Thyroid problems in pediatric oncology: damage, prevention and consequences
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Citation for published version (APA):

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High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during $^{131}$I-meta-iodobenzylguanidine treatment in children with neuroblastoma.

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Cancer, 2002, April 1, Vol 94 (7); 2081-2089
Abstract

BACKGROUND. Treatment modalities like targeted radiotherapy with $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-MIBG) improve survival rates after neuroblastoma (NB). Radiation to the thyroid gland can lead to hypothyroidism and even malignancy. Because hypothyroidism after $^{131}$I-MIBG treatment was reported, the current potassium iodide (KI) prophylaxis against thyroidal radiation damage was evaluated.

METHODS. The incidence, pathogenesis and consequences of thyroid dysfunction among 42 NB patients treated with $^{131}$I-MIBG were evaluated retrospectively. Efficacy of KI prophylaxis was established by measuring thyroidal radioiodide uptake. Thyroid damage was expressed as thyrotropin elevation (TE, plasma concentration of thyroid stimulating hormone $\geq 4.5 \text{ mU} / \text{L}$).

RESULTS. The mean follow-up was 2.3 yrs (range 0.1-8.5). The mean number of treatments with $^{131}$I-MIBG was 3.3. Of 428 scintigrams, uptake of $^{131}$I in the thyroid was visible in 92 (21.5%). Twenty-two patients (52.4%) presented TE after a mean period of 1.4 years (range 0.1 – 5.8). Clinical signs of hypothyroidism were not observed. Eight patients received suppletion therapy with thyroxine. Thyrotropin elevation was transient in four patients. Of 25 survivors, with a mean follow-up of 3.5 years, 16 (64%) developed TE. No correlation was found between TE and thyroid visualization after $^{131}$I-MIBG administration or number of treatments. No abnormalities were seen by ultrasound imaging of the thyroid.

CONCLUSIONS. Occurrence of thyroid dysfunction after treatment with $^{131}$I-MIBG for NB is high, in spite of KI prophylaxis. Close follow-up of thyroid function and structure is required in patients treated with $^{131}$I-MIBG. New ways of protecting the thyroid during exposure to radio-iodine should be developed.
Introduction

A consequence of the gradually improving survival rates in pediatric oncology is an increasing occurrence of long term adverse effects. This increases the need for preventive action during oncologic treatment, especially when given in childhood. Neuroblastoma (NB), a malignant embryonal tumor of the peripheral sympathetic nervous system, is one of the most common solid tumors of infancy. Thanks to the rising knowledge of treatment modalities, prognosis, although still disappointing, keeps improving. Treatment for NB depends on patient age and tumor stage at diagnosis. Treatment varies from wait and see via surgery alone to an intensive treatment with chemotherapy, sometimes followed by autologous stem cell reinfusion. New treatment modalities like targeted radiotherapy with $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) are under investigation. Due to its biochemical similarity to norepinephrine, MIBG is selectively concentrated by adrenergic tissue, including NB. It has been shown that MIBG labeled with $^{123}$I or $^{131}$I is very sensitive and specific in the diagnostic work up. In treatment of NB, high dose $^{131}$I-MIBG can be very effective with moderate side effects. In order to reduce tumor size and facilitate surgery, since 1989 all patients with NB inoperable Evans Stage III, Stage IV and some patients with Stage IVS in Emma Children's Hospital, Academic Medical Center, The Netherlands are treated up front by $^{131}$I-MIBG. The total radioactivity of therapeutic doses of $^{131}$I-MIBG is almost entirely excreted in urine after being metabolized to a minor degree. But, due to instability of the $^{131}$I-MIBG as well as metabolism by the liver, free $^{131}$I is formed.

As thyroid hormone ($T_4$) is essential for growth, development and the metabolic activity of almost all tissues of the body, prevention of thyroid damage is of importance especially in children. In the first years of life $T_4$ is essential for optimal brain development. To produce $T_3$, the thyroid gland actively accumulates iodine. As a consequence, the thyroid will also concentrate radioiodine derived from $^{131}$I-MIBG. Effects of radioiodine on the thyroid can vary from hypothyroidism, thyroiditis, thyroid nodules, and single follicular adenomas to malignancies. Although doses of radiation to the thyroid during treatment with $^{131}$I-MIBG are much lower compared to external radiation, it is important to realize that the risk of secondary malignancies developing after a prolonged period of thyrotropin (TSH) elevation (TE) after external
radiation, due to a continuous elevated metabolic activity and mitotic activity of the
damaged thyroid tissue, has been suggested in literature. Also, an increased risk
of thyroid damage after radiation in children compared to adults has been described
These facts emphasize the importance of proper thyroid prophylaxis during
diagnosics and/or treatment with I\textsuperscript{131}I/ I\textsuperscript{123}I-MIBG in children with NB. To prevent
uptake of radioiodide in the thyroid, the patient is routinely treated with excessive
amounts of stable iodide (100 mg potassium iodide daily, during the diagnostics with
I\textsuperscript{123}I-MIBG for 3 days and during treatment with I\textsuperscript{131}I-MIBG for 14 days).

The protection of the thyroid with KI is based first on dilution and second on a
downregulation of the sodium-iodide-symentor, both resulting in a lower uptake of
radio-iodide. In spite of this prophylaxis with KI, a variable percentage of children were reported
to develop thyroid dysfunction after treatment with I\textsuperscript{131}I-MIBG, although without
indicating the underlying causes or consequences. To investigate the incidence,
severity and possible pathogenesis of this primary hypothyroidism after diagnostics
and treatment with I\textsuperscript{123}I-/ I\textsuperscript{131}I-MIBG for NB, we performed a retrospective analysis of
a Dutch population of NB patients.

**Materials and methods**

In the period 1989-1999, 73 patients with histologically confirmed inoperable Stage
III, Stage IV or Stage IVS NB as staged by Evans and International Neuroblastoma
Staging System (INSS) staging criteria had been treated with I\textsuperscript{131}I-MIBG in Emma
Children's Hospital, the Netherlands. To investigate the total incidence of thyroid
function after treatment with I\textsuperscript{131}I-MIBG, all patients whose thyroid function were
known, whether deceased or survivor, were included. At time of evaluation, 40 of 73
patients had died. In 17 deceased patients, thyroid functions could be established
afterwards in stored frozen plasma samples. Of 33 surviving children, the thyroid
function of 6 patients could not be retrieved because of change in address. Two
surviving patients were excluded because a different kind of prophylaxis for the thyroid
than KI was used. In total 42 patients could be evaluated, of which 25 were still
survivors in December 1999 (Table 1).
In all 42 patients that could be included in the current study, $^{123}$I-MIBG had been used for diagnostic purposes. After confirming the diagnosis of neuroblastoma Stage III or IV, an initial treatment of at least two therapeutic doses of $^{131}$I-MIBG, administered by a 4 hour infusion, with 7.4 GBq and 3.7 GBq, respectively, with an interval of four weeks was started. If surgery was feasible at this point it was performed. Otherwise $^{131}$I-MIBG-treatment was continued for one or more courses. After surgery, treatment consisted of four courses of vincristin, VP16, carboplatin and ifosfamide. For Stage IV patients this was followed by high dose melphalan and carboplatin supported by autologous bone marrow transplantation or peripheral blood stem cell-reinfusion. None of the patients received total body irradiation.

To protect the thyroid from radiation, patients received 100 mg KI for 3 days during use of (diagnostic)$^{123}$I-MIBG and for 14 days during treatment with (therapeutic)$^{131}$I-MIBG. Plasma TSH levels had been measured to screen for thyroid dysfunction. Thyrotropin elevation was defined as TSH $\geq$ 4.5 mU/L. Total $T_4$ and, if possible, free $T_4$ were also measured. Of surviving children, thyroid function was evaluated by extension with $T_4$, thyroxin binding globulin, thyroglobulin (by radioimmunoassay and immunoenzymometric assay), and thyroid antibodies (antithyroglobulin and anti-thyroperoxidase). Of the six surviving patients with TE, sonographic images of the gland were performed. In three patients thyrotropin releasing hormone (TRH)-tests were done.

Patient characteristics were collected. Special attention was given to demographics, endocrine determinants (height, weight, symptoms of thyroidal dysfunction, pubertal
stage), number of courses and dosage of $^{125}\text{I}/^{131}\text{I}$-MIBG received, dose and duration of KI prophylaxis, and the use of gastrointestinal feeding tubes or occurrence of vomiting during prophylaxis. Radionuclide imaging for diagnostic purposes was performed 24 h after injection of $^{125}\text{I}$ or $^{131}\text{I}$-MIBG. Posttherapeutic imaging was performed three days and one week after high dose $^{131}\text{I}$-MIBG. All available $^{125}\text{I}$ and $^{131}\text{I}$-MIBG scintigraphic studies were re-examined by two experienced nuclear medicine physicians (BvE & CN). Thyroid uptake of radioactive iodide was assessed on computer display if available. Studies performed before 1995 were only available on hard copy. Radionuclide uptake in the thyroid gland was semiquantitatively scored using a 3 point grading scale: 0 = no thyroid image detectable, 1 = weak image of the thyroid, 2 = clear image of the thyroid (Figure 1). When it was not

![Figure 1. Uptake of $^{131}\text{I}$ in the thyroid during $^{131}\text{I}$-MIBG](image)

Meta-iodobenzylguanidine (MIBG) scintigram with use of $^{131}\text{I}$-MIBG. On the right side: adequate blocking of uptake of $^{131}\text{I}$ of the thyroid, with no thyroid visible. On the left side: a failing prophylaxis with a clear image of the thyroid gland (scored as 2).
possible to judge thyroidal uptake of $^{131}$I due to a missing image or uptake in cervical spine, bone metastases or briviaic catheter the score was set at 9.

Descriptive statistics were calculated with SPSS 8.0.2 (SPSS, Inc., AMC, Amsterdam) and MS Excel 97 (Microsoft) software.

Results

Plasma TSH and total T$_4$ concentrations of 42 patients (23 male and 19 female) could be evaluated. Clinical patient characteristics are summarized in Table 3. The average age at time of diagnosis of the 42 included patients was 2.9 yrs (range, 0.1 - 17.9). Mean follow-up of all included patients was 2.3 yrs (range, 0.1-8.5 yrs). The average number of $^{131}$I-MIBG courses was 3.3 per patient. In total, 428 MIBG-radio-nuclide images were re-examined, of which 183 were made after diagnostic $^{123}$I-MIBG, 28 after a diagnostic dose of $^{131}$I-MIBG, and 217 after a therapeutic dose of $^{131}$I-MIBG.

No uptake (0) of radioactive iodine in the thyroid was seen in 295 studies, weak uptake (1) in 55, and clear uptake (2) in 37 studies. In 41 images it was not possible to judge uptake in the thyroid (9) because of interference by (bone) metastases or cervical tumor mass, because of the presence of a briviac catheter or port-a-cath, or the image was not retrievable. In total, in 92 radionuclide images (21.5 %) the patient's thyroid was visible (Figure 3). The thyroid was visible one or more times in a total of 35 patients.

Thyroid function (Table 2 and Figure 2).

In 52.4 % (22 patients) of the 42 NB patients whose thyroid function could be evaluated, T$_4$ developed within an average time of 1.4 years (range, 0.1-5.8 years) after the first treatment with $^{131}$I-MIBG. In 18 patients (42.9 %) T$_4$ was permanent. TRH-tests

<table>
<thead>
<tr>
<th>Table 2. Patients and TSH Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No TE</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td><strong>Non-survivors</strong></td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>42</td>
</tr>
</tbody>
</table>

TE: thyrotropin (TSH) elevation. T$_4$: is defined as TSH $\geq$ 4.5 mU/L, with a normal plasma T$_4$-concentration (for age-related normal values).
performed in three patients showed thyroidal hypothyroidism. The TE of four patients turned out to be transient (9.5\%). Average TSH value in all patients with TE was 11.0 mU/l (range, 4.5-59.2), compared to 1.92 mU/L (range, 0.6-3.8) in the group with repeatedly normal plasma TSH concentrations. Thyrotropin elevation was seen in 35.3\% (6 patients) of 17 deceased patients, compared to 64.0\% (16 patients) of 25 survivors. In both groups TE was transient in two patients.

All patients had $T_4$-values within age-related normal values. None of the patients showed clinical signs of hypothyroidism. Of 14 surviving patients with permanent TE, 7 were given thyroxine to normalize TSH values. Of the deceased patients with TE, one patient had received suppletion therapy. On ultrasound images made of the thyroid gland in six surviving patients with TE and thyroxine treatment, no abnormalities were found.

**Follow-up**

The average time-lag between the first $^{131}$I-MIBG treatment and TSH elevation in the permanent TSH-elevated group was 1.4 yrs (range, 0.1–5.8 years). In the transient group TSH levels were raised within one month and had all returned to normal within 0.8 years (range, 0.3-1.2 years). Mean time lag in the normal TSH group between the first course of $^{131}$I-MIBG and the TSH-measurement was 0.7 yrs (range, 0.1-2.9 years). The follow-up time for the deceased patients was 0.4 years (range, 0.1-1.3 years) compared to a follow-up of 3.5 years (range, 0.3-8.5 years) for the surviving patients. Longitudinal growth data were available for 23 patients. In 13 patients growth
The thyroid after MIBG for neuroblastoma

retardation was observed during NB-treatment. Seven patients, however, six with TE, did not return to their own growth percentile. Of the 23 patients, mean standard deviation scores (SDS) declined from −0.26 at diagnosis of NB to −0.67 SDS at follow-up. Looking at the difference in decline of mean SDS between the group of patients with TE compared to those patients without TE, the difference was −0.7 SD compared to 0.0 SD.

Age

Average age at the first treatment with 131I-MIBG of the TE group was 2.4 yrs (range, 0.1-9.3), compared with 3.7 years (range, 0.2-17.9) for the normal TSH group (Table 3). The four patients with transient TE were an average age of 2.7 years (range, 0.5-4.7). The average age of the deceased patients was 3.5 years, versus 2.6 years in the survivors. The youngest group was the group of survivors with TE, with an average age 2.1 years (range, 0.2-6.6 years). The group of deceased patients with normal TSH values were an average age of 3.9 yrs (range, 0.6-17.9 years). Age differences between groups were not statistically significant.

Table 3. Relation between TSH Elevation and Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>No TE (n=20)</th>
<th>TE (n=18)</th>
<th>Transient TE (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>3.7 (0.2-17.9)</td>
<td>2.4 (0.1-9.3)</td>
<td>2.7 (0.5-4.7)</td>
</tr>
<tr>
<td>Death rate (%/0)</td>
<td>55</td>
<td>22.2</td>
<td>50</td>
</tr>
<tr>
<td>Gender</td>
<td>10 m / 10 f</td>
<td>10 m / 8 f</td>
<td>3 m / 1 f</td>
</tr>
<tr>
<td>Neuroblastoma stage</td>
<td>3 at III, 15 at IV</td>
<td>5 at III, 11 at IV</td>
<td>2 at IV, 1 at</td>
</tr>
<tr>
<td>Vomiting (no.)</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Naso-gastric tube (no.)</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Number of 131I-MIBG</td>
<td>3.6 (range, 1.8)</td>
<td>3.4 (range, 1.7)</td>
<td>2.2 (range, 2-4)</td>
</tr>
<tr>
<td>Number of 131I-MIBG</td>
<td>2.6 (range, 0-6)</td>
<td>3.3 (range, 0-9)</td>
<td>4 (range, 0-4)</td>
</tr>
<tr>
<td>Months from 1st MIBG to TSH measurement</td>
<td>8 (range, 1-35)</td>
<td>17.3 (range, 0-70)</td>
<td>1 (range, 0-1)</td>
</tr>
<tr>
<td>Number VECI-courses</td>
<td>2.5 (range, 0-6)</td>
<td>2.5 (range, 1-6)</td>
<td>2.2 (range, 0-7)</td>
</tr>
<tr>
<td>Chemotherapy before MIBG</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ABMT</td>
<td>6</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1 (abdomen)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Toxicity (mx)</td>
<td>9 (nephro +)</td>
<td>9 (nephro +)</td>
<td>0</td>
</tr>
</tbody>
</table>

TSH: thyrotropin, TE: thyrotropin elevation; m: male, f: female, MIBG: meta-iodobenzylguanidine, VECI: vincristin, etoposide, carboplatin, and ifosfamide, ABMT: autologous bone marrow transplant. No significant differences were found in gender, number of treatments with 131I-MIBG or chemotherapy, or toxicity of treatment.
Neuroblastoma therapy (Table 3).
The 20 patients with normal TSH values had a mean of 3.6 $^{131}$I-MIBG courses (range, 1-8); the 18 patients with TE had a mean of 3.4 courses (range, 1-7). No differences were observed in adjuvant treatments, such as chemotherapy, external radiotherapy, autologous bone marrow transplantation, hyperbaric oxygen and vitamin A suppletion. Differences were also not found among stage of disease, naso-gastric tube feeding, or occurrence of vomiting during KI prophylaxis.

Radionuclide imaging (Figure 3).
In total 428 scintigrams were scored, in 92 (21.5%) of which the thyroid gland was visible. In 35 of 42 patients, the thyroid was visible in one or more $^{123}$I- or $^{131}$I-MIBG scintigrams. Sixteen patients (80%) without TE had visible uptake of radioactive iodide on one or more $^{123}$I or $^{131}$I images, compared to 16 (89%) with TE. No relation was found between numbers of scintigrams with visible thyroids and the occurrence of TE.

![Graph](image)

Figure 3. Scintigraphic assessment of iodine uptake in the thyroid after administration of $^{123}$I- and $^{131}$I during MIBG, in spite of KI prophylaxis.

Discussion
Potassium iodide has been widely used for protection of the thyroid against radionuclide exposure, including $^{131}$I-MIBG. Nevertheless, Picco reported 12 cases of primary hypothyroidism after treatment with $^{131}$I-MIBG for NB in a group of 14 surviving patients. Those children received KI prophylaxis from one week in advance of the $^{131}$I-MIBG treatment until seven days after. Conversely, Garaventa reported that
only 2 out of 31 children treated with $^{131}$I-MIBG needed thyroxine suppletion 30. During treatment with $^{131}$I-MIBG, approximately 2.5% of the radionuclide enters the circulation as $^{131}$I, mainly due to instability of the radiopharmaceutical but also due in small part to metabolism in the liver 12,33,34. The hazardous effects of $^{131}$I on the thyroid have been well described in literature. Moreover, in children with NB the thyroid function should especially be screened thoroughly after irradiation, since it has been stated that these children have an even higher susceptibility for secondary thyroid malignancies than those exposed to external irradiation for other childhood malignancies 35. The production and secretion of thyroid hormone is regulated at the central level (hypothalamus and pituitary gland) and at thyroidal level. In response to thyroid damage by internal or external radiation, the synthesis of thyroid hormone becomes distorted. Diminished thyroid hormone concentration in the circulation will increase TSH secretion in order to stimulate thyroid hormone production. Even thyroid hormone concentrations within the normal range may be too low for the individual patient. In these cases TSH will remain increased, until free thyroid hormone concentrations reach normal values and an equilibrium is established. This would mean that patients with TE are in fact (mildly) hypothyroid, also called subclinical hypothyroidism 26,29,36. Although indirect, plasma TSH concentration is the most sensitive test to establish thyroid damage. For that reason we use the term TSH elevation to express the occurrence and severity of thyroid damage after irradiation.

In this retrospective analysis of children with NB treated with $^{131}$I-MIBG, 52.4% of patients developed thyroid dysfunction in spite of KI prophylaxis. In the group of surviving children with a mean follow-up of 3.5 years, this percentage was as high as 64.0%. The average follow-up time of the deceased patients was shorter than that of the surviving children.

In 35 of 42 patients, the thyroid gland was visible on at least one MIBG scintigram in spite of KI prophylaxis. However, uptake of radioiodide in the thyroid as seen on a MIBG scan did not help to determine who was or was not at risk for thyroid dysfunction. The duration and/or intensity of radioiodide uptake might have differed between the groups. This could not be evaluated since all images were routinely taken on Days 3 and 7 after administration of the MIBG, and quantification of uptake was, retrospectively, not possible.
An obvious explanation for the failure of prophylaxis would be an insufficient intake of KI, due to its bad taste, vomiting or naso-gastric-tube feeding or an insufficient period in which the prophylaxis is given. However, we could not find any proof for an intake problems as cause for the occurrence of TR.

As described in the introduction, the protection of the thyroid gland by administration of high doses of KI is based on the saturation and extreme dilution of radioiodide. Such protection is also based on the intra-thyroidal regulatory system (the acute Wolff-Chaikoff effect and its escape-mechanism) depending on the concentration of dietary iodine. To produce thyroid hormone, the thyrocytes take up iodide via the sodium-iodide symporter (NIS). Once taken up, iodide is oxidized and bound to tyrosine residues in thyroglobulin. Increasing plasma iodide concentration will lead to higher uptake and incorporation into the thyroid gland (organification). At higher intracellular iodide concentration organification will be inhibited (Wolff-Chaikoff effect), resulting in a diminished $T_4$ production. Because the iodide transport into the cell is inhibited, the accumulation of iodinated compounds decreases and the gland escapes from the Wolff-Chaikoff effect. The existence of an escape mechanism prevents the development of hypothyroidism $^{16,26,28,37}$. When KI is given shortly before exposure to $^{131}$I a greater than 90% blockade can be reached $^{17,28}$.

When this escape mechanism fails, the high amounts of iodide taken up by the thyroid will result in diminished thyroid hormone production and subsequently a rise in TSH-secretion. The rise in TSH will stimulate even more iodide uptake and counteract the protective effect. The tendency to become hypothyroid at young ages upon excessive iodine exposure implicates that failure of the escape mechanism occurs more often in young children and fetuses $^{16,38}$. When radioiodide has entered the thyroid in this phase, lasting radiation damage can be expected. This would imply that KI as a prophylaxis for uptake of radioiodide in the thyroid is not protective in a relatively large group of children.

Administration of chemotherapeutics might be another possible cause of TR in these patients. Vincristin interferes with the microtubular microfilament of the thyrocyte and inhibits the endocytosis of thyroglobulin by thyroid cells and the secretion of thyroid hormone $^{39}$. Cisplatin has a direct cytotoxic effect on thyrocytes $^{40}$. Thyroid
damage has not been described with regard to the etoposide and ifosfamide also given to these NB patients. In children with brain tumors an adjuvant risk for developing thyroid or pituitary damage on chemotherapy has been described after external radiotherapy. As the chemotherapeutic regimen in patients with TE and without TE was the same (Table 3), we feel that that the chemotherapy used in these patients is not the explanation for the rise in TSH. However, we cannot exclude the adverse effect of chemotherapy. Further research on this should be done.

We did not find elevated levels of TG, anti-thyroperoxidase or anti-TG in any patient. No patient had ultra-sonographic thyroid abnormalities or clinical signs of hypothyroidism. However, when looking at height SDS of the 23 surviving patients, the group with TE seems to have slight growth retardation compared to the group with normal thyroid functions.

An important question to address is what the long term consequences for these patients will be due to this radiation exposure and the elevation of TSH, with respect to thyroid function and structure and their own growth and development. Especially, in the first years of life, thyroid hormone plays an essential role in growth and maturation. In this period it is indispensable for proper brain development, which stresses the need to prevent damage to the thyroid and its regulatory system. If prevention is not possible, at least a correction of insufficient thyroid hormone supply should be made immediately.

Recently, subclinical hypothyroidism has been proved to be associated with significant metabolic changes and may be linked to lipid, vascular and hematological disorders. The thyroid hormone supply is thought to be clinically relevant in children as well, especially in childhood-cancer survivors. It has been shown that TE in combination with irradiation exposure creates a higher risk for developing thyroid carcinoma. The need for thyroid hormone during childhood for optimal mental and motor development and growth and to combat the risk of thyroid malignancy are arguments for the performance of sonography and the starting of treatment with thyroxine when TE is found after external radiation or treatment with $^{131}$I-MIBG, even while FT$_4$ levels are still within the normal range.

In conclusion, KI provides unreliable prophylaxis during childhood against thyroidal damage due to radioiodide dissociated from radioactive therapeutics. New prophylactic approaches should be investigated.
Chapter 2

Acknowledgments

The authors thank Dr C.A. Hoefnagel, nuclear physician in the Netherlands Cancer Institute, for his support in analyzing the radionuclide (MIBG) images. Financially supported by the Dutch Stichting Kindergeneeskundig Kankeronderzoek (SKK) and Pharmacia B.V.
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