ELSEVIER

European Journal of Cancer 41 (2005) 1767–1774

European Journal of Cancer

www.ejconline.com

Endocrine late effects from multi-modality treatment of neuroblastoma

H.M. van Santen [a,*], J. de Kraker [b,1], T. Vulsma [c,2]

[a] Department of Paediatric Endocrinology, Emma Children's Hospital AMC, G8-205, Academic Medical Center (AMC), University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands

[b] Department of Paediatric Oncology, Emma Children's Hospital AMC, F8-241, Academic Medical Center (AMC), University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands

[c] Department of Paediatric Endocrinology, Emma Children's Hospital AMC, G8-220, Academic Medical Center (AMC), University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands

Received 29 November 2004; received in revised form 16 February 2005; accepted 25 February 2005
Available online 20 July 2005

Abstract

Thyroid dysfunction has been reported after ^{131}I-MIBG-treatment for neuroblastoma. In this study, we have evaluated all endocrine functions from patients who were given multi-modality treatment including ^{131}I-MIBG. Twenty-five neuroblastoma survivors who were off therapy for a median period of 6.0 years (range 1.3–11.1) were evaluated and their median age was 8.1 years (range 2.2–14.7). All patients had received ^{131}I-MIBG, 16 chemotherapy, and 16 surgery. Fourteen patients (56%) had permanently elevated thyrotropin levels and 9 received thyroxine. Two patients had a small thyroid volume while 6 had thyroid nodules or cysts. Two boys showed hypergonadotropic hypogonadism. Growth was retarded in 39% of children. Mean Target Height Standard Deviation Score of patients with thyrotropin elevation was lower than those without ($P = 0.019$). Children treated for neuroblastoma with ^{131}I-MIBG, chemotherapy and surgery were seen to be at risk from developing irreversible thyroid function loss, thyroid nodules, hypergonadotropic hypogonadism, and growth retardation. We recommend that during follow-up of neuroblastoma children, special attention should be paid to their endocrine state.

Keywords: Late effects; Neuroblastoma; ^{131}I-MIBG; Chemotherapy; Hypogonadism; Hypothyroidism; Thyroid nodules; Growth retardation; Childhood cancer survivors

1. Introduction

Neuroblastoma is one of the most challenging tumours for paediatric oncologists. Some have a favourable outcome, but prognosis for children with stage 4 neuroblastoma and >1 year of age is still only approximately 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 have focused on the endocrine late effects of treatment. As the integrity of the endocrine system is essential for growth and development especially in young children, it is important that paediatric oncologists and endocrinologists improve their detection strategies and ways to prevent endocrine adverse events.

* Corresponding author. Tel.: +31 20 5669111, tracer 58559; fax: +31 20 6917735.
E-mail addresses: h.m.vansanten@amc.uva.nl (H.M. van Santen), j.dekraker@amc.uva.nl (J. de Kraker), t.vulsma@amc.uva.nl (T. Vulsma).
[1] Tel.: +31 20 5669111, tracer 65661; fax: +31 20 6917735.
[2] Tel.: +31 20 5669111, tracer 62951; fax: +31 20 6917735.

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doi:10.1016/j.ejca.2005.02.036

In a previous study, we had demonstrated that after treatment with the radionuclide ^{131}I-MIBG, a permanently elevated plasma thyrotropin (TSH) level was seen in 56% of survivors of neuroblastoma, despite thyroid protection with potassium iodide (KI) [2]. The thyroid function is especially important in this patient group due to young age [3], making them vulnerable to disturbances in growth and development. In addition to function, the structure of the thyroid can also be damaged by irradiation [4,5]. The young age [6,7] as well as the fact of having a neuroblastoma [8] can both be considered risk factors for radiation damage. However, it is unknown if the reported thyroid damage is transient or permanent. In cases where permanent elevated levels of TSH are seen, it is of interest to evaluate whether this state of (subclinical) hypothyroidism has any consequences for the patients such regarding growth or lipid profiles. Furthermore, it must also be evaluated whether the radioiodide exposure, in combination with TSH elevation in the years following ^{131}I-MIBG treatment, could also lead to proliferative structural abnormalities in the thyroid gland. It must be noted that not only the thyroid gland, but also other endocrine glands may become damaged due to the use of one or more modalities in treating neuroblastoma, such as alkylating agents that can cause gonadal damage [9]. Considering the primary localisation of neuroblastoma, which is often in the adrenal region, damage to the adrenal (cortex) function has also to be considered.

To address these questions, survivors of neuroblastoma treated in our center according to the ''MIBG-de-novo-protocol'' were evaluated for changes in their endocrine state.

2. Patients and methods

Twenty-five survivors with histologically confirmed neuroblastoma, stage 2, 3, 4 and 4s according to the International Neuroblastoma Staging System (INSS), and treated during 1989–1999 according to our ''MIBG-de-novo'' protocol were evaluated. Out of the original 73 treated patients, of whom 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 2, 3, and 4s ($n = 12$), this treatment was followed by chemotherapy if the response to ^{131}I-MIBG appeared to be insufficient. Ten patients received ^{131}I-MIBG only, and in two it was followed by two to four courses of vincristine 1.5 mg/m^2, etoposide 150 mg/m^2, carboplatin 400 mg/m^2 and ifosfamide 3000 mg/m^2 (VECI). In stage 4 patients, ^{131}I-MIBG treatment was followed by surgery, four courses of VECI, and high dose carboplatin (800 mg/m^2) and melphalan (180 mg/m^2) 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 that started one 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 (Tg), thyroxine-binding globulin (TBG), anti-thyroperoxidase (anti-TPO) antibodies, anti-thyroglobulin (anti-Tg) antibodies, and calcitonin. Determinants for adrenocortical function were: fasting cortisol and fasting ACTH (all drawn between 9.00 AM and 10.30 AM); for gonadal function: luteinising hormone (LH), follicle stimulating hormone (FSH) in combination with testosterone/SHBG in male patients, or 17-β-estradiol in female girl, prolactin (PRL) and insuline-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 μg/kg body mass (maximum 200 μg) intravenously. Subsequently, blood samples were taken 15, 30 and 60 min 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× the baseline value or the peak TSH concentration was found to be delayed (>60 min after administration of TRH). In survivors using T_4 supplementation, medication was withdrawn after the first visit. After three months, patients were evaluated with a full physical examination and a second TRH-stimulation-test with determination of fasting glucose and cholesterol-profiles. Informed consent was obtained from parents of all patients.

Plasma T_4, T_3 and anti-Tg were measured by in-house radio-immunoassay methods; plasma FT_4 and TSH were measured by a time resolved fluoro-immunoassay (Delfia® Free T_4 and Delfia® hTSH Wallac Oy, Tuurku, Finland); Tg was measured by an immuno-luminometric

assay (ILMA, Brahms®, Germany); anti-TPO antibodies by luminescence immunoassay (LIA, Brahms®, Germany) and TBG by radio-immunoassay (Eiken Chemical Co, Tokyo, Japan). Ultrasound imaging of the thyroid gland was done using Siemens Elegra, 13 MHz linear probe to measure thyroid volume and detect thyroid nodules ($n = 21$). If a nodule was found suspicious, fine needle aspiration cytology 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.

3. Results

3.1. Patients

At time of evaluation, the 25 patients (12 boys) had been off therapy for a median period of 6.0 years (range 1.3–11.1 yrs). Median follow-up time after the first ^{131}I-MIBG treatment was 6.0 years (range 1.4–11.9 yrs). Median age at last follow-up was 8.1 years (range 2.2–14.7 yrs).

Stage distribution was stage 2: $n = 2$, stage 3: $n = 7$, stage 4: $n = 13$ and stage 4s: $n = 3$. 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 doses of melphalan and carboplatin followed by autologous bone marrow transplantation. One girl had received treatment with actinomycin and carboplatin under suspicion of a Wilms tumour. Thirteen patients had adrenal surgery for a primary abdominal neuroblastoma, and 2 had laminectomy for a dumbbell tumour.

Two survivors had recurrence of their neuroblastoma at time of evaluation (3 and 4 years, respectively, after diagnosis) and had restarted ^{131}I-MIBG treatment. Both these patients did not survive the recurrence and the last available follow-up data of thyroid function and thyroid ultrasound imaging, before recurrence of disease, was used. Of the 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 neuroblastoma, was diagnosed with B-cell leukaemia, 5.9 years after the last radio-MIBG treatment.

In the remaining 21 patients, one did not agree to the determination of fasting cholesterol and bone-age while 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.

3.2. Thyroid gland

3.2.1. Thyroid function

From 25 patients 17 (68%) had an elevated TSH more or equal than once in the past, of whom 14 (56%) had an elevated TSH at the last evaluation, nine of whom used T4 supplementation. The three survivors who had transient TSH elevation, maximum TSH at time of TSH elevation ranged from 5.2–6.2 mU/L. 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 T_4 levels were all within the normal range and mean Tg was 24 pmol/L (range 2–55).

Anti-TPO concentrations, measured in 24 patients were negative ($\leqslant$30 kU/L) in 18 survivors, weakly positive (40–50 kU/L) in four (one patient had permanent elevated TSH and one with transient TSH elevation), and positive in two survivors (110–120 kU/L, one with a permanent elevated TSH and another without a TSH elevation). Anti-Tg was absent in all 24 patients. In 15 patients TRH-tests were performed, where 8 children had received no T_4 supplementation and in seven cases, after a 3-month T_4 withdrawal (Fig. 1). In all cases, mean TSH after 15 min 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 min with a mean concentration of 43.55 mU/L (range 10.8–158), which was higher than 5× the baseline value in 14 patients. For the seven patients on T_4 supplementation, the mean plasma TSH after stopping T_4 was 11.6 mU/L (6.0–28.5), with a peak TSH after 30 min to a mean concentration of 66.2 mU/L (29.8–158.0). With T_4 supplementation, mean TSH at baseline was 3.4 mU/L (1.5–5.4) with a peak TSH at 30 min of 18.4 mU/L (4.8–30.5) to indicate a lowered but not suppressed level of TSH. In 15 children, calcitonin was measured, showing normal levels in all. Four children with permanent elevated TSH had a positive family history for thyroid disease *versus* one child without TSH elevation. One mother had developed hypothyroidism of unknown cause in the years after the ^{131}I-MIBG treatment of her child (during which she had taken KI-prophylaxis 200 mg daily).

3.2.2. Thyroid ultrasound imaging

In 21 survivors, ultrasound imaging of the thyroid gland was performed. In two patients, thyroid volume was small for age and in five survivors (24%), one or more nodules (range 1–4) were found, ranging in size from 1 to 10 mm. In two survivors, fine needle aspiration cytology was performed, showing dys- and hyperplastic thyroid cells, but no malignant cells. In one patient, several small thyroid cysts were found. As

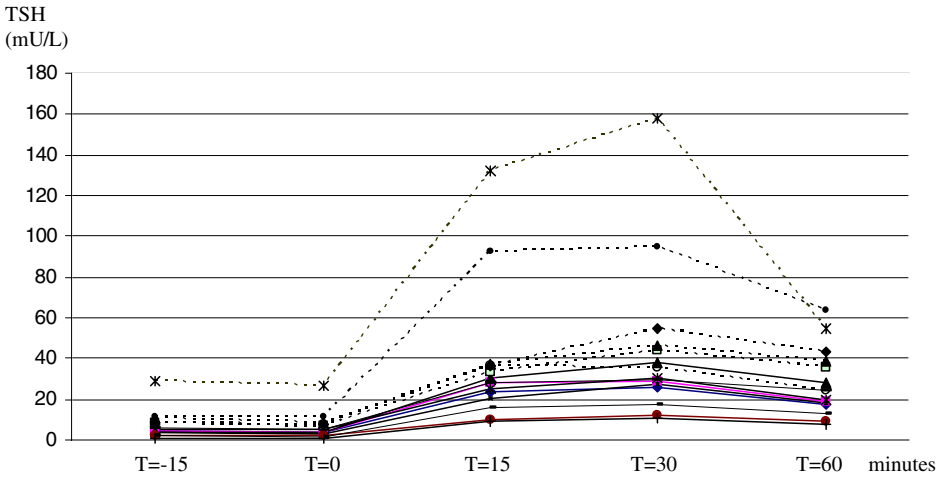

Fig. 1. TRH-stimulation tests after treatment (including ^{131}I-MIBG) for neuroblastoma. Stimulation tests performed in 15 patients during follow-up after treatment for neuroblastoma. At time $t = 0$, TRH 10 μg/kg body mass (max 200 μg) was given intravenously as bolus. Seven patients, who used T_4 supplementation, were withdrawn from T_4 for three months (dotted lines), 8 patients did not receive T_4 supplementation (solid lines).

shown in Table 1, from 21 survivors in whom ultrasound and thyroid function was measured, three patients (14%) had TSH elevation together with thyroid nodules, two (9.5%) survivors just had nodules, one case had thyroid cysts (5%) and nine survivors (42.9%) had elevated TSH levels only. Five survivors (24%) had normal thyroid function and no abnormalities could be detected by thyroid ultrasound imaging.

Number of ^{131}I-MIBG scans or uptake of radioiodide by the thyroid gland was not significantly different between survivors with or without elevated TSH or with thyroid nodules. Of the 11 patients without elevated

Table 1
Plasma TSH elevations and/or presence of thyroid nodules after treatment with ^{131}I-MIBG for neuroblastoma

Patient-ID	Gender	Plasma TSH elevation	T_4-supplementation	Number of thyroid nodules	TSH elevation + thyroid nodules
1	M	Yes	No	0	No
2	F	Yes	No	1	Yes
3	F	yes	Yes	0	No
4	M	yes	Yes	1	Yes
5	F	Yes	Yes	0	No
6	F	Yes	Yes	0	No
7	F	Yes	Yes	0	No
8	M	Yes	Yes	0	No
9	F	No	No	0	No
10	F	No	No	0	No
11	F	Yes	No	0	No
12	M	Transient	No	n.a.	No
13	M	Yes	No	n.a.	No
14	M	Yes	Yes	0	No
15	M	No	No	0	No
16	M	Yes	Yes	4	Yes
17	M	No	No	0	No
18	M	No	No	2	No
19	F	Transient	No	2	No
20	F	Yes	No	0	No
21	F	Yes	Yes	0	No
22	F	No	No	Cysts	No
23	M	No	No	0	No
24	M	No	No	n.a	No
25	F	No	No	n.a.	No
Total		14/25	9/25	6/21	3/21
%		56	36	29	14

Gender: M, male; F, female; n.a., not assessed.

TSH, two had received thyroid protection with T_4, KI and methimazole.

3.3. Gonadal function

Of the female patients, whose gonadal function was tested ($n = 8$), four 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. From four girls who were older than or equal to 8 years, one had stage M1, two had stage M2 and the remaining patient had 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, which is consistent with prepubertal state. In Table 2, pubertal stages of the boys, older than 6 years of age ($n = 11$) are shown. Of the three boys examined below the age of nine, none had any signs of puberty. One boy had bilateral cryptorchidism. In one pre-pubertal boy, the testicular vessels had been situated over the ventral side of the neuroblastoma, which were removed together with the tumour.

In the six boys ⩾9 years, three had stage P1, one had P3 and two had P4. Two boys with pre-pubertal testicular volume (<4 mL) had elevated LH and FSH levels indicating hypergonadotropic hypogonadism. In one boy with asymmetrical prepubertal testes, the neuroblastoma for which ^{131}I-MIBG had been given had originated in the left testis. In another boy, orchidopexy of the left testis had been performed for cryptorchidism.

3.4. Adrenocorticotropic function

In 13 patients, the primary tumour was situated in the adrenal gland and required unilateral adrenalectomy. In these patients, no signs of hypocortisolism were found in their history or from 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 their history, significantly lower mean cortisol concentrations were found (292 *versus* 397 nmol/L, $P = 0.026$).

There were no signs or symptoms of mineralocorticoid deficiency and in all children normal plasma sodium and potassium concentrations were found at follow-up.

3.5. 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 from 17 patients was 36 nmol/L (range 13–116). 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 THSDS.

Significant difference in THSDS, but not for bone age, was found for patients with an elevated TSH compared to those without and mean THSDS was −1.89 and −0.38, respectively ($P = 0.019$). Also the difference in height SDS between patients on T_4 treatment ($n = 8$) and others was significant THSDS −2.68 and −0.35, respectively ($P = 0.001$). However, in the 8 children known with T_4 supplementation other factors that could also have contributed to growth retardation were present in five patients: three had tubulopathy (mean THSDS −2.1), one had laminectomy for dumbbell neuroblastoma (THSDS −1.0) and one boy (THSDS −3.5) was recently diagnosed with the LEOPARD syndrome

Table 2
Gonadal development of boys >6 years of age after treatment for neuroblastoma

Patient ID	Age (years)	Pubertal stage	Testicular volume		LH (U/L)	FSH (U/L)	Testosterone (nmol/L)
			R (mL)	L (mL)			
1	10.7	P3 G2 A2	2	4	3	10.5	4.0
4	8.7	P1 G1 A1	np	np	<1.0	0.6	0.3
8	10.6	P1 G3 A1[a]	3	1	<1.0	2.2	1.6
12	13.1	P1 G1 A1	3	2	5.2	37.7	3.3
13	6.2	n.a.[b]	n.a.	n.a.	n.a.	n.a.	n.a.
14	10.3	P1 G1 A1	3	3	<1.0	4	1.9
15	6.6	n.a.[c]	n.a.	n.a.	<1.0	0.5	0.3
16	14.7	P4 G4 A4	15	20	6.9	9.3	7.5
17	6.6	P1 G1 A1[d]	2	2	<1.0	1.0	<0.6
18	14.1	P4 G3 A3	6	8	2.2	5.3	15.1
23	9.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

R, right testis; L, left testis; np, non palpable; n.a., not assessed.
[a] Neuroblastoma originally located in the left testis.
[b] Answered to questionnaire, no physical examination performed.
[c] Agreed to blood investigation only, no physical examination performed.
[d] Testicular vessels situated on primary neuroblastoma.

(proven germ line PTPN11 mutation) that is associated with a short stature. In the patients without T_4 supplementation, one girl with a THSDS of −3.0 had also been treated with laminectomy (dumbbell neuroblastoma).

3.6. Cholesterol profiles

In five patients, a family member with hypercholesterolemia was reported. In two patients (one with transient TSH elevation and the other with normal TSH), slightly elevated total cholesterol concentrations were found, where one patient also had elevated LDL. No differences were seen between the children with or without T_4 supplementation or with or without elevated TSH (with T_4 supplementation). No changes were seen in cholesterol profiles after three months of T_4 withdrawal.

4. Discussion

In this cohort of patients surviving neuroblastoma in stages 2–3–4 and 4s, 20 of 25 children (80%) developed endocrine late effects involving the thyroid gland or the gonads.

In a previous study, we had demonstrated that the administration of KI for thyroid protection during ^{131}I-MIBG was inadequate [2] and resulted in thyroid dysfunction due to radiation damage from $^{131}I^-$. This conclusion was again confirmed in the presented cohort of survivors, in which 14 patients (56%) presented thyroid dysfunction and in whom nine patients required T_4 supplementation. In addition to thyroidal hypothyroidism, 6 of 21 children (29%) who underwent thyroid ultrasound imaging showed the formation of nodules or cysts.

As stated briefly in Section 1, the protection of the thyroid gland against radioiodide in this group of patients is of special importance. Neuroblastoma manifests mainly in children below the age of 4 years (30% below the age of 1) [3]. 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 radiosensitive than that of adults [6,7]. 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 the risk of developing thyroid carcinoma from a radiation dose of 0.1 Gy [4,5,7,10]. Of all children with childhood malignancies, children with neuroblastoma have, for unknown reasons, an even greater risk of developing thyroid damage after radiation exposure when compared to children with other malignancies [8]. The time needed to develop thyroid tumours can be quite long [5,11], 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% [12], which would imply that the incidence that we found in this study in children treated with ^{131}I-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 TSH elevation [13,14]. However, before we can draw the same conclusion from treatment with ^{131}I-MIBG, the current normal incidence rate of thyroid nodules in healthy children from this age group (0–4 years) has to be established. The sensitivity of ultrasound imaging to detect nodules has greatly improved over the past 10 years and the high incidence rate may be explained in part by increased surveillance. Also, the possibility that children with neuroblastoma may have more thyroid nodules than other children must be considered. Support for this hypothesis comes from the observation that children with neuroblastoma have more radiosusceptible thyroid glands than children with other malignancies [8]. Although evidence against this hypothesis comes from the fact that in a previous study, we could not detect any thyroid nodule in children with neuroblastoma, immediately before or immediately after ^{131}I-MIBG treatment [15]. 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 neuroblastoma who have not been treated with ^{131}I-MIBG. Currently, we have screened seven such children with a history of neuroblastoma, a mean follow-up of 9 years after diagnosis (range 1.0–16.0) and a mean age of 11 years at follow-up (range 1.6–17.1). In these seven children no thyroid nodules have 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 neuroblastoma. The damage is most likely caused by radiation, as a consequence of ^{131}I-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 were found, and no clinical signs of hypothyroidism were reported during the 3-months of T_4 withdrawal. Treatment goals for elevated TSH levels found in children after treatment for neuroblastoma can now be considered.

The first goal is to ensure euthyroidism in the developing child. An elevated TSH in combination with FT_4 levels in the normal range with no clinical signs is often described as subclinical hypothyroidism, 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 of whether to treat or not treat subclinical hypothyroidism [16,17]. Possible consequences of subclinical hypothyroidism for adults may be cardiac dysfunction, elevations of total and LDL-cholesterol and progression to clinical hypothyroidism. In a recent scientific review, strong evidence was found in adults for the progression of subclinical to overt hypothyroidism [18]. Evidence for the benefits of treatment for subclinical hypothyroidism was provided by a randomized controlled trial (in adults), which demonstrated that T_4-treatment improves both the atherogenic lipoprotein profile and intima-media thickening [19]. We believe that for developing children and for adults, subclinical hypothyroidism must be considered as thyroidal hypothyroidism in which the pituitary elevates its TSH in response to very low concentration of FT_4. For young children, this implies that subclinical hypothyroidism 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 subclinical hypothyroidism by TSH elevation.

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 [20–22]. 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 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 [23–25]. For these reasons, it is important that, in patients who have been exposed to thyroid radiation, plasma TSH is monitored and if found elevated, it should be adequately treated, but not suppressed.

In this study, some of the patients have not only been treated with radiation therapy but also with extensive chemotherapy and it must be considered that, in addition to thyroid dysfunction, pituitary and hypothalamic dysfunction may also be present [26]. 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.

Considering all the above, our current advice is to monitor the plasma concentration of TSH and FT_4 every 6 months in children with neuroblastoma after ^{131}I-MIBG treatment. We recommend T_4 supplementation to normalise plasma TSH concentrations when it is once >10 mU/L or repeatedly >6.0 mU/L. In these patients the detection of thyroid nodule was increased and we recommend that they 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 potassiumiodide, but also methimazole and T_4 (dilute, block and replace: DBR) [15]. This was also used in two patients of this cohort, both of whom did not develop thyroid dysfunction. Although the incidence of TSH elevation is substantially diminished from 56% to 14% with DBR [15], 100% protection was not attained.

In this study, in addition 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 neuroblastoma was located in the testicular region, and may have caused testicular damage. Considering the young age of most survivors, it is anticipated that after longer follow-up damage to the gonads will become evident in more children, 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 however, affected in 39% of the children. In children with TSH elevation, 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 and there was no delay in bone age or 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 diminished thyroid and kidney function, poor clinical condition for several years, and, in one patient, growth retardation was based on an associated syndrome. Optimising T_4 concentrations and all other metabolic parameters may help to normalise their THSDS.

In conclusion, children treated with ^{131}I-MIBG for neuroblastoma, chemotherapy and surgery are at risk for developing irreversible hypothyroidism, thyroid nodules, hypogonadism and growth retardation. As these treatment schedules are not international standard treatments, late endocrine effects in other survivor cohorts may be different. However, these findings imply that during follow-up of children with neuroblastoma, special attention must be paid to their endocrine state.

Conflict of interest statement

None declared.

Acknowledgements

We like to thank N. Smits, R van Rijn and A. Smets on behalf of the Department of Radiology, Academic Medical Center for performing thyroid ultrasound. This work was supported financially by Stichting Kindergeneeskundig Kankeronderzoek (SKK) and Pfizer BV.

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