Thyroid problems in pediatric oncology: damage, prevention and consequences
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Chapter 3

Endocrine late effects after multi-modality treatment, including $^{131}$I-MIBG, for neuroblastoma

HM van Santen, J de Kraker, T Vulsma

Submitted for publication
Abstract

BACKGROUND Endocrine late effects of treatment for neuroblastoma (NB) are important as the hormones produced by this system are necessary for growth and development into adolescence. Thyroid dysfunction was reported after $^{131}$I-MIBG-treatment. Since these patients are given multi-modality treatment, our aim was to evaluate all endocrine functions.

METHODS Twenty-five NB survivors off therapy for a mean period of 6.2 years (range 1.3-11.1), were evaluated. Mean age was 8.5 years (range 2.2-14.7). All patients had received $^{131}$I-MIBG, 16 chemotherapy, and 16 surgery, of who 13 adrenal surgery, and 3 laminectomy. History, physical examination, cholesterol profile and determinants of the thyrotropic, corticotropic, gonadotropic, lactotropic and somatotropic function were obtained. TRH-testing was performed in 15 and thyroid ultrasound imaging in 21 patients. Patients using thyroxine were evaluated twice: before and after a 3-month period of thyroxine withdrawal.

RESULTS Fourteen patients (56 %) had a permanent thyrotropin elevation, 9 received thyroxine supplementation. A small thyroid volume was found in 2 patients. Six patients had thyroid nodules or cysts. Two boys showed hypergonadotropic hypogonadism, after treatment with alkylating agents. IGF-1 levels were all within the normal range, however growth was retarded in 39 % of children. Mean Target Height Standard Deviation Score of patients with thyrotropin elevation was lower than those without (p=0.019).

CONCLUSION Children treated for NB with $^{131}$I-MIBG, chemotherapy and surgery are at risk for developing irreversible thyroid function loss, thyroid nodules, hypergonadotropic hypogonadism, and growth retardation. During follow-up of children with NB, special attention should be paid to their endocrine state.
Introduction

Neuroblastoma (NB) is one of the most challenging tumors for pediatric oncologists. Some have a favorable outcome, but the prognosis for children with stage IV NB and > 1 year of age is still only around 30-40% \(^1\). In our setting, multi-modality treatment, including \(^{131}\)I-MIBG, surgery, different kinds of cytotoxic agents, and bone marrow transplantation is necessary to cure such a patient.

For surviving patients who have been treated with cytotoxic drugs or irradiation, it is important that attention is paid to the possible late effects of treatment. In this paper, we focus on the endocrine late effects of treatment. Because the integrity of the endocrine system is essential for growth and development, especially in young children, it is important that pediatric oncologists and pediatric endocrinologists improve their detection strategies and ways of prevention of endocrine adverse events. For this, we first need to know the incidence figures of endocrine adverse events in the NB-patients. In a previous study we have demonstrated that after treatment with the radionuclide \(^{131}\)I-MIBG, a permanently elevated plasma thyrotropin (TSH) concentration (TE) was seen in 56% of survivors of NB, despite thyroid protection with potassium iodide (KI) \(^2\). The thyroid function is especially important in this patient group because of their young age \(^3\), making them vulnerable to disturbances of growth and development.

Next to the function, also the structure of the thyroid can be damaged by irradiation \(^4\). The young age \(^6\) as well as the fact of having a NB \(^8\) can both be considered risk factors for radiation damage.

It is unknown, however, whether the reported thyroid damage is transient or permanent. In case of permanent TE, it is of interest to evaluate whether this state of (subclinical) hypothyroidism has any consequences for the patients, e.g. regarding growth or lipid profiles. Furthermore, it must be evaluated whether the radio-iodide exposure, in combination with TE in the years after \(^{131}\)I-MIBG treatment, also leads to the forming of proliferative structural abnormalities in the thyroid gland.

Not only the thyroid gland, but also other endocrine glands may be damaged due to one or more treatment modalities used in NB. For example, alkylating agents can cause gonadal damage \(^9\). Considering the primary localization of NB, often in the adrenal region, damage to the adrenal (cortex) function has to be considered.

To address these questions, survivors of NB treated in our center according to the
"MIBG-de-novo-protocol", were evaluated regarding their endocrine state.

**Patients and Methods**

Twenty-five survivors with histologically confirmed NB, stage II-III-IV-IVs according to the International Neuroblastoma Staging System (INSS), and treated in the period 1989-1999 according to our "MIBG-de-novo" protocol were evaluated. Out of the original 73 treated patients, of who 27 were still alive, 2 were lost to follow-up after moving abroad or to an unknown address.

The treatment protocol consisted of initial administration of $^{131}$I-MIBG (3.7-7.4 GBq). For stage II, III and IVs (n=12), this treatment was followed by chemotherapy if the response to $^{131}$I-MIBG appeared to be insufficient: 10 patients received $^{131}$I-MIBG only, and in two it was followed by 'VECI'-courses (vincristine, etoposide, carboplatin and ifosfamide). In stage IV patients, $^{131}$I-MIBG treatment was followed by surgery,'VECI'-courses, and high dose carboplatin and melphalan with autologous bone marrow transplantation.

To protect the thyroid from radiation by $^{123}$I$^-$ and $^{131}$I$^-$ during radio-MIBG administration, 23 patients received 100 mg KI orally per day, starting the day before radio-MIBG administration. This was administered for 3 days in case of (diagnostic) $^{123}$I-MIBG and for 14 days in case of treatment with (therapeutic) $^{131}$I-MIBG. Two patients had received thyroid protection with KI, thyroxine ($T_4$)(37.5 μg/day) and methimazole (2.5 mg twice a day).

A complete history of the patient and family history for thyroid diseases, other endocrine disorders and familial hypercholesterolemia was taken. Physical examination was performed with special attention for the thyroid gland, growth determinants and pubertal stage.

Baseline endocrine examination consisted of the thyroid function determinants: TSH, total $T_4$, free $T_4$ ($FT_4$), tri-iodothyronine ($T_3$), thyroglobulin ($T_g$), thyroxine-binding globulin (TBG), anti-thyroidperoxidase (anti-TPO) antibodies, anti-thyroglobulin (anti-Tg) anti-bodies, and calcitonin; determinants of the adrenocortical function: fasting cortisol and fasting ACTH (all drawn between 9.00 AM and 10.30 AM); the gonadal function: lutropin (LH), follitropin (FSH) in combination with testosterone/ SHBG.
in case of a boy, or 17β-estradiol in case of a girl, prolactin (PRL) and insulin-like growth factor-1 (IGF-1). A general biochemical evaluation was performed including fasting glucose and total cholesterol profile (HDL-cholesterol, LDL-cholesterol, lipoprotein (a), apo-lipoprotein a and b, triglycerides and apo-E genotype), liver enzyme (ASAT), kidney function (creatinine, sodium and potassium), C-reactive protein (CRP), LDH and a full blood count.

TRH-testing was done in 15 patients by the administration of TRH, 10 mcg/kilogram body mass (maximum 200 mcg) intravenously. Subsequently, blood samples were taken 15, 30 and 60 minutes after TRH-administration, to determine the concentrations of TSH and PRL. A TRH test result was defined aberrant when baseline TSH was above 4.5 mU/L, peak TSH concentration increased to > 5 x the baseline value or the peak TSH concentration was found delayed (≥ 60 minutes after administration of TRH). 

In survivors using T₄ supplementation, medication was withdrawn after the first visit. After three months, patients were evaluated with a history of this 3-months period, full physical examination and a second TRH-stimulation-test with determination of fasting glucose and cholesterol-profiles. From all parents of these patients, informed consent was obtained.

Plasma T₄, T₃ and anti-Tg were measured by in-house radio-immunoassay methods; plasma FT₄ and TSH were measured by a time resolved fluoro-immunoassay (Delfia® Free T₄ and Delfia® hTSHWallas Oy, Tuurku, Finland); Tg was measured by an immuno-luminometric assay (II.A, Brahms®, Germany); anti-TPO anti-bodies by luminescence immunoassay (LIA, Brahms®, Germany) and TBG by radio-immuno assay (Eiken Chemical Co, Tokyo, Japan). Ultrasound imaging of the thyroid gland was made, using the Siemens Elegra, 13 MHz linear probe, for measurements of thyroid volume and detection of thyroid nodules (n=21). If a nodule was found suspicious, fine needle aspiration cytology (FNAC) was performed. Bone age was assessed according to Greulich and Pyle (n=16).

Statistical analysis was performed using Excel MSO and SPSS 11.5.1, Microsoft XP.
Results
Patients
At time of evaluation, the 25 patients (12 boys) were off therapy for a mean period of 6.2 years (range 1.3-11.1). Mean follow-up time after the first $^{131}$I-MIBG treatment was 7.5 years (range 1.4-11.9 yrs). Mean age at last follow-up was 8.5 years (range 2.2-14.7). Stage distribution was stage II: n=2, stage III: n=7, stage IV: n=13 and stage IVs: n=3. Mean number of treatments with $^{131}$I-MIBG per patient was 3 (range 1-7), with a mean cumulative dose per patient of 12.5 GBq $^{131}$I-MIBG (range 1.8-33).
In 15 patients chemotherapy was given with VECI, 13 patients also received high dose melphalan and carboplatin followed by autologous bone marrow transplantation. One girl had received treatment with actinomycin and carboplatin under suspicion of a Wilms tumor. Thirteen patients had adrenal surgery for a primary abdominal NB, and 2 had laminectomy for a dumbbell tumor.
Two survivors had recurrence of their NB at time of evaluation (3 and 4 years respectively after diagnosis) and had restarted $^{131}$I-MIBG treatment. Of these 2, who both did not survive the recurrence, the last available follow-up data of thyroid function and thyroid ultrasound imaging, before recurrence of disease, was used. Of 2 other survivors, only follow-up data on thyroid function, expressed as TSH and FT$_4$ measurements, were available for evaluation. One of these patients, who had been treated with laminectomy and twice with $^{131}$I-MIBG for a dumbbell NB, was diagnosed with B-cell leukemia, 5.9 years after the last radio-MIBG treatment.
Of the 21 other patients, one did not agree to the determination of fasting cholesterol and bone-age, and another answered a questionnaire and gave permission to retrieve the data of thyroid function from another center. One survivor using T$_4$ refused a second TRH-test after stopping for 3 months but agreed with the determination of baseline determinants.

Thyroid Function
Of 25 patients, 17 (68 %) had "ever" TE, and 14 had TE at the last evaluation (56 %), of which 9 patients used T$_4$ supplementation. Of the 3 survivors with transient TE, maximum TSH at time of TE ranged from 5.2-6.2 mU/1. The mean TSH of patients at follow-up (after withdrawal of T$_4$ for 3 months or at last evaluation) was 6.3 mU/
L (range 1.1-28.5). Free T₄ levels were all within the normal range, mean Tg was 24 pmol/L (range 2-55).

Anti-TPO concentrations, measured in 24 patients, were negative (≤ 30 kU/L) in 18 survivors, weakly positive (40-50 kU/L) in 4 (1 TE and 1 transient TE), and positive in 2 survivors (110-120 kU/L, 1 with TE, and 1 without TE). Anti-Tg was absent in all 24. In 15 patients TRH-tests were performed, in 8 children who received no T₄ supplementation, and in 7 after a 3-month T₄ withdrawal (figure 1). In all, mean TSH after 15 minutes declined from 7.25 (range 1.10-28.5) to 6.6 (range 1.1-26.3) mU/L.

After administration of TRH, in all but one patient, the highest peak of TSH was found after 30 minutes with a mean concentration of 43.55 mU/L (range 10.8-158), which was higher than 5 times the baseline value in 14 patients. For the 7 patients on T₄ supplementation, the mean plasma TSH after stopping T₄ was 11.6 mU/L (6.0-28.5), with a peak TSH after 30 minutes to a mean concentration of 66.2 mU/L (29.8-158.0).

With T₄ supplementation, mean TSH at baseline was 3.4 mU/L (1.5-5.4) with a peak TSH at 30 minutes of 18.4 mU/L (4.8-30.5), indicating lowered but not suppressed levels of TSH. In 15 children calcitonin was measured, showing normal levels in all.

Four children with TE had a positive family history for thyroid disease versus one child without TE. One mother had developed hypothyroidism of unknown cause in

![Figure 1. TRH-stimulation tests after treatment for NB, including ¹³¹I-MIBG](image)

Stimulation tests performed in 15 patients during follow-up after treatment for NB. At time t=0, TRH 10 μg/kg body mass (max 200 μg) was given iv as bolus. Seven patients, who used T₄ supplementation, were withdrawn of T₄ for three months (dotted lines), 8 patients did not receive T₄ supplementation (solid lines). NB=neuroblastoma
the years after the $^{131}$I-MIBG treatment of her child (during which she had taken KI-prophylaxis 200 mg daily).

**Thyroid ultrasound imaging**

In 21 survivors, ultrasound imaging of the thyroid gland was performed. In 2, thyroid volume was small for age and in 5 survivors (24%) 1 or more nodules (range 1 to 4) were found, ranging in size from 1 to 10 mm. In 2 survivors, FNAC was performed, showing dys- and hyperplastic thyroid cells, but no malignant cells. In 1 patient, several small thyroid cysts were found.

As shown in table 1, of 21 survivors in whom both ultrasound and thyroid function was measured, 3 patients (14%) had TE together with thyroid nodules, 2 (9.5%) survivors just had nodules, 1 had thyroid cysts (5%) and 9 survivors (42.9%) had TE only. Five survivors (24%) had a normal thyroid function and no abnormalities at thyroid ultrasound imaging.

Number of $^{131}$I-MIBG scans or uptake of radio-iodide in the thyroid gland were not significantly different between survivors with or without TE or with thyroid nodules. Of the 11 patients without TE, 2 had received thyroid protection with $T_4$, KI and methimazole.

**Gonadal function**

Of the girls, whose gonadal function was tested (n = 8), 4 were aged below 8 years. None of them had any sign of puberty and their plasma concentrations of LH and FSH were within pre-pubertal values. Of the 4 girls older than or equal to 8 years; 1 had stage M1, 2 stage M2, 1 stage M3. Concentrations of LH were all < 0.1 U/L, mean FSH was 2.12 U/L and 17-β-estradiol levels were below the detection limit, consistent with a prepubertal state.

In table 2, pubertal stages of the boys older than 6 years of age (n = 11) are shown. Of the 3 boys examined below the age of 9, none had any signs of puberty. One boy had bilateral cryptorchidism. Of one pre-pubertal boy, the testicular vessels had been situated over the ventral side of the NB, which were removed together with the tumor.

Of the 6 boys ≥ 9 years; 3 had stage PI, 1 P3 and 2 had P4. Two boys with pre-pubertal testicular volume (< 4 cc) had elevated LH and FSH levels indicating
Table 1. Plasma TSH elevations and/or presence of thyroid nodules after treatment with $^{131}$I-MIBG for NB

<table>
<thead>
<tr>
<th>Patient- ID</th>
<th>Gender</th>
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<th>T4 supplementation</th>
<th>number of thyroid nodules</th>
<th>TE + thyroid nodules</th>
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<td>M</td>
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</tr>
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<td>F</td>
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<td>yes</td>
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</tr>
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<td>F</td>
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<td>no</td>
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<td>F</td>
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<th>9/25</th>
<th>6/21</th>
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<td>%</td>
<td>56</td>
<td>36</td>
<td>29</td>
<td>14</td>
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NB=neuroblastoma, TE=TSH elevation, Gender: M=male, F=female, n.a. =not assessed

Hypergonadotropic hypogonadism. In one boy with asymmetrical prepubertal testes, the NB for which $^{131}$I-MIBG had been given was originated in the left testis. In another boy, orchidopexy of the left testis had been performed for cryptorchidism.

Adreno-corticotrophic function

In 13 patients, the primary tumor was situated in the adrenal gland and required adrenalectomy. In these patients, no signs of hypocortisolism were found in the history or at physical examination. Mean morning fasting cortisol concentration in tested survivors was 325 nmol/L (range 180-550) with mean concentration of ACTH of 55 ng/L (range 14-155). In patients with an adrenalectomy in the history, significantly lower mean cortisol concentrations were found (292 versus 397 nmol/L, p=0.026).
Table 2. Gonadal development of boys > 6 years of age after treatment for NB

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>Pubertal stage</th>
<th>Testicular volume</th>
<th>LH (U/L)</th>
<th>FSH (U/L)</th>
<th>Testosterone (nmol/L)</th>
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<td></td>
<td></td>
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<td>Testicular volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R (ml)</td>
<td>L (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>P3 G2 A2</td>
<td>2</td>
<td>4</td>
<td>3</td>
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<tr>
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<td>8.7</td>
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<td>np</td>
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<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>10.6</td>
<td>P1 G3 A1</td>
<td>*</td>
<td>3</td>
<td>1</td>
<td>&lt;1.0</td>
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<tr>
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<td>10.3</td>
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<td></td>
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</tr>
</tbody>
</table>

R=r=right testis, L=l=left testis, np= non palpable, n.a. = not assessed, NB=neuroblastoma, * NB originally located in the left testes, ** answered to questionnaire, no physical examination performed, *** agreed to blood investigation only, no physical examination performed, **** testicular vessels situated on primary NB.

Growth

Target Height Standard Deviation Score for mid-parental height (THSDS) was calculated for 18 patients. Mean THSDS was -1.4 (range -4.5 to +1.5). Mean delay in bone age was 5 months (range -17 to +36). Mean concentration of IGF-1, measured in 17 patients, was 36 nmol/l. (range 13 to 116). All concentrations of IGF-1 were within the normal range adjusted for age. Growth was affected in 39% of the children, expressed as height < -1.3 THDS.

Significant difference in THSDS, but not for bone age, was found for patients with T4 compared to those without T4; mean -1.89 and -0.38 respectively (p=0.019). Also the difference in height SDS between patients already on T4 treatment (n=8) and the others was significant; THSDS -2.68 and -0.35 respectively (p=0.001). However, of the 8 children known with T4 supplementation, other factors that could also have attributed to growth retardation were present in 5 children; 3 had tubulopathy (mean THSDS -2.1), in 1 a lamincetomy had been performed for dumbbell NB (THSDS -1.0) and 1 boy (THSDS -3.5) was recently diagnosed with the LEOPARD syndrome (proven germ line PTPN11 mutation) which is associated with a short stature (JHM Merks. Thesis 2004). In the patients without T4 supplementation, 1 girl with a THSDS of -3.0 also had been treated with lamincetomy (dumbbell neuroblastoma).
Cholesterol profiles
In 5 patients, a family member with hypercholesterolemia was reported. In 2 patients, 1 with transient TE and 1 with a normal TSH, slightly elevated total cholesterol concentrations were found, in 1 with elevated LDL. No differences were seen between the children with or without $T_4$ supplementation or with or without TE (with $T_4$ supplementation). No changes were seen in cholesterol profiles after three months of $T_4$ withdrawal.

Discussion
In this cohort of patients surviving neuroblastoma in stages II-III-IV and IVs, 20 of 25 children (80%) developed endocrine late effects, involving the thyroid gland or the gonads.
In 14 patients (56%) thyroid dysfunction was present, of whom 9 used $T_4$ supplementation. Due to the fact that these children have not only been treated with radiation therapy but also with extensive chemotherapy, it must be considered that, next to thyroid dysfunction, also pituitary or hypothalamic dysfunction may be present. For this reason, TRH-testing was performed, to gather more detailed information about the thyroid axis. We found no evidence for pituitary or hypothalamic thyroid dysfunction. Next to thyroidal hypothyroidism, also in 6 of 21 children (29%) in which ultrasound imaging was performed, thyroid nodules or cysts were found.

As stated briefly in the introduction, the protection of the thyroid gland against radio-iodide in this group of patients is of special importance. NB manifests mainly in children below the age of 4 years (30% below the age of 1). At this age, an adequate thyroid hormone state is essential for optimal growth and development into adulthood. Furthermore, it has been demonstrated that thyroid tissue of young children is more radio-sensitive than that of adults. It has been extensively reported that irradiation of the thyroid gland with $^{131}I$ or with external beam can cause benign and malignant thyroid lesions, with a risk to develop thyroid carcinoma already from a radiation dose of 0.1 Gy. Of all children with childhood malignancies, children with NB have, for unknown reasons, even an increased risk to develop thyroid damage after radiation exposure when compared to children with other malignancies.
The time needed to develop thyroid tumors can be quite long \(5,12\), implying the need for prolonged follow-up.

In a survey performed in 1995 and 1996, the reported incidence of thyroid nodules in 937 healthy school children in The Netherlands was found to be 1.2 % \(13\), which would imply that the incidence that we found in children treated with \(^{131}\text{I}-\text{MIBG}\) is very high. An increased incidence of thyroid nodules up to 65 % has been described after X-irradiation for childhood cancer, which was related to young age, the length of follow-up and the duration of TE \(14,15\). However, before we may draw the same conclusion from treatment with \(^{131}\text{I}-\text{MIBG}\), it must first be defined what the normal incidence of thyroid nodules in healthy children of this age group is, at this point in time. The sensitivity of ultrasound imaging has substantially improved over the past 10 years and nodules are detected more easily nowadays and the high incidence may be explained by increased surveillance. Also, the possibility that children with NB may have more thyroid nodules than other children must be considered. Support for this hypothesis is the fact that it has been reported that children with NB have more radiosusceptible thyroid glands than children with other malignancies \(8\). An argument against this hypothesis, though, is the fact that we did not detect any thyroid nodule in 14 ultrasound images that were made in children with NB, right before or right after \(^{131}\text{I}-\text{MIBG}\) treatment, who were included in a new prospective study \(16\). However, the mean age of the cohort in this study is significantly younger (mean age 2.8 years (range 0.04-10.7)). For this reason, we are currently conducting ultrasound images of the thyroid gland in survivors of NB who have not been treated with \(^{131}\text{I}-\text{MIBG}\). Currently, we have screened 7 such children with a history of NB, a mean follow-up of 9 years after diagnosis (range 1.0 to 16.0) and a mean age of 11 years at follow-up (range 1.6 to 17.1). In these 7 children not any thyroid nodule has been found (data not shown). This indicates that the increase in occurrence of thyroid nodules cannot be attributed to the improvements in detection technique or the history of NB. The damage is most likely caused by radiation, as a consequence of \(^{131}\text{I}-\text{MIBG}\)-treatment, and other possibilities that may be considered are treatment with chemotherapy or even KI. The clinical consequences of this finding will have to be determined in time.

Regarding the consequences of thyroid function, no effects of hypothyroidism on
cholesterol level was found, and no clinical signs of hypothyroidism were reported in the 3-months of $T_4$ withdrawal. With this in mind, it can be discussed whether these children should be treated with $T_4$ supplementation. There are two different treatment goals that can be aimed for.

The first goal is to ensure euthyroidism in the developing child. An elevated TSH in combination with FT$_4$ levels in the normal range and no clinical signs is often described as subclinical hypothyroidism (SH), a term which implies that there are no clinical consequences present or to be expected. However, much controversy exists on this subject and the subsequent question whether to treat or not to treat SH $^{17,18}$. Possible consequences of SH for adults may be cardiac dysfunction, elevations of total and LDL-cholesterol and progression to clinical hypothyroidism. In a recent scientific review, for adults, only strong evidence was found for progression to overt hypothyroidism $^{19}$. For benefits of treatment for SH, evidence was provided by a RCT (in adults), which demonstrated that $T_4$-treatment improves both the atherogenic lipoprotein profile and intima-media thickening $^{20}$. We believe that for developing children and for adults, SH must be considered as thyroidal hypothyroidism in which the pituitary elevates its TSH in response to a too low concentration of FT$_4$. For young children, this implies that SH may have clinical consequences in the long run, such as growth and even mental retardation in the very young and cardiovascular complications. For this reason, we prefer to replace the term ‘SH’ by ‘TSH elevation’ (TE).

The second treatment goal, which is also still controversial, can be to reduce the number of radiation-induced thyroid neoplasms by lowering or suppressing the concentration of TSH. In humans, several prospective trials have demonstrated that $T_4$ supplementation reduces the occurrence of (spontaneous and radiation-induced) thyroid nodules $^{21-23}$. However, it has never been proven, in humans, that $T_4$-suppression therapy reduces the occurrence of thyroid carcinoma. Furthermore, continuous TSH suppression (subclinical hyperthyroidism) might have negative effects such as an increased bone mineral density due to an increased bone turn-over. In contrast to TSH suppression, it has been demonstrated that a prolonged TSH elevation may increase the occurrence of carcinoma after irradiation $^{24-26}$. For these reasons, it is important that, in patients who have been exposed to radiation of the thyroid, plasma TSH is
monitored and if found elevated, it should be adequately treated, but not suppressed. Considering all the above, our current advice is to monitor the plasma concentration of TSH and FT$_4$ every 6 months in children with NB after $^{131}$I-MIBG treatment. We recommend T$_4$ supplementation to normalize plasma TSH concentrations, when the plasma concentration of TSH is once $> 10$ mU/L or repeatedly $> 6.0$ mU/L. Because the implication of the finding of thyroid nodules is unsure, we recommend that these patients are followed for life in prospective trials to determine the risk of developing thyroid malignancies.

To prevent thyroid irradiation during $^{131}$I-MIBG-treatment we have introduced an extended way of thyroid protection, using not only potassium iodide, but also methimazole and T$_4$ (dilute, block and replace: DBR) $^{16}$. This was also used in 2 patients of this cohort, who indeed both did not develop thyroid dysfunction. Although the incidence of TE is substantially diminished from 56 to 14% with DBR $^{16}$, we have still not realized a 100% protection.

Next to damage to the thyroid gland, we found evidence for hypergonadotropic hypogonadism in two boys in the pubertal age, most probably due to treatment with the alkylating agents (ifosfamide, melphalan and busulphan) $^{9,27}$. The testosterone deficiency can be adequately treated with testosterone supplementation, however fertility will not be likely. Furthermore, in two other boys, the primary NB was located in the testicular region, and may have caused testicular damage. Considering the young age of most survivors, it can be expected that in the following years in more children damage to the gonads will become evident, indicating the need to screen for hypergonadotropic hypogonadism.

Significantly lower cortisol concentrations were found in patients after adrenalectomy. This finding, however, does not seem to reflect a clinically relevant problem.

Growth was affected in 39% of the children. In children with TE the mean THSDS was even impaired to $-2.68$ SD, which implies significant growth retardation. GH stimulation-tests were not performed, but the fact that plasma IGF-1 concentrations were all within the normal range, there was no delay in bone age and that these patients did not receive cranial irradiation makes central GH deficiency or secretory dysfunction unlikely. Many different factors were present that may have contributed to the growth
retardation, such as a diminished thyroid and kidney function, poor clinical condition for several years, and, in one, growth retardation based on an associated syndrome. Optimizing $T_{4}$ concentrations and all other metabolic parameters may help to normalize their THSDS.

In conclusion, children with NB, treated with $^{131}$I-MIBG, chemotherapy and surgery are at risk for developing irreversible hypothyroidism, thyroid nodules, hypogonadism and growth retardation. These findings imply that during follow-up of children with NB, special attention should be paid to their endocrine state.

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