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Reseach Article

Thyroid Hormone Parameters During Cancer Treatment In Children: Results Of The Thyro-Dynamics Study.

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Abstract

Context: Thyroid dysfunction is a well-known late effect of child cancer survivors, but its prevalence during childhood cancer treatment remains unclear.
Objective: To prospectively study the prevalence of thyroid dysfunction and changes in thyroid hormone parameters during childhood cancer treatment, including its effect on height and weight.
Design: Thyroid hormone parameters were prospectively collected at four time points in children with newly diagnosed cancer at the Princess Máxima Center during and shortly after systemic antineoplastic therapy.
Participants: 286 children diagnosed with leukemia, lymphoma, sarcoma, or a brain tumor (not involving the hypothalamic–pituitary region) were included.
Main outcomes: Prevalence of primary thyroid dysfunction and changes in thyroid function parameters.
Results: None of the included patients developed overt primary hypothyroidism. Subclinical hypothyroidism was present in 8.2% (18/219) at diagnosis, in 2.9% (8/275) three months after diagnosis and in 5.3% (9/171) post-therapy. Non thyroidal illness (NTI) was found in 1.5% (4/265) of children, three months after start of treatment. However elevated concentrations of reverse T3 (rT3) were observed in 31.5% (46/146) at diagnosis, in 46.4% (123/265) at three months, and in 41% (25/61) three months posttherapy. In 27.7% (54/195) of patients, FT4 declined ≥20 % from start to three months after diagnosis and persisted until the end of therapy in 30.2% (13/43). Linear growth and BMI were unaffected by an FT4 decline ≥20%.
Conclusion: Children currently treated for cancer have low risk of primary thyroid dysfunction or NTI during treatment. Although changes in thyroid hormone parameters are common, they do not seem to influence linear growth or BMI.

Keywords: childhood cancer treatment, thyroid dysfunction, pediatrics.

INTRODUCTION

Thyroid hormones are essential for quality of life, normal growth and neurocognitive development of children. Hypothyroidism in children can lead to symptoms such as declining height velocity, weight gain, fatigue and constipation.[1] In the very young (age <2.5 years) hypothyroidism may lead to cognitive impairment.[2] Recognition of clinical thyroid dysfunction in children treated for cancer can be challenging because symptoms can be nonspecific and mimic symptoms regularly seen in childhood cancer (such as fatigue).

In childhood cancer survivors, primary hypothyroidism is a well described late effect and seen in around 15%, especially after radiotherapy involving the thyroid gland or following metaiodobenzylguanidine (MIBG) therapy.[3–7] Chemotherapy also was reported to increase the risk of late primary hypothyroidism in some studies (busalfan, idarubicin and trofosfamide).[6,8] However, studies regarding the acute or

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short term effects of chemotherapy on thyroid function for childhood cancer are scarce.[9–14]

Thyroid hormone parameters can be affected during childhood cancer therapy in multiple ways: due to direct effects on the thyroid gland (e.g. by radiotherapy, MIBG or autoimmunity such as caused by tyrosine kinase inhibitors or checkpoint inhibitors[3–5,15])or due to effects on the hypothalamic-pituitary region (e.g., surgery for brain tumor or radiotherapy involving the hypothalamic-pituitary-thyroid axis) leading to central hypothyroidism.[16,17] Thyroid hormone parameters can also change in response to severe illness or malnutrition, also referred to as non-thyroidal illness (NTI). In acute illness, changes in deiodinase enzyme activity are seen: the conversion of thyroxine (T4) to active triiodothyronine (T3) is reduced due to a decreased activity of deiodinase 1, while conversion of T4 to reverse T3 (rT3) is increased due to increased activity of deiodinase 3.[18–20] In more severe and prolonged illness an additional downregulation of the hypothalamic-pituitary thyroid axis is seen with a decrease in thyroid stimulating hormone (TSH) and subsequently T4. The biochemical profile of central hypothyroidism and NTI may overlap with both a low-normal TSH and low T4 concentration. rT3 can be used to distinguish central hypothyroidism from NTI, in which rT3 is elevated.[18,20]

The reported prevalence of NTI during childhood cancer therapy varies widely between 0 and 100%.[9,11,13,14], This broad variation in prevalence may partly be explained by the absence of an internationally accepted definition of NTI. Recent studies suggest that acute changes seen in NTI may be adaptive and beneficial to reduce energy expenditure and play a role in activating the immune system. However, the more severe and prolonged forms of NTI, characterized by additional downregulation of the hypothalamic–pituitary–thyroid axis, may no longer be adaptive and could instead exert harmful effects.[20] In children developing mild central hypothyroidism after treatment for a brain tumor, a decline in free T4 (FT4) of ≥20% within the reference range has been shown to be clinically relevant (e.g. weight gain).16 It may therefore be hypothesized that prolonged NTI with an FT4 decline ≥20 % in children treated for childhood cancer, such as over a period of one to two years in children with leukemia, might be associated with adverse clinical consequences.

Upcoming drugs, such as checkpoint inhibitors, are known to cause immune related adverse events such as primary hypothyroidism, thyroiditis but also central hypothyroidism in the context of hypophysitis.[21–23] Checkpoint inhibitors are increasingly used for pediatric cancers, either as monotherapy or in combination with other antineoplastic agents.[24] To evaluate the effects of immune checkpoint inhibitors on thyroid function in the future, it is essential to first understand the impact of currently used antineoplastic agents on thyroid hormone parameters.

In this prospective study of children newly diagnosed with childhood cancer, we evaluated the prevalence of thyroid dysfunction and NTI, as well as the changes in thyroid hormone parameters and its possible influence on linear growth and weight, during treatment with chemotherapy.

METHODS

We conducted a prospective observational cohort study including children and adolescents (age < 21 year) between (January 2020 to December 2021) with a new diagnosis of leukemia, lymphoma, sarcoma, or a brain tumor (not involving the hypothalamic–pituitary region) at the Princess Máxima Center for Pediatric Oncology. Exclusion criteria were prior thyroid disease, Down syndrome, thyroid cancer predisposition syndromes, history of neck irradiation or MIBG treatment. Children treated with hematopoietic stem cell transplantation have been reported separately.[25]

Thyroid hormone parameters (TSH, FT4, T3, rT3) were measured at diagnosis (range ±35 days), three months after diagnosis (range 60-160 days after diagnosis), at the end of therapy (range -28 to 45 days), and three months posttherapy (range -45 days to 326 days). Antithyroid peroxidase (anti-TPO) concentrations were measured at diagnosis and at the end of therapy. Thyroid hormones were evaluated, and children were referred to the pediatric endocrinologist if needed. Anthropometric measurements (height, weight, body mass index (BMI)) were collected at every timepoint.

Primary hypothyroidism was defined as a TSH concentration above the age-adjusted reference range. Overt primary hypothyroidism was defined as a TSH concentration above the age adjusted reference range with an FT4 concentration below the reference range. Subclinical hypothyroidism was defined as a TSH concentration above the reference range with an FT4 concentration within the reference range. Primary hyperthyroidism was defined as a TSH concentration below the age adjusted reference range with an FT4 concentration above the reference range. Central hypothyroidism was defined as an FT4 concentration below the reference range, with a non-elevated TSH concentration and a non-elevated rT3 concentration. NTI was defined as an FT4 concentration below the reference range, a non-elevated TSH concentration and a rT3 concentration above the reference range. Low T3 syndrome was defined as an isolated low concentration of total T3.

Continuous data are presented as means (±SDS) or medians (range) depending on the distribution. Categorical outcomes are presented as contingency tables (frequencies and percentages). Chi-square tests or Fisher's exact tests were used to test statistical difference between groups for categorical variables. Correlation was estimated using Pearson's or Spearman's rank correlation coefficient, depending on the

variables. Differences between paired observations were assessed using paired t-tests for normally distributed data. For departure from normality, Wilcoxon signed rank was employed. Logistic regression model was used to estimate the effect of possible risk factors for the dependent outcome elevated rT3 or a ≥20% decline of FT4. Variables with a p-value <0.10 in the univariable analysis were included in the multivariable model. Statistical significance was defined as p <0.05.

Linear mixed effects models were used to analyze the estimated means of thyroid hormone parameters, height and BMI standard deviation score (SDS) across four timepoints. Estimated marginal means with 95% confidence intervals for each timepoint were reported.

The research protocol was approved by the medical ethical committee of Princess Máxima Center (NedMec NL69960.041.19). For ethical reasons, blood samples were only collected when sampling was also performed for clinical indications. Informed consent was given by all children and/or their parents/legal representatives depending on age.

RESULTS

Among 519 children assessed for eligibility, 286 were included in the study (**Figure 1**). Children were diagnosed with leukemia in 142 of 286 (49.7%), lymphoma in 75 of 286 (26.2%), sarcoma in 38 of 286 (13.3%) and brain tumors in 31 of 286 (10.8%). The median age at diagnosis was 9.4 (range 0-19.7) years and 129 of 286 (45%) children were females. The median anti-neoplastic treatment duration was 386 days (range 36–1093 days). Treatment duration varied by cancer diagnosis and was longest among children treated for leukemia (median 760 [range, 95–1093] days). See **Table 1** for all baseline characteristics.

Figure 1. Inclusion flowchart of THYRO-Dynamic study.

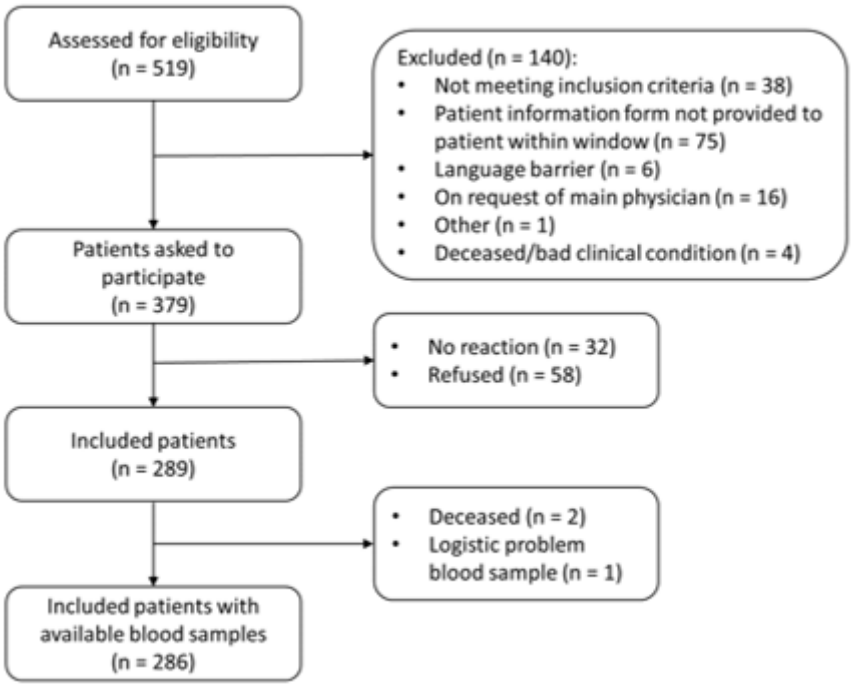


Table 1. Baseline patient characteristics (n = 286).

Age at diagnosis, median years (range)	9.4 (0-19.7)
No. of females (%)	129 of 286 (45%)
Childhood cancer (number, % of total cohort) Leukemia Lymphoma Sarcoma Brain tumor	142 (49.7%) 75 (26.2%) 75 (26.2%) 31 (10.8%)

Treatment	
including corticosteroids	236 of 286 (83%)
including alkylating agents	213 of 286 (74%)
Including antimetabolites	189 of 286 (66%)
including anthracyclines	200 of 286 (70%)
including asparaginase	130 of 286 (45%)
including platinating compounds	24 of 286 (8%)
including protein kinase inhibitors	5 of 286 (2%)
including topoisomerase inhibitors	82 of 286 (29%)
including immunotherapy	20 of 286 (7%)
Treatment with radiotherapy	30 of 286 (10%)
Anti-neoplastic treatment duration, median in days (range)	
Leukemia	760 (95-1093)
Lymphoma	128 (36-769)
Sarcoma	246 (97-577)
Brain tumor	271 (117-637)

Table 2. Height and BMI SDS in children in relation to presence of NTI during cancer treatment.

	Mean SDS at diagnosis (95% CI)	Mean SDS 3 months after diagnosis (95% CI)	Mean SDS at end of therapy (95% CI)	Mean SDS three months after end of therapy (95% CI)
Height SDS*				
No FT4 decline	0.07 (-0.12 to 0.26)	-0.20 (-0.38 to -0.01)	-0.20 (-0.44 to 0.04)	-0.12 (-0.36 to 0.13)
FT4≥20% decline	0.15 (-0.16 to 0.46)	-0.15 (-0.46 to 0.16)	-0.23 (-0.62 to 0.16)	-0.11 (-0.54 to 0.32)
BMI SDS				
No FT4 decline	0.04 (-0.19 to 0.26)	0.18 (-0.44 to 0.40)	0.55 (0.26 to 0.83)	0.37(0.07 to 0.66)
FT4≥20% decline	0.09 (-0.27 to 0.46)	0.22 (-0.14 to 0.58)	0.88 (0.43 to 1.34)	0.51 (0.01 to 1.01)
Height SDS*				
Normal rT3	0.15 (-0.07 to 0.36)	-0.14 (-0.32 to 0.05)	-0.71 (-0.31 to 0.17)	-0.20 (-0.44 to 0.05)
Elevated rT3	0.13 (-0.23 to 0.25)	-0.30 (-0.51 to -0.10)	-0.29 (-0.55 to -0.02)	-0.14 (-0.42 to 0.13)
BMI SDS				
Normal rT3	-0.09 (-0.34 to 0.16)	0.10 (-0.12 to 0.32)	0.48 (0.20 to 0.77)	0.50 (0.21 to 0.79)
Elevated rT3	0.14 (-0.13 to 0.42)	0.43 (0.19 to 0.67)	0.88 (0.58 to 1.19)	0.54 (0.22 to 0.86)

**Height SDS for children <16 yrs at diagnosis*

Abbreviations: SDS: standard deviation score, CI: confidence interval, BMI: body mass index, FT4: free thyroxine, rT3: reverse triiodothyronine.

Prevalence of primary hypo- and hyperthyroidism

None of the children developed overt primary hypothyroidism. Subclinical hypothyroidism was present in 18 of 219 (8.2%) children at diagnosis and was transient in all of them. Subclinical hypothyroidism was seen in 8 of 275 (2.9%) children three months after diagnosis, in 2 of 167 (1.2%) children at the end of therapy and in 9 of 171 (5.3%) children three months posttherapy. Subclinical hypothyroidism was mild (TSH <10 mIU/L), except for two children who had TSH concentration of 11 mIU/L; in both cases, TSH values normalized spontaneously during follow-up without intervention.

Subclinical hyperthyroidism was seen in 7 of 219 (3.2%) children at diagnosis, in 2 of 275 (0.7%) children three months after diagnosis and in 2 of 167 (1.2%) children at the end of therapy and in none of the children three months posttherapy. Transient overt hyperthyroidism at diagnosis was seen in one child. **Supplementary table 1**.

Table 1. Prevalence of primary thyroid dysfunction in children during cancer treatment.

	At diagnosis n/N (%)	3 months after diagnosis n/N (%)	At the end of therapy n/N (%)	3 months post therapy n/N (%)
Primary hypothyroidism	18 of 219 (8.2%)	8 of 275 (2.9%)	2 of 167 (1.2%)	9 of 171 (5.3%)
Subclinical hypothyroidism	0 of 218	0 of 275	0 of 167	0 of 171
Overt hypothyroidism				
Primary hyperthyroidism	7 of 219 (3.2%)	2 of 275 (0.7%)	2 of 167 (1.2%)	0 of 171
Subclinical hyperthyroidism	1 of 217 (0.5%)	0 of 275	0 of 167	0 of 171
Overt hyperthyroidism				

Abbreviations: TSH: *thyroid stimulating hormone, mIU/L: milli-international units per liter. NA: not applicable. TSH in medians or means depending on distribution.*

Non thyroidal illness, low T3 syndrome, central hypothyroidism and isolated elevated rT3

NTI, defined as an FT4 concentration below the reference range in combination with a non-elevated TSH concentration and a rT3 concentration above the reference range, was seen in 4 of 265 (1.5%) children three months after diagnosis and absent at all other time points. NTI was moderate in one child (FT4 8 pmol/l) and mild in three children (FT4 10-11 pmol/l). Low T3 syndrome was seen in 8 of 144 (5.6%) children at diagnosis, in 1 of 264 (0.4%) three months after diagnosis and in 0 of 153 and 0 of 140 children at the end and three months posttherapy, respectively. Central hypothyroidism (Low TSH, with low FT4 and non-elevated rT3) was present in 5 of 265 (1.9%) children three months after diagnosis with spontaneous recovery in all. An isolated elevated rT3 concentration was observed in 123 of 265 (46.4%) of children three months after diagnosis (median rT3 0.28 ng/ml [range 0.22-0.87]). This elevated rT3 was associated with a slight decrease in FT4 (median 16 pmol/L [range 11-29] to 15 [range 8-22]) but an increase in T3 (mean 2.30 ±0.67 to 2.66 ±0.80 nmol/L). TSH concentration in this group remained unchanged. The elevated rT3 was persistent in 48 of 117 (41.0%) children at the end of therapy and in 25 of 61 (41%) posttherapy. (**Supplementary table 2**). In multivariable logistic regression analysis, younger age showed a borderline association with elevated rT3 concentrations (odds ratio (OR) 0.96 [95% CI 0.91-1.00]). In multivariable logistic analysis no single agent could be directly related to an elevated rT3. (**Supplementary table 3**).

Table 2. Prevalence of non-thyroidal illness, isolated elevated rT3. low T3 syndrome or central hypothyroidism in children during cancer treatment.

	At diagnosis n/N (%)	**3 months after diagnosis n/N (%)**	**At the end of therapy n/N (%)**	**3 months post therapy n/N (%)**
NTI	0 of 143	4 of 265 (1.5%)	0 of 116	0 of 61
Isolated elevated rT3 (>0.218 ng/mL)	46 of 146 (31.5%)	123 of 265 (46.4%)	48 of 117 (41.0%)	25 of 61 (41.0%)
Low T3 syndrome	8 of 144 (5.6%)	1 of 264 (0.4%)	0 of 153	0 of 140
Central hypothyroidism	1 of 219*	5 out of 265 (1.9%)	5 of 168**	1 of 170*

**NTI: Non thyroidal illness defined as an FT4 concentration below the reference range, a non-elevated TSH concentration and a rT3 concentration above the reference range. rT3 presented in medians (range). Central hypothyroidism defined as an FT4 concentration below the reference range, with a non-elevated TSH concentration and a non-elevated rT3 concentration.*

** no rT3 data, **rT3 available in 2 of 5 pt (normal).*

Table 3. Odds ratio (OR) and 95% confidence interval (CI) for risk factors for high rT3 three months after diagnosis (n=123).

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age at diagnosis	0.94 (0.90-0.99)	0.96 (0.91-1.00)
Diagnosis category (leukemia)		
Lymphoma	0.96 (0.53-1.71)	
Sarcoma	0.92 (0.44-1.91)	
Brain tumor	3.43 (1.35-8.72)	
Leukemia vs non-leukemia	0.84 (0.52-1.36)	
Brain tumor vs no brain tumor	3.52 (1.43-8.70)	2.29 (0.83-6.29)
Underweight (< -2 SDS)	1.46 (0.38-5.57)	
Corticosteroids	0.64 (0.33-1.23)	
Chemotherapy		
Alkylating agents	0.97 (0.57-1.68)	
Antimetabolites	0.66 (0.39-1.10)	
Anthracyclines	**0.43 (0.25-0.74)**	0.63 (0.33-1.19)
Asparaginase	0.93 (0.57-1.51)	
Platinum compounds	1.56 (0.66-3.70)	
Protein kinase inhibitors	0.77 (0.13-4.67)	
Topoisomerase inhibitors	1.06 (0.63-1.80)	
Vinca alkaloids	1.05 (0.55-2.01)	
Immunotherapy	0.65 (0.25-1.72)	
Radiotherapy	1.70(0.72-3.97)	

Changes in thyroid hormone parameters

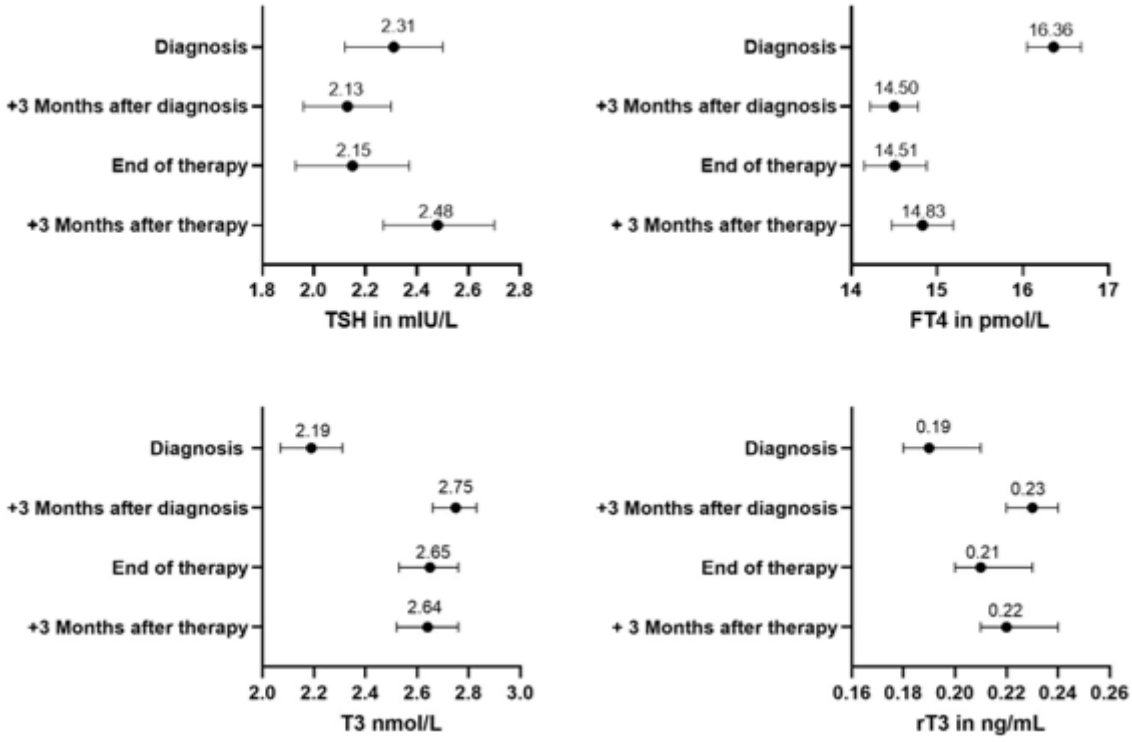
TSH

From start to three months after diagnosis, the mean TSH concentration declined marginally (mean 2.31 [95% CI 2.12-2.50] to 2.13 [95% CI 1.96-2.30] mIU/L). At the end of therapy, the mean TSH concentration was 2.15 [95% CI 1.93-2.37]. Three months posttherapy a slight increase in mean TSH concentration was observed (2.48 [95% CI 2.27-2.70] mIU/L), which was comparable to the mean TSH concentration at diagnosis (**Figure 2**).

FT4

FT4 concentration declined slightly three months after diagnosis (mean: 16.36 [95% CI 16.05-16.68] vs. 14.50 [95% CI 14.22-14.78] pmol/L) and remained lower until three months posttherapy (mean: 14.83 [95% CI 14.47-15.19]) (**Figure 2**).
A decline of FT4 of ≥20% was seen in 54 of 195 (27.7%) children three months after diagnosis. In this group, the FT4 concentration declined from median 18 pmol/l [range 10-20] to 12 [range 8-15] pmol/L which persisted until the end of therapy/three months posttherapy in 13 of 43 (30.2%) children. This decline of FT4 of ≥20% was related to an increase in T3 (median: 2.1 [range 0.74-4.1] to 3.2 [range 1.6-4.0] nmol/L), but unrelated to changes in TSH or rT3. In multivariable logistic regression analysis, younger age showed a borderline association with FT4 decline of ≥20% (OR 0.94 [95% CI 0.88-1.00]). In multivariable logistic analysis no single chemotherapy agent could be directly related to a decline of FT4 of ≥20%. (**Supplementary table 4**).

Figure 2. Estimated means of thyroid hormones concentrations with 95% confidence interval during childhood cancer treatment.



Abbreviations: TSH: *thyroid stimulating hormone, mIU/L: milli-international units per liter, FT4: free thyroxine, pmol/L: picomole/liter, T3: total triiodothyronine, nmol/L: nanomole/liter, rT3: reverse triiodothyronine, ng/mL: nanograms/milliliter.*

Table 4. Odds ratio (OR) and 95% confidence interval (CI) for possible risk factors for ≥20% FT4 decline three months after diagnosis (n=54)

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age at diagnosis	0.93 (0.87-0.99)	0.94 (0.88-1.00)

Diagnosis category (vs leukemia)		
Lymphoma	0.75 (0.35-1.61)	
Sarcoma	0.38 (0.13-1.06)	
Brain tumor	0.24 (0.05-1.07)	
Leukemia vs non-leukemia	1.99 (1.05-3.78)	0.87 (0.25-3.05)
Brain tumor vs no brain tumor	0.29 (0.07-1.30)	
Steroids on T1	0.42 (0.16-1.15)	
Underweight (< -2 SD)	0.95 (0.19-4.85)	
Corticosteroids	2.37 (0.87-6.46)	
Chemotherapy		
Alkylating agents	1.18 (0.58-2.42)	
Antimetabolites	2.55 (1.16-5.62)	1.61 (0.56-4.64)
Anthracyclines	0.80 (0.41-1.56)	
Asparaginase	2.59 (1.37-4.91)	1.56 (0.35-7.2)
Platinum compounds	0.29 (0.07-1.30)	
Protein kinase inhibitors	0.95 (0.10-9.33)	
Topoisomerase inhibitors	0.49 (0.23-1.05)	0.99 (0.36-2.74)
Vinca alkaloids	2.78 (1.03-7.52)	1.81 (0.43-7.65)
Immunotherapy	0.70 (0.19-2.57)	
Radiotherapy	0.51 (0.14-1.81)	

T3 and rT3

An increase in T3 concentration was observed three months after diagnosis (mean: 2.19 [95% CI 2.07-2.31] vs. 2.75 [95% CI 2.66-2.83] nmol/L), and T3 concentration remained higher until three months posttherapy (mean: 2.64 [95% CI 2.52-2.76]). rT3 was not normally distributed and outliers (rT3 > 0.500 ng/mL; 16 of 589 measurements) were excluded from the analysis. A marginal increase in rT3 concentration was observed three months after diagnosis (mean: 0.19 [95% CI 0.18-0.21] vs. 0.23 [95% CI 0.22-0.24 ng/mL), and rT3 concentration remained slightly higher until three months posttherapy (mean: 0.22 [95% CI 0.21-0.24]). (**Figure 2**).

Anti-TPO

Elevated anti-TPO concentrations were seen in 2 of 175 (1.1%) children at diagnosis with a normal thyroid function. At the end of therapy 0 of 139 children had an elevated anti-TPO concentration.

Height and weight

To evaluate the effect of a decline in FT4 ≥20 % on height SDS, we only included children <16 years with growth potential at cancer diagnosis. Following cancer diagnosis, mean height SDS declined and remained slightly reduced until three months posttherapy (mean height SDS at diagnosis: 0.04 SDS [95% CI -0.11 to 0.20) vs -0.18 SDS [95% CI -0.36 to -0.01] three months posttherapy). Overall, children gained weight during therapy (BMI SDS at diagnosis: 0.04 SDS [95% CI -0.13 to 0.22] versus 0.55 SDS [95% CI 0.34 to 0.76] three months posttherapy. **Supplementary table 5**. No significant differences in height or BMI SDS were observed during the study between children with or without an FT4 decline ≥20% nor in children with or without an elevated rT3 three months after diagnosis. Table 4. A linear mixed model showed no effect of the T3/rT3 ratio on height SDS (<16 years) over time. Also, no statistically significant association was observed between the T3/rT3 ratio and changes in weight SDS over time (p=0.051); the borderline significance of the interaction term suggests that a small time-dependent effect cannot be ruled out, although the analysis was limited by the low number of children with available post treatment T3/rT3 ratio measurements (n=51).

Table 5. Estimated means of growth data of all children during cancer treatment

	Mean SDS at diagnosis (95% CI)	**Mean SDS 3 months after diagnosis (95% CI)**	**Mean SDS at end of therapy (95% CI)**	**Mean SDS 3 months after end of therapy (95% CI)**
Height SDS*	0.04 (-0.11 to 0.20)	-0.22 (-0.36 to -0.09)	-0.20 (-0.37 to -0.03)	-0.18 (-0.36 to -0.01)
BMI SDS	0.04 (-0.13 to 0.22)	0.27 (0.11 to 0.42)	0.68 (0.48 to 0.88)	0.55 (0.34 to 0.76)

**Height SDS for children < 16 yrs at diagnosis (n= 240)*

Abbreviations: SDS: standard deviation score, CI: confidence interval, BMI: body mass index

Leukemia versus other childhood cancers

Children with leukemia had a higher mean TSH concentration at diagnosis (mean: 2.78 [95% CI 2.51-3.03] compared to children with other cancer diagnoses (mean 1.81 [95% CI 1.54-2.08] mIU/L) as well as a slightly lower FT4 concentration three months after diagnosis (mean: 13.97 [95% CI 13.57-14.37] versus 15.01 [95% CI 14.62-15.41] pmol/L). At all other timepoints, no differences in thyroid hormones concentrations were observed between children with or without leukemia. No differences in height SDS (<16 years) were observed between children with or without leukemia at any time point. Similarly, no differences in BMI SDS were observed at diagnosis or three months after diagnosis. Children with leukemia had a higher BMI at the end of treatment (BMI SDS: 1.04 [95% 0.77-1.32]) and three months posttherapy (BMI SDS 0.91 [95% CI 0.59-1.23]) compared to children with other cancer diagnosis (BMI SDS: 0.26 [95% CI -0.04 to 0.55] respectively 0.30 [95% CI 0.04 to 0.57]), which was not related to FT4 concentrations. **Supplementary table 6**.

Table 6. Estimated means of thyroid hormone concentrations and growth in children with or without leukemia.

	Mean SDS at diagnosis (95% CI)	Mean SDS +3 months after diagnosis (95% CI)	Mean SDS at end of therapy (95% CI)	Mean SDS 3 months after end of therapy (95% CI)
TSH				
Non-leukemia	1.81 (1.54 -2.08)	2.01 (1.78-2.25)	2.02 (1.70-2.33)	2.44 (2.15-2.72)
Leukemia	2.78 (2.51 -3.03)	2.25 (2.01-2.49)	2.27 (1.98- 2.57)	2.54 (2.23-2.86)
FT4				
Non-leukemia	16.65 (16.19-17.11)	15.01 (14.62-15.41)	14.39 (13.86-14.91)	15.22 (14.74-15.70)
Leukemia	16.11 (15.67-16.54)	13.97 (13.57-14.37)	14.62 (14.13-15.11)	14.34 (13.81-14.88)
rT3				
Non-leukemia	0.20 (0.16-0.24)	0.28 (0.25-0.30)	0.25 (0.20-0.30)	0.23 (0.15-0.31)
Leukemia	0.20 (0.16-0.24)	0.24 (0.21-0.26)	0.23 (0.19-0.27)	0.24 (0.19-0.29)
T3				
Non-leukemia	2.26 (2.08-2.44)	2.84 (2.72-2.96)	2.76 (2.59-2.93)	2.73 (2.57-2.89)
Leukemia	2.14 (1.98-2.30)	2.65 (2.52-2.77)	2.56 (2.40-2.71)	2.53 (2.35-2.71)
Height SDS*				
Non-leukemia	-0.09 (-0.31 to 0.13)	-0.27 (-0.46 to -0.09)	-0.08 (-0.33 to 0.18)	-0.23 (-0.46 to 0.00)
Leukemia	0.16 (-0.05 to 0.37)	-0.17 (-0.36 to 0.02)	-0.31 (-0.54 to -0.07)	-0.12 (-0.40 to 0.15)
BMI SDS				
Non-leukemia	-0.06 (-0.32 to 0.19)	0.22 (0.00 to 0.44)	0.26 (-0.04 to 0.55)	0.30 (0.04 to 0.57)
Leukemia	0.14 (-0.10 to 0.38)	0.31 (0.09 to 0.53)	1.04 (0.77 to 1.32)	0.91 (0.59 to 1.23)

**Height SDS for children < 16 yrs at diagnosis (n= 240). Non-leukemia: lymphoma, sarcoma, or brain tumors (not involving the hypothalamic–pituitary region)*

Abbreviations: SDS: standard deviation score, CI: confidence interval, TSH: thyroid stimulating hormone in milli-international units per liter, FT4: free thyroxine in pmol/L: picomole/ liter, T3: total triiodothyronine in nanomole/liter, rT3: reverse triiodothyronine in nanograms/milliliter., BMI: body mass index

DISCUSSION

In this unique prospective study including 286 children with newly diagnosed cancer, we were able to analyze the prevalence of thyroid dysfunction and the changes in thyroid hormone parameters during chemotherapy and its possible association with linear growth and BMI. The low prevalence and self-limiting nature of primary hypo- and hyperthyroidism, as well as changes in thyroid hormone parameters, observed in our study are reassuring. Therefore, our findings do not support routine screening of thyroid hormone parameters during treatment with currently used antineoplastic protocols. Although changes were seen in the individual thyroid parameters, such as TSH, FT4, T3 and rT3 concentrations, the prevalence of NTI as entity was low. An isolated elevated rT3 concentration or an isolated decline of FT4 of ≥20% three months after diagnosis was prevalent and seen in 46% and 28%, respectively. Although it is difficult to assess the effect of the different chemotherapeutic agents in multiagent chemotherapy, in multivariable logistic analysis no single agent could be directly related to an elevated rT3 or a decline of FT4 of ≥20%. In multivariable logistic analysis, younger age at diagnosis showed a borderline association with both elevated rT3 concentration and a ≥20% decline in FT4. The decline in FT4 might be explained by changes in parameters due to increasing age, especially since this change did not reverse after the end of cancer treatment.

We did not find an association with prolonged FT4 decline ≥20 % and linear growth or BMI in our cohort. This is in contrast to the findings of Van Iersel et al., who did find an association in children with central hypothyroidism between FT4 decline and weight gain after cranial irradiation in children with brain

tumors.[16] These different observations may be explained by the fact that the irradiated cohort of van Iersel truly had mild central hypothyroidism, while in the non-irradiated cohort described here, the decline in FT4 is a reflection of NTI and may be considered a physiological response.[26]

The association we observed between an elevated rT3 concentration and increased T3 concentration is remarkable, and may point toward recovery from illness, although it could also result from assay effects or other hormonal influences. [20,27] Importantly, alterations in total T3 concentrations do not necessarily reflect changes in free T3 concentrations. The increase in T3 concentration may still reflect NTI as it has been described that in this situation the body may increase conversion toward rT3 while still maintaining or even elevating T3 in some tissues. Typically, however, an increase in rT3 is accompanied by a decrease in T3, reflecting altered deiodinase activity and for which reason NTI is also referred to as the low T3 syndrome.[20,27]

Unfortunately, there is no internationally accepted definition of NTI which explains the broad range in prevalence described in literature of 42-100%. [9,11,13,14] In studies defining NTI with low total T4 and/or T3, the higher reported prevalence in patients treated with chemotherapy may not reflect true NTI but could instead be explained by thyroid-binding globulin deficiency, which can be seen during treatment with asparaginase. [9,13,28]

Corticosteroids affect thyroid hormone concentrations in several ways: by suppression of TSH, by decreasing the conversion of T4 to T3 and by increasing the conversion of T4 to rT3, changes that are also observed in NTI.[29] In our study, corticosteroids were used in 83% of children. Despite this high use of corticosteroids, the prevalence of NTI was low and an isolated elevated rT3 could not be related to the use of corticosteroids.

The low prevalence of NTI in our study may be explained to the strict criteria we used with non-elevated TSH, low T3 and a high rT3 concentration. A less strict approach could be to evaluate NTI by analyzing the T3/rT3 ratio (which is low in case of NTI because of the decreased conversion of T4 to T3 and increased conversion of T4 to rT3). However, no significant association was found between T3/rT3 ratio and changes in height SDS or weight SDS over time. The borderline significance of the T3/rT3 ratio and weight SDS over time (p=0.051) suggests that a small time-dependent effect cannot be ruled out. Interpretation of this analysis should be made with caution given the small number of children with available post-treatment T3/rT3 ratio measurements (n=51).

Because thyroid hormones are essential for daily quality of life, normal growth and neurocognitive development of children, we were especially worried about the presence of NTI or a decline of FT4 ≥20% in children treated for leukemia with prolonged treatment protocols during 1 to 2 years. In children with leukemia thyroid hormone concentrations were only slightly different at two timepoints: TSH was higher in children with leukemia at diagnosis (2.78 versus 1.81 mIU/L in children without leukemia) and FT4 concentration was slightly lower three months after diagnosis (14 versus 15 pmol/L in children without leukemia), which we do not deem clinically relevant. At all other timepoints, thyroid hormone concentrations were similar in children with or without leukemia. The BMI change in children with leukemia we found has been described before and is a well-known complication during treatment and not thyroid hormone related.[30–32]

Our study is unique as it represents the first large prospective study with longitudinal follow-up evaluating thyroid function during antineoplastic therapy in children. To date, in literature, thyroid function during cancer treatment has been evaluated in only 91 children [9–14]. Furthermore, by including rT3 measurements, we were able to distinguish central hypothyroidism from NTI. The availability of anthropometric data enabled us to evaluate the clinical consequences of thyroid dysfunction and alterations in thyroid function parameters.

Of course, our study also had several limitations. In our study we had loss to follow-up at the end of therapy and three months posttherapy, mainly due to continuation of care in shared care centers. Another limitation is that our findings may not be generalizable to all future children with cancer, as we focused on children with leukemia, lymphoma, sarcoma, and brain tumors. In addition, treatment protocols are evolving rapidly over time, which may result in different effects on thyroid hormone parameters. An important limitation regarding the growth data is the lack of information on pubertal stage. Some children had likely already reached their final height at the start of therapy. Given this limitation, we chose to evaluate height SDS only in children who were younger than 16 years at diagnosis (n = 240). Repeating the height SDS analysis in children younger than 14 years (n= 204) yielded similar results.

CONCLUSION

Children with cancer receiving antineoplastic therapy have a low risk of developing primary thyroid dysfunction, or anti-TPO antibodies during or shortly after antineoplastic therapy. Although Changes in thyroid hormones are common during cancer treatment, a prolonged FT4 decline ≥20% nor an elevated rT3 could be associated with altered linear height SDS or BMI SDS. Based on this study, there is no indication for routine screening of thyroid hormone parameters during cancer treatment in childhood with current treatment protocols. Of course, this recommendation may need to be adjusted when new treatments are introduced that could influence thyroid function during therapy, such as immunotherapy. Given the largely transient nature of the changes in thyroid

hormone concentrations, a watchful waiting approach is justified in cases of mild thyroid function abnormalities.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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