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Endocrine consequences of neuroblastoma treatment in children: 20 years' experience of a single center

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Abstract

Background: Neuroblastoma (NBL) is a child neoplasia affecting extracranial tissue of neuroectodermal origin. It accounts for 10% of solid malignancies in children and is characterized by a survival rate approaching 70%, confronting physicians with the emergence of an adult survivor population who have been previously exposed to surgery, cytotoxic drugs, radiation therapy or metaiodobenzylguanidine (MIBG) therapy. All these treatments potentially affect the endocrine system. Our study consists in a retrospective review of late endocrine effects arising in survivors treated for NBL during childhood.

Methods: The medical files of 47 patients (M/F=26/21) treated for NBL were reviewed. Collected data consisted of age, height, weight and biological hormonal values at diagnosis and at the last follow-up consultation. The incidence of late effects in our sample was compared to the data from the literature.

Results: Patients were between 0 and 15.8 years of age at diagnosis (median: 1.16 years) and between 1 and 25 years of age at last follow-up (median: 16 years). Twenty-six patients were treated with chemotherapy (CT), 11 underwent CT and radiation therapy and five were treated with CT and MIBG therapy. Ten percent of the patients died before reaching the end of therapy. Late effects occurred in 54% of the patients. Thirty-six percent of patients had non-endocrine complications (musculoskeletal, neurological, hematological or hepatic chronic conditions). Endocrine complications (28%) affected mainly patients

treated with CT and consisted of gonadal dysfunction (up to 42% patients of over 12 years of age at follow-up) and hypothyroidism (21%). Our analysis revealed that CT had a significant impact on final height ($p < 0.05$).

Conclusions: Treatment for childhood malignancies exposes children to late effects affecting the endocrine system. In children treated for NBL, hypothyroidism, gonadal failure and impaired growth appear to be the main endocrine complications. Close follow-up of survivors is thus appropriate.

Keywords: cancer survivorship; endocrine system; growth; hypothyroidism; late effects.

Introduction

Neuroblastoma (NBL) is a childhood neoplasia affecting extracranial neuroectodermal tissue. It is diagnosed in about 1/100,000 children every year, mostly toddlers, and accounts for about 10% of childhood solid malignancies [1].

The disease affects cervical, thoracic and abdominal sympathetic nodes or adrenal glands. Clinical presentation depends on the volume and localization of the tumor. It can exert a mass effect on adjacent tissues, leading to nervous compression, dyspnea, abdominal pain or palpable mass. In some cases, NBL secretes the intestinal vasoactive peptide, a vasomotor peptide causing refractory diarrhea. The diagnosis rests on ultrasound, high level of urinary catecholamines and serum neuron-specific enolase (NSE).

Treatment intensity depends on age at diagnosis, staging of the disease, the molecular and the biological pattern of the tumor (nMYC status). Low-risk NBLs mainly occur in children below 12 months of age and are often managed with surgery alone. If tumor localization, local extension or metastatic diffusion makes it inoperable, chemotherapy (CT) is used as a first-line therapy [1, 2]. High-risk NBL therapy requires CT, radiation therapy and sometimes autologous hematopoietic stem cell transplant (HSCT) with or without anti-GD2 and transretinoic acid [1, 3]. I^{131} iodine metaiodobenzylguanidine (MIBG) therapy is used as an adjuvant treatment in

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high-risk NBL refractory to first-line therapy with positive MIBG scintigraphy [4].

These different treatment modalities have enabled to achieve a 5-year survival rate currently approaching 70% [1]. In consequence, there is a growing population of adolescent or adult survivors at risk of developing effects of cytotoxic drugs or other therapies, including endocrine complications.

Adequate management of late effects requires appropriate awareness. This is the reason why our team led a retrospective study to assess the nature and incidence of endocrine toxicity of NBL therapy.

Materials and methods

Our study consists in a retrospective review of endocrine late effects arising in survivors of childhood NBL.

We retrospectively reviewed medical files of 47 patients treated for NBL at our institution (Centre Hospitalier Régional de La Citadelle in Liège, Belgium) between 1994 and 2016. Patients attended a specialized pediatric endocrinology consultation annually. In the case of an endocrine anomaly, they were seen every 6 months. The length of follow-up was variable (median: 4.85 years, range 1–16.04). Collected data consisted of sex, age, height and weight at diagnosis and at last endocrine follow-up. Standard deviation (SD) values were computed for these parameters to enable comparison. Biological values such as thyroid-stimulating hormone (TSH), thyroxin (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), morning cortisol, adrenocorticotrophic hormone (ACTH), insulin-like growth factor-1 (IGF-1), testosterone and estradiol levels were recorded at the time of last follow-up (median: 16 years, range 9.51–14.63). Growth hormone stimulation tests were performed in patients demonstrating low growth velocity with low IGF-1 levels (four patients). Dual-energy X-ray absorptiometry scans were performed every 2 years to assess bone mineral density. Height at follow-up was unfortunately not available for some patients who had spontaneous regressing neonatal NBL ($n=2$) or patients treated with surgery alone who benefited from lightened, spaced-out follow-up ($n=8$). This data was also unavailable for deceased patients ($n=5$) and patients lost to follow-up ($n=3$).

Our study aimed at assessing the prevalence of endocrine complications and the impact of antineoplastic therapy on follow-up weight and height of patients treated for NBL. Our results were compared with the incidence of late endocrine effects of NBL therapy described in the literature in order to enhance knowledge of therapy-related toxicity and guide long-term toxicity monitoring.

Comparison of height and weight between groups was based on SD according to the World Health Organization (WHO) Child Growth Standards values to facilitate interpretation. All SDs were provided at a 95% confidence level.

Statistical analysis through analysis of variance (ANOVA) with repeated measures and a Wilcoxon non-parametric analysis (STATISTICA, Dell Software, Round Rock, TX, USA) were conducted to study height and weight evolution of patients after therapy. SD for height and weight at diagnosis was compared to SD for height at the time of the last follow-up consultation, and height at the last follow-up was compared to target height, defined as $([\text{father's height} + \text{mother's}$

$\text{height}]/2) + 6.5$ for boys and $([\text{father's height} + \text{mother's height}]/2) - 6.5$ for girls. For the latter analysis, a non-parametric test was used due to the small number of patients for whom these data were available ($n=16$).

For the purpose of statistical analysis, patients were divided into four groups: (1) patients treated with surgery alone; (2) patients treated with CT; (3) patients treated with radiotherapy in combination with CT (RCT); and (4) patients treated with a combination of CT and MIBG therapy. The impact of the treatment group on height and occurrence of endocrine late effects was also studied.

Endocrine conditions studied were as follows:

- Hypothyroidism, which was diagnosed in patients whose blood TSH level was higher than 4.9 mUI/L with a decreased T4 level. Compensated hypothyroidism was defined as a high TSH level with a normal T4 level.
- Gonadal dysfunction, defined as premature ovarian insufficiency in girls, manifests as delayed or unprogressive puberty, with low levels of estradiol and normal to high levels of LH and FSH. Boys usually develop Sertoli cell dysfunction, manifesting as small-sized testicles with normal to high FSH levels affecting spermatogenesis. On the contrary, Leydig cell dysfunction manifests as delayed or unprogressive puberty. It is diagnosed in boys exhibiting elevated LH with low testosterone levels.
- Growth deficiency, which was suspected on the basis of low growth velocity with a low IGF-1 level and then confirmed by the absence of response to a glucagon stimulation test.
- Obesity, corresponding to a body mass index over the 95th percentile according to the WHO Child Growth Standards. Overweight was defined as a body mass index ranging between the 85th and the 95th percentiles according to the same standards.
- Prediabetes or diabetes, defined as a fasting blood glucose level between 100 and 125 mg/dL or greater than 126 mg/dL, respectively, on two different occasions.
- Low bone mineral density was diagnosed in patients exhibiting a bone mineral density Z-score below -2.0 on dual-energy X-ray absorptiometry scans. Patients with a bone mineral density Z-score between -1 and -2 were qualified as having mildly low bone mineral density.

We aimed at determining the incidence of these complications in each subgroup. We also studied the influence of age at diagnosis, sex and treatment modality on the incidence of hypogonadism in our teenage population using, respectively, T-test and Pearson's chi-squared (χ^2) test.

Ethical statement

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' Institutional Review Board.

Results

Patients included in the study were between 0 and 15.8 years of age at diagnosis (median 1.1 years) and

between 1 and 25 years of age at follow-up (median: 16 years). Twenty-six of these patients were male, 21 were female. The median length of follow-up was 4.85 years (range 1–16). Fifteen of our patients (31%) were treated with surgery alone (group 1), 12 patients (25%) were treated with CT with or without HSCT (six patients) (group 2), 11 (23%) underwent radiation therapy (group 3) and five (11%) were treated with MIBG therapy (group 4).

Patients were subsequently enrolled in ongoing NBL therapeutic protocols (SIOP-LINES [5, 6] protocol, NB99 protocol, Neuroblastoma Infant). Antineoplastic drugs were alkylating agents (melphalan, busulfan, cyclophosphamide, cisplatin, carboplatin), antitumoral antibiotics (doxorubicine), pervench alcaloid (vincristin) or topo-isomerase inhibitors (etoposid). Patients exposed to CT received a combination of etoposid-vincristine and cyclophosphamide. Doxorubicine, cisplatin, carboplatin and busulfan-melphalan combination were added to this scheme in, respectively, 65%, 65%, 75% and 60% of patients.

The overall survival in our population reached 90%, which means that 42 patients survived their malignancy.

Fifty-four percent of our patients suffered from chronic consequences of cancer therapy: 27% of patients in the group were treated with surgery (group 1), 72% of patients were exposed to CT (group 2), 70% in the group were treated with RCT (group 3), 100% of patients were exposed to CT and MIBG therapy (group 4).

The complications encountered by the treatment groups are listed in Table 1.

Endocrine complications

Endocrine complications affected 28% of all patients: 0% of patients in group 1, 35% of patients in group 2, 50% of patients in group 3 and 100% of patients in group 4. Endocrine complications were higher in patients treated with CT, especially when combined with MIBG therapy.

Most frequent endocrine complications were hypothyroidism (nine cases, 21%) and gonadal dysfunction (five cases, 14%). There were three cases of obesity and one case of overweight in patients whose weight ranged

Table 1: Late effect incidence according to treatment arm.

	All	Group 1 surgery alone	Group 2 chemotherapy alone	Group 3 chemotherapy + radiation therapy	Group 4 chemotherapy + MIBG therapy	No treatment
Number of patients	47	15 (31%)	12 (25%)	11 (23%)	5 (11%)	4 (8%)
Deaths	5 (10%)	0 (0%)	1 (8%)	1 (9%)	2 (40%)	0 (0%)
Any late effects	23 (54%)	4 (27%)	8 (72%)	7 (70%)	3 (100%)	0 (0%)
Endocrine late effects	13 (28%)	0 (0%)	4 (36%)	6 (55%)	3 (100%)	0 (0%)
Hypothyroidism	9 (21%)	0 (0%)	2 (18%)	4 (40%)	3 (100%)	0 (0%)
Gonadal dysfunction	6 (14%)	0 (0%)	1 (9%)	2 (20%)	3 (100%)	0 (0%)
Premature ovarian insufficiency	2 (4%)	0 (0%)	0 (0%)	1 (10%)	1 (33%)	0 (0%)
Sertoli cell Dysfunction	4 (8%)	0 (0%)	1 (9%)	1 (10%)	2 (66%)	0 (0%)
Obesity/overweight	3 (7%)/0 (0%)	1 (6.5%)/0 (0%)	1 (9%)/0 (0%)	0 (0%)/1 (10%)	1 (33.3%)/0 (0%)	0 (0%)/0 (0%)
Bone mineral density Z-score ≤ -1.0 SD to -2 SD	1 (2%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Bone mineral density Z-score -2.0 SD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-endocrine late effects	15 (32%)	4 (27%)	5 (45%)	5 (45%)	0 (0%)	0 (0%)
Deafness	4 (9%)	0 (0%)	2 (18%)	3 (30%)	0 (0%)	0 (0%)
Hypogammaglobulinemia	3 (7%)	1 (6.5%)	2 (18%)	1 (10%)	0 (0%)	0 (0%)
Alopecia	2 (4.5%)	0 (0%)	1 (9%)	1 (10%)	0 (0%)	0 (0%)
Proteinuria	1 (2%)	2 (13%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Renal atrophy	1 (2%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Hydronephrosis	2 (4.5%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Neuropathy/CBH	3 (7%)	2 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Paraplegia	1 (2%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Hepatic condition (nodular focal hyperplasia, fibrosis)	2 (4.5%)	0 (0%)	2 (18%)	0 (0%)	0 (0%)	0 (0%)
Hyperferritinemia	1 (2%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)

HSCT, hematopoietic stem cell transplant; MIBG, metaiodobenzylguanidine; CBH, Claude-Bernard-Horner; N/A, non-available.

within normal values before therapy. One patient was diagnosed with osteopenia. We had no case of growth hormone deficiency (GHD) in our population.

Primary hypothyroidism affected only patients treated with CT with or without adjuvant therapy. It was diagnosed in 18% of patients treated with CT alone, but in 100% of patients treated with a combination of CT and MIBG therapy, and 40% in the RCT group. Patients with hypothyroidism had significantly undergone more I^{123} -MIBG scans (mean: 8.3 scans for patients with hypothyroidism against 3.4 scans for euthyroid patients, $t(26)=3.32$, $p=0.0027$), but this only reflects the fact that patients treated with I^{131} -MIBG therapy have had more MIBG scans (mean: 8.8 vs. 3.6, $p<0.0001$). The mean TSH level at diagnosis of hypothyroidism was 7.4 mU/L (minimal and maximal values: 3.13–11.4) (normal range: 0.15–4.9 μ U/mL), and the mean T4 level was 9.8 pmol/L (4.3–12.8) (normal range: 8.6–25 pmol/L). Hypothyroidism was compensated in 33% of cases. Thyroid ultrasound was performed in seven patients affected with hypothyroidism. The most common finding was a small-sized or inexistent thyroid (five patients). Imaging was normal in the remaining two patients.

In our series, 14% of patients suffered from gonadal dysfunction (M/F: 1/1). Statistical analysis revealed no influence of age at diagnosis ($T(32): 0.42$, $p=0.68$) on the development of this complication. Yet, there was a significant effect of treatment modality on the occurrence of gonadal dysfunction: the incidence was much higher in patients exposed to MIBG and radiation therapy ($\chi^2(4): 3.91$, $p=0.008$). Premature ovarian failure was diagnosed in two girls, one was treated with MIBG and the other was in the radiation therapy group. The mean age at diagnosis was 12 years (11–13). These patients represent 28% of the female population aged over 12 years at the time of last follow-up in our series. Diagnosis was made on the basis of high LH and FSH levels with a low estradiol level. Anti-Müllerian hormone levels were not tested. Treatment with estradiol was started at diagnosis for both patients. Sertoli cell dysfunction affected four boys, i.e. 57% of boys over 12 years of age at follow-up. The mean age at diagnosis was 15 (13–17). Fifty percent of patients had been exposed to MIBG therapy. The diagnosis of Sertoli cell dysfunction was based on small-sized testicles and biological analysis revealing low inhibin B and high FSH levels. Leydig cell dysfunction, associated with low testosterone and elevated LH levels, was diagnosed in one of those four cases. This patient is the only male patient over 12 years of age at follow-up who had been exposed to abdominal radiation therapy, highlighting the radiosensitivity of Leydig cells. He received substitutive treatment by testosterone at adult age due to hypergonadotropic hypogonadism.

Spontaneous onset of puberty was observed in two boys, through preservation of function in Leydig cells. One of the patients had been started on a substitutive hormonal therapy by testosterone 3 years prior to the diagnosis of Sertoli cell dysfunction due to delayed onset of puberty with infantile testosterone, LH and FSH levels. He successfully entered puberty and later developed FSH elevation and Sertoli cell dysfunction with normal testosterone levels.

The incidence of obesity was not affected by the type of treatment received ($\chi^2(3): 3.43$, $p=0.32$). Yet, as the analysis was conducted on a very small number of patients, its significance is debatable.

We also studied the impact of therapy on growth in our cohort. The mean SD for height at diagnosis and at the time of last follow-up consultation was compared ($n=29$) and, for patients over 16 years of age, mean SD for height at follow-up was also compared to mean SD for genetic target height ($n=16$). ANOVA with repeated measures revealed that among those 29 patients, those treated with CT lost 1.35 in mean height SD at follow-up compared to that at diagnosis ($p<0.05$, mean height SD at diagnosis=0.79 and at follow-up=−0.56), whereas no significant difference on follow-up height was found in the subgroup treated by SCT (six patients) in addition to CT compared to CT alone ($F(3)=2.08$, $p=0.14$). No similar effect was found regarding weight or body mass index at follow-up (all p values >0.59). The Wilcoxon non-parametric analysis revealed that target height was not reached in patients over 16 years of age at follow-up ($Z=2.02$, $T=0$, $p=0.043$). Comparison of height SD at diagnosis and follow-up in patients affected with hypothyroidism ($p=0.14$) or gonadal dysfunction ($p=0.14$) showed no significant alteration of growth in these subgroups, which means that this effect is independent of other endocrine conditions, rather than being a consequence of CT itself. Regression analysis conducted to determine if there was an influence of age at diagnosis on growth found that the effect of CT on patients' growth rate depended on age at diagnosis ($p=0.0016$, $\beta=0.73$). This means that the impact on growth is more severe when treatment was started at a younger age.

Complete anthropometric data according to treatment modalities are available in Table 2. Figure 1 illustrates the comparison of diagnostic height SD with final height SD according to the treatment groups.

Non-endocrine complications

Non-endocrine complications occurred in 36% of patients and manifested as skeletal complications (scoliosis

Table 2: Anthropometric data of the population.

	All	Group 1 surgery alone	Group 2 chemotherapy alone	Group 3 chemotherapy + radiation therapy	Group 4 chemotherapy + MIBG therapy
Number of patients	47	15	12	11	5
Number of survivors	42	15	11	10	3
Median age at diagnosis (years) (minimal–maximal value)	1.16 (0–15.8)	0.66 (0–15.8) ^a	1.16 (0–5.1)	3.5 (0.5–5.75)	1 (0.4–5.08) ^a
Median age at follow-up (years) (minimal–maximal value)	8 (1.25–25)	9 (2–25)	15 (1.25–19)	9 (1.9–17)	17 (13–17)
Height SD at diagnosis (minimal–maximal value)	0.27 (–2.2 to 4.6)	–0.80 (–2.2 to 1.1)	1.44 (–0.5 to 4.6)	0.74 (–1.45 to 4.6)	–0.08 (–2.2 to 1.1)
Height SD at last follow-up (minimal–maximal value)	–0.39 (–4 to 2)	0.34 (–1.5 to 1.9)	–0.14 (–3.3 to 1.5)	–0.83 (–4 to 0.5)	–0.67 (–1.1 to 0)
Height SD at last follow-up – height SD at diagnosis (n = 29)	–0.218	+0.78 ^a	–2.72 ^a	–1.72	–0.44
Target height SD (minimal–maximal value)	0.07 (–0.9 to 0.9)	Not available	0 (–0.8 to 0.8)	–0.04 (–0.9 to 0.7)	0.7 (0.5 to 0.9)
Target height SD – adult height SD (n = 16)	0.5	Not available	–0.32	+0.54	+1.25
Weight SD at diagnosis (minimal–maximal value)	–0.09 (–4.1 to 4.9)	–0.47 (–4.1 to 1.29)	0.69 (–1.8 to 4.93)	–0.16 (–1.1 to 0.92)	0.24 (–0.4 to 1.46)
Weight SD at last follow-up (minimal–maximal value)	–0.18 (–2.7 to 2.2)	0.62 (–0.19 to 2.06)	–0.24 (–2.7 to 2.2)	–0.44 (–1.4 to 0.78)	–0.29 (–1.59 to 1.5)
BMI SD at diagnosis (minimal–maximal value)	–0.45 (–5 to 1.9)	0.67 (–1.5 to 1.9)	–0.45 (–2.7 to 1.8)	–1.1 (–5 to 1.5)	0.73 (–1 to 1.8)
BMI SD at last follow-up (minimal–maximal value)	–0.23 (–1.6 to 2.7)	0.46 (–0.6 to 2.7)	–0.56 (–1.4 to 1.7)	–0.34 (–1.6 to 1.2)	–0.13 (–1.3 to 2.1)
BMI SD at follow-up SD – BMI SD at diagnosis (n = 16)	–0.11	0	–0.25	0.8	–2.85

SD, standard deviation; BMI, body mass index. ^aStatistical significance.

[n = 2], persistent alopecia [n = 2]), neurosensorial defects (partial deafness [n = 4]), neurological impairment (Claude-Bernard-Horner syndrome [n = 2], paraparesis and incontinence [n = 2], neuropathy [n = 1]), nephrologic complications (proteinuria [n = 1], hydronephrosis [n = 2]), hepatic complications (n = 2) or immunity defects (hypogammaglobulinemia [n = 3]). These complications affected up to 27% of patients treated with surgery alone, 45% of patients treated with CT, 60% of patients managed with RCT and no patient who underwent MIBG therapy combined with CT.

Discussion

Chronic endocrine conditions are common complications of cancer therapy. According to Laverdière [1], they affect 62% of females and 45% of males treated for childhood

malignancies, which underlines the fact that the endocrine system is a preferential target for antineoplastic treatments and should thus be the focus of practitioners following childhood cancer survivors [7].

It is important to diagnose and manage endocrine conditions early to avoid impact on quality of life. Final growth and fertility can be affected by treatment, and these are two major aspects of adulthood with potentially serious psychological repercussions.

Fifty-four percent of patients in our series developed a long-term effect of NBL therapy, and 28% of all our patients developed endocrine complications.

The incidence of late effects is higher in the literature, with larger follow-up series finding that up to 89% of patients treated for NBL in childhood suffer from at least one medical condition due to therapy and that endocrine complications occur in over 50% of them [8, 9]. This difference is probably due to the selected population (higher

Figure 1: Comparison of diagnostic height SD to final height SD according to the treatment groups.

*Statistical significance.

incidence of late effects in high-risk NBL exposed to more aggressive therapy) and to a lower threshold in the definition of complication.

Our study enabled us to define the incidence of endocrine complications according to therapeutic regimen and to assess the effect of NBL treatment on height and weight of adult survivors.

The main endocrine complications were as follows:

- Hypothyroidism is the most frequent complication in our series, with up to 21% of survivors affected. As the prevalence of subclinical hypothyroidism in pediatric population approaches 2%, NBL survivors have at least a nine-fold increased risk of developing altered thyroid function compared to basal population [10]. Hypothyroidism was diagnosed in 100% of survivors treated with MIBG injections and 18% of patients treated with CT alone. These figures confirm data from the literature highlighting the thyroid toxicity of MIBG. MIBG is an adjuvant therapy in some tumors positive to MIBG scintigraphy. This diagnostic and therapeutic agent is well known for its interference with thyroid function, once believed to be transient. Therefore, it is recommended to administer iodide 3 days prior to MIBG injection to prevent the thyroid from storing MIBG. Yet, despite this common practice, recent studies have found that, in patients treated with MIBG, hormonal

dysfunction remain present years after therapy, with a sustained need for hormonal replacement [11]. As all patients undergo diagnostic I^{123} MIBG scintigraphy, and as the incidence of hypothyroidism is much higher in the group of patients treated with I^{131} MIBG therapy (21% vs. 100%), thyroid dysfunction seem to be linked to I^{131} , which is the therapeutic agent, rather than I^{123} , which is used as a diagnostic agent. Yet, we observed that patients diagnosed with hypothyroidism were significantly exposed to a greater amount of I^{123} as they underwent more MIBG scans. This observation should be considered with caution as patients treated with I^{131} -MIBG therapy significantly underwent more MIBG scans than other patients to assess response to therapy.

- Cases of thyroid second malignancies have been described in the literature consecutive to the use of alkylating agents, radiation therapy and MIBG administration. We did not observe any cases in our population, mainly due to the relatively short length of follow-up of our patients. Ultrasound monitoring of thyroid should be promoted in those patients, as suspicious thyroid nodules have been described in patients exposed to MIBG [11].
- Cancer therapy, mainly radiation therapy and CT regimens with alkylating agents, affects the gonadal system, leading to gonadal dysfunction [3]. In girls, a four-fold increased risk of developing premature ovarian failure has been described in teenagers treated with CT [12]. In females treated below the age of 13 years, cases of transient ovarian failure have been described, which suggests that prepubertal state during therapy might protect against irreversible ovarian failure [1]. Girls with premature ovarian insufficiency in our cohort had been exposed to CT and either radiation therapy or MIBG therapy. Boys exposed to CT and MIBG therapy might develop Sertoli cell dysfunction. Leydig cell insufficiency has also been described in boys exposed to relatively low-dose radiation therapy [13]. The role of MIBG is unclear, and probably holds more to the fact that patients requiring MIBG therapy are exposed to higher doses of CT due to refractory primary tumor. Due to relatively short length of follow-up in our series, we were not able to study the hypothesized reversibility of gonadal failure.
- The rationale for assessing the impact of therapy on patient growth emerged from the observation by several study groups of an alteration in final height among patients treated for NBL [3, 10, 14]. This growth alteration is associated with treatment by CT and with young age at initiation of therapy. There was no

additional effect of HSCT combined to CT on height at follow-up in our patients. Yet, these results should be considered with caution due to the small number of patients in this subgroup. Our analysis also reveal that target height was not reached in patients treated by CT, which confirms the impact of treatment on growth. The effect of CT on growth can be exerted through different pathways. In our patients there is no argument for GHD as none of them received cranial irradiation prone to damage the hypothalamo-hypophyseal hormone secretion. A dynamic testing of growth hormone secretion has only been conducted in patients with growth failure associated with low IGF1 levels and no GHD was observed. In fact the literature supports other factors besides GHD compromising growth in this population. Potential explanations are as follows: (1) a direct skeletal toxicity affecting growth plate in young childhood. Transretinoic acid, when combined with radiation therapy, CT and HSCT, has been associated with premature epiphyseal closure [15]; (2) an hormonal-induced growth alteration, through gonadal or thyroid toxicity, which was not confirmed by our analysis, as final height does not seem to be more severely affected in patients suffering from hypogonadism or hypothyroidism (all $p > 0.5$). Skeletal toxicity appears as a valid hypothesis, but requires further studies assessing bone age, among others, to be rigorously validated.

Of course our study was limited by the relatively small sample size and the limited length of follow-up. Analysis of height at follow-up was limited by the fact that the adulthood, and thus adult height, was not reached by all patients, which can lead to a bias in comparison with genetic target height. To limit this bias, we chose to include in this analysis only patients over 16 years of age at last follow-up. In addition, we were limited by the fact that height and weight at follow-up were lacking for some patients, due to death, interruption of follow-up or lightened follow-up (for patients treated with surgery alone). It would be interesting to follow up a whole cohort through adulthood to be able to compare not only height after and before treatment, but final adult height and height at diagnosis. This would also enable a valid assessment of the difference between real adult height and genetic target height.

On the other hand, to further confirm our finding that CT affects growth and final height without affecting the hypothalamic-pituitary axis, prospective studies with dynamic hypothalamic-pituitary axis testing, repeated bone age assessment and rigorous follow-up through adulthood should be performed.

Interestingly, endocrine complications occur mainly in patients treated with CT and/or radiotherapy and MIBG therapy. No patient in the surgery group developed endocrine pathologies. This means that only patients with high-risk NBL treated with CT benefit from endocrine follow-up. Such a selection of eligible population for follow-up should enable a cost-limiting practice.

Recommendations that can be inferred from this study include endocrine follow-up of patients treated with CT with or without HSCT, radiation therapy and MIBG therapy. This follow-up should include repeated biometric measurements, physical examinations with an assessment of pubertal development, periodical biological analysis of thyroid function and hormonal testing, mainly in patients treated with MIBG [8].

Conclusions

There is a high incidence of endocrine conditions in childhood NBL survivors exposed to CT, radiation therapy or MIBG therapy as part of their treatment. Hypothyroidism, gonadal failure and altered growth independently of any GHD appear as the main complications. These findings suggest a potential direct skeletal toxicity affecting growth in patients exposed to CT. A risk-stratified close follow-up of survivors is thus highly appropriate.

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References

1. Cheung N-K, Cohn SL, editors. Neuroblastoma, 1st ed. Berlin: Springer, 2005:305pp.
2. Parikh NS, Howard SC, Chantada G, Israels T, Khattab M, et al. Clinical practice guidelines – SIOP-PODC adapted risk stratification and treatment guidelines: recommendations for neuroblastoma in low- and middle-income settings. *Pediatr Blood Cancer* 2015;62:1305–16.

3. Cohen LE, Gordon JH, Popovsky EY, Gunawardene S, Duffey-Lind E, et al. Late effects in children treated with intensive multimodal therapy for high-risk neuroblastoma: high incidence of endocrine and growth problems. *BMT* 2014;49:502–8.
4. Quach A, Ji L, Mishra V, Sznewajski A, Veatch J, et al. Thyroid and hepatic function after high-dose ¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG) therapy for neuroblastoma. *Pediatr Blood Cancer* 2011;56:191–201.
5. SIOPEN RNET. European Low and Intermediate Risk Neuroblastoma Protocol: A SIOPEN Study, version 4.2. Available at: http://sfce.sfpediatric.com/sites/default/files/LINES_Protocol_version_4.2_2_janvier_2013_01.pdf. Accessed 17 Feb 2019.
6. SIOPEN RNET. High Risk Neuroblastoma Study 1.7 of SIOP-Europe (SIOPEN). Available at: http://sfce.sfpediatric.com/sites/default/files/hrnbl1_7_protocol_r4_randomisation_juni_2014.pdf. Accessed 17 Feb 2019.
7. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics* 2007;119:554–68.
8. Laverdière C, Liu Q, Yasui Y, Nathan PC, Gurney JG, et al. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2009;101:1131–40.
9. Nandogopal R, Laverdière C, Mulroney D, Hudson MM, Meacham L. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Horm Res* 2008;69:65–74.
10. Monzani A, Prodam F, Rapa A, Moia A, Agarla V, et al. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. *Eur J Endocrinol* 2013;168:R1–11.
11. Van Santen HM, de Kraker J, Vulsma T. Endocrine late effects from multi-modality treatment of neuroblastoma. *Eur J Endocrinol* 2005;41:1767–74.
12. Goswami D, Conway GS. Premature ovarian failure. *Horm Res* 2007;68:196–202.
13. Stukenborg J-B, Jahnukainen K, Hutka M, Mitchell RT. Cancer treatment in childhood and testicular function: the importance of the somatic environment. *Endocr Connect* 2018;7:R69–87.
14. Knijnenburg SL, Raemaekers S, van den Berg H, van Dijk IW, Lieverst JA, et al. Final height in survivors of childhood cancer compared with height standard deviation scores at diagnosis. *Ann Oncol* 2013;24:1119–26.
15. Hobbie WL, Mostoufi S, Carlson CA, Gruccio D, Ginsberg JP. Prevalence of advanced bone age in a cohort of patients who received cis-retinoic acid for high-risk neuroblastoma. *Pediatr Blood Cancer* 2011;56:474–6.