20</td>
<td>asparaginase</td>
</tr>
<tr>
<td>Day 21</td>
<td>mitoxantrone and vincristine</td>
</tr>
<tr>
<td>Day 27</td>
<td>vincristine, asparaginase and methotrexate</td>
</tr>
<tr>
<td>Day 34</td>
<td>vincristine</td>
</tr>
</tbody>
</table>

was correlated to the most complaints (table 3). The administration of anti-neoplastic agents was correlated to fewer complaints.

No significant changes were found between complaints and thyroid function determinants, at baseline or during the administration of chemotherapy. The complaints stomach ache and energy loss (scored by the child) were significantly of influence on the change in concentration of plasma cortisol (p=0.030 and p=0.023 resp.) and
Table 3. Significant changes in complaints during chemotherapy as scored on the questionnaire by patients and their parents.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Drug</th>
<th>β</th>
<th>p-value</th>
<th>95 % C-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td>Anti-neopl.</td>
<td>-0.677</td>
<td>0.042</td>
<td>-8.81 to -0.18</td>
</tr>
<tr>
<td>Diminished appetite</td>
<td>Cisplatin</td>
<td>0.591</td>
<td>0.026</td>
<td>0.67 to 8.91</td>
</tr>
<tr>
<td>Nausea</td>
<td>Cisplatin</td>
<td>0.771</td>
<td>0.003</td>
<td>2.38 to 9.32</td>
</tr>
<tr>
<td>Loss of energy</td>
<td>Cisplatin</td>
<td>0.738</td>
<td>0.004</td>
<td>1.92 to 8.46</td>
</tr>
<tr>
<td>Parent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Topo-isom.</td>
<td>0.395</td>
<td>0.037</td>
<td>0.02 to 0.67</td>
</tr>
<tr>
<td>Tiredness</td>
<td>Anti-neopl.</td>
<td>-0.808</td>
<td>0.012</td>
<td>-8.61 to -1.15</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>0.653</td>
<td>0.003</td>
<td>2.04 to 8.91</td>
</tr>
<tr>
<td>Nausea</td>
<td>Anti-neopl.</td>
<td>-0.521</td>
<td>0.039</td>
<td>-5.82 to -0.17</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>0.738</td>
<td>0.001</td>
<td>0.33 to 8.50</td>
</tr>
<tr>
<td></td>
<td>Topo-isom.</td>
<td>0.452</td>
<td>0.002</td>
<td>1.15 to 4.33</td>
</tr>
<tr>
<td>Day mark</td>
<td>Cisplatin</td>
<td>0.659</td>
<td>0.002</td>
<td>1.60 to 6.44</td>
</tr>
<tr>
<td></td>
<td>Anti-neopl.</td>
<td>-0.780</td>
<td>0.009</td>
<td>-6.23 to -1.01</td>
</tr>
<tr>
<td></td>
<td>Amsacrine</td>
<td>0.388</td>
<td>0.020</td>
<td>0.84 to 8.96</td>
</tr>
<tr>
<td>Loss of energy</td>
<td>Anti-neopl.</td>
<td>-0.764</td>
<td>0.014</td>
<td>-8.11 to -0.02</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>0.649</td>
<td>0.002</td>
<td>2.12 to 8.66</td>
</tr>
</tbody>
</table>

ANOVA linear regression for all significant changed complaints in the univariate analysis and the difference in endocrine determinant on day ≥ 1 and day 0 (after logarithmic transformation), in 39 courses of chemotherapy with dexamethasone administration. topo-isom. inh. = topo isomerase inhibitor, anti-neopl. = anti-neoplastic agents

mucositis (scored by the child), fever and cough scored by the parent were significantly correlated to changes in plasma concentration of IGF-1 (p=0.010, p=0.042 and p=0.040 respectively).

Tumour types
At baseline, children with leukaemia compared to children with solid tumours, had significantly higher mean TSH (2.3 vs. 1.3, p=0.014), lower T4 (104 vs. 133, p=0.002), lower TBG (362 vs. 460, p=0.001), lower IGF-1 (31 vs. 45, p=0.023), and lower rT3 (0.17 vs. 0.24, p=0.007) plasma concentrations. Also, at baseline, small but significant differences were found for tiredness (1.7 and 0.7, p=0.044) and diminished appetite (2.4 and 0.9, p=0.023) both scored by the parent. Type of malignancy did not influence the changes of any of the endocrine determinants during treatment with chemotherapy.

Discussion
In this heterogeneous group of children with cancer, 90% of the children showed changes in their thyroid hormone state during one or more courses with chemotherapy. In 61% of courses one or more thyroid function determinant was already aberrant at baseline,
and in 87% of all courses at least one thyroid function determinant became aberrant during treatment. Not the deterioration in physical well-being, but the administration of dexamethasone appeared to be the most important contributing factor.

Depending on the definition that was used (the combination of a low T₃, low T₄, low-normal TSH and a high rT₃ or a low T₃ alone), the phenomenon of NTI occurred during 2-22% of the courses. Comparing these results with other published findings is difficult however, because of the many different definitions that are being used for NTI. For this reason, international consensus on the definition of NTI should be made.

Despite the heterogeneity of this cohort the results of this evaluation demonstrate that considerable changes occur in the thyroid state of children receiving chemotherapy. The observed aberrations illustrate the combination of disturbances on all levels of the thyroid hormone homeostasis. The fact that TSH is low while T₄ and T₃ are low is typically seen in central hypothyroidism, while the decrease of plasma T₃ with an increased rT₃ concentration in combination with a normal concentration of plasma T₄ points towards a peripheral disturbance regarding the action of type I, II and III-deiodinases. For young children the most important thyroid function determinant for brain development is the concentration of plasma FT₄ or, in absence of a reliable FT₄, the ratio [T₄] / [TBG]. As these determinants did not change much, permanent negative consequences are not to be expected. However, as the concentration of plasma T₃ greatly decreases (67% of baseline), transient adverse effects on peripheral tissues cannot be excluded and this may have consequences for the healing process in the child with cancer treated with chemotherapy.

We expected that chemotherapy would negatively influence the physical well-being of the patient and that this would result in the changes in the thyroid hormone state. However, for all complaints the reported changes in scores were very small. Although some were found to be statistically significant, it can be discussed whether these were clinically relevant. Also, no correlations were found between tumour type and changes in (thyroid) hormones during treatment with chemotherapy.

It may be questioned whether the changes we found in thyroid hormone determinants are caused by dilution, because in 40 of 46 courses, hyperhydration (NaCl 0.45% and glucose 2.5%, 3 L/ m² iv per day with a maximum of 5 L per day) was given. To
quantify changes in volemic state of our patients, plasma creatinine concentrations were measured before and during chemotherapy. No changes were found in mean plasma creatinine concentrations (34.9 and 34.5 μmol/L, respectively; p=0.935, ANOVA, data not shown), indicating that there were no relevant changes in volemic state. Moreover, the concentrations of PRL did not diminish. Furthermore, the mean concentration of plasma reverse T₃ increased, fitting with an altered deiodinase activity. Taking these facts into account, it must be concluded that the observed endocrine changes were directly caused by the cytotoxic drugs, dexamethasone in particular. The influence of dexamethasone on TSH secretion is well known: short term administration of pharmacological doses of glucocorticoids suppress the secretion of TSH, and also of PRL. Glucocorticoids are also known to lower plasma TBG binding capacity by lowering the plasma TBG concentration and inhibit the peripheral conversion of T₄ into T₃. Furthermore, glucocorticoids are known to suppress the adreno-corticotropic axis and the growth hormone response to insulin at the hypothalamic-pituitary level. With these facts in mind, the endocrine disturbances we found can be explained by glucocorticoids administration, although we did not find a change in the mean concentration of IGF-1 as was previously described.

The fact that the children and their parents scored well in the questionnaire reflects a rather good clinical condition during chemotherapy. These reassuring clinical scores may for a great deal be explained by the use of dexamethasone. However, it may be questioned, whether the endocrine effects caused by dexamethasone are also reassuring. Dexamethasone may cause continuously low thyroid hormone and low IGF-1 concentrations and also the long-term effects of glucocorticoids on growth, osteoporosis, and the adrenal function should be considered.

Although the current dogma is not to treat NTI, except for situations in which extremely low T₄ concentrations are found, it should be investigated whether chronically ill children might benefit from treatment of altered thyroid hormone states. If NTI occurs as a consequence of a diminished physical well-being it may be a physiological phenomenon, but when NTI is pharmacologically induced it might be considered a negative side effect which should be prevented. For children receiving frequent and high doses of dexamethasone, for instance, this could imply simultaneous supplementation of T₄ and/or T₃. This should be evaluated in a prospective clinical trial.
Although only small changes in physical well-being were indicated by the child and their parents, it should be taken into account that, despite this fairly "well" physical condition, in 19% of courses the concentration of IGF-1 was found to be lower than the P$_{95}$ reference value. This might reflect an altered perception of sickness and health in this patient group, causing a relative good clinical score, while in fact these children are in a worse metabolic condition than their healthy peers of the same age group.

This study has several limitations. Firstly, the fact that in our study in 88% of the courses dexamethasone was administered can be considered a limitation. However, nowadays, dexamethasone is always an important drug during chemotherapy, and subsequently will always be interfering with the thyroid function determinants during chemotherapy and this is important for clinicians to be aware of. Secondly, due to ethical restrictions, blood was only sampled on days that sampling was already indicated for clinical reasons. For this reason, the value on day $\geq 1$ is the mean value of the days after starting chemotherapy. As can be seen in figure 2, however, hormonal fluctuations in the days after administration of chemotherapy occur and this information is missed by this method of analysis. To screen for possible missed information, an additional analysis was done on the endocrine determinants of day 0 compared to the value of the determinant on the worst day after starting chemotherapy, as scored in the questionnaire. This analysis did not reveal different results (data not shown), concluding that the mean value of day $\geq 1$ is a realistic representation of the changes after starting chemotherapy.

At baseline, between the dexamethasone-treated and the non-dexamethasone-treated group, we observed differences in baseline TSH, rT$_3$ and PRL that we do not fully understand. The differences in physical well-being, sex (predominantly male), age (older) and % of patients with leukaemia (higher), could all have contributed. Also at baseline, significant differences were found for almost all thyroid hormone determinants between patients with leukaemia and solid tumours. The fact that patients with leukaemia use dex more frequently and for longer time-periods could perhaps explain a continuous low T$_4$ and lower TBG. The increase in plasma TSH could then be explained by a transient (rebound) phenomenon, suggesting a previous period of hypothyroidism.

In conclusion, the thyroid hormone state is disturbed in almost all children with cancer during chemotherapy, not clearly pointing to alterations in physical well-being, but
indicating interference of drugs, especially dexamethasone, with the endocrine homeostasis. Further investigations should be aimed at evaluating the changes in thyroid state during cytotoxic treatment without dexamethasone, and at evaluating the consequences of an altered endocrine state during childhood. Prevention of these endocrine alterations might, in the long run, improve development of the child with cancer.

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