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Original Paper

Long-term Neuro-endocrine Sequelae After Treatment for Childhood Medulloblastoma

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The occurrence of neuro-endocrine deficiencies following craniospinal irradiation for medulloblastoma is well known, but data concerning the spectrum and prevalence of endocrine abnormalities in adulthood are scarce. We studied endocrine function in 20 (median age 25 years) adult subjects, 8–25 years (median 16 years) after therapy. The radiation dose to the whole cranium and spinal axis was 35 ± 2.6 Gray (mean ± standard deviation) with a boost to the posterior fossa of 18 ± 3.7 Gray. 13 subjects had received additional chemotherapy. In 15 of 20 (75%) subjects, endocrine abnormalities were observed. In 14 (70%), growth hormone (GH) secretion was impaired; 7 (35%) subjects had an absolute GH deficiency, while 7 (35%) showed subnormal responses to insulin-induced hypoglycaemia. In contrast, only 20% (4) of these subjects showed impairment of the hypothalamus–pituitary–thyroid (HPT) axis, while 15% (3) showed central impairment of hypothalamus–pituitary–gonadal (HPG) function. Central impairment of the HPG axis was associated with impaired GH secretion in all cases. Central adrenal insufficiency was not observed. Basal levels of prolactin were normal in all subjects. Young age at treatment was a determinant of GH deficiency in adulthood ($P = 0.014$). Neither post-treatment interval, nor the use of chemotherapy were determinants of central endocrine impairment in adulthood. In long-term survivors of medulloblastoma, GH deficiency has a high prevalence. In contrast, impairment of the HPG and HPT axis is less common, while central adrenal insufficiency was not observed.

Key words: medulloblastoma, long-term survivors of childhood cancer, late effects, endocrine function, GH deficiency, cranial irradiation therapy
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INTRODUCTION

In children with medulloblastoma, long-term survival rates of 50% have been achieved [1]. Cranial radiation therapy is invariably required for successful treatment. The radiation portal generally includes the hypothalamus and pituitary gland. These structures are particularly vulnerable to radiation therapy [2], which may explain the occurrence of endocrine impairment in later life. Deterioration of hypothalamus–pituitary function is believed to be slow, with adverse endocrine sequelae emerging only many years later.

Most studies assessing these late sequelae have been performed in childhood [3]. Follow-up data into adulthood are scarce. Moreover, the prevalence of endocrinopathies has been examined in studies including a variety of diagnoses, for example, brain tumours, acute lymphatic leukaemia (ALL) or nasopharyngeal malignancies. This has resulted in marked variation in irradiation doses studied. For instance, subjects with nasopharynx carcinoma are irradiated with a much higher dose, up to 70 Gray (Gy), than prophylactic irradiation in ALL (18–24 Gy). Finally, some studies have included subjects treated during childhood as well as during adulthood [4], thereby introducing marked variation in post-treatment interval. Since the incidence of endocrinopathies has been shown to depend, for example, on the dose of irradiation and age of treatment [5], these factors may explain, in part,

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differences in reported frequencies of endocrine deficiencies. The reported frequency of hypothyroidism ranges from 8 to 60% [6]. Impaired gonadotropin secretion occurring as a consequence of cranial irradiation varies from 25 to 50% [7], while growth hormone (GH) deficiency has been described in 60–80% [8].

Therefore, the aim of this study was to investigate long-term endocrine sequelae of cranial irradiation in a homogeneous group of adult subjects, treated for medulloblastoma during childhood.

PATIENTS AND METHODS

Subjects

The study was performed in subjects treated for medulloblastoma during childhood at the Emma Kinderziekenhuis, Amsterdam, The Netherlands. Subjects were eligible if it was more than 5 years after the cessation of treatment and if they were older than 18 years at the time of the investigation. Exclusion criteria were recent seizures, symptomatic ischaemic heart disease and pregnancy. 2 mentally retarded patients were excluded because no written informed consent could be obtained. The study protocol was approved by the Medical Ethics Committee of our hospital and written informed consent was obtained from all subjects.

Clinical data are summarised in Table 1. We studied 20 long-term survivors of medulloblastoma (6 women and 14 men) ranging from 19 to 33 years of age (median 25 years). In all subjects a medical history and complete physical examination were performed. All were postpubertal (Tanner V). Testicular size was assessed by the Prader orchidometer; with normal testicular volume in adult males defined as 15–20 ml. None had symptoms of diabetes insipidus. The median age at the time of diagnosis was 8 years (range 4–17 years). The median interval between the cessation of treatment and the investigation was 16 years (range 8–25 years). After surgery, all subjects were treated with craniospinal radiation therapy. The radiation dose to the whole cranium was 35 ± 2.6 Gy (mean ± standard deviation), with a boost to the posterior fossa of 18 ± 3.7 Gy. The irradiation doses to the craniospinal axis were fractionated as follows: fractions of 1.5 Gy to the cranium, fractions of 1.5 Gy on the spinal axis and boost fractionation doses between 1.5 and 1.8 Gy. Radiation doses were reduced in case of leuco- and/or thrombocytopenia. 13 subjects received additional chemotherapy (Table 1).

Methods

Endocrine evaluation. All tests started at 0900 h in the postabsorptive state. On day 1, an insulin tolerance test (ITT) was performed for the assessment of GH and cortisol responses. Blood samples were drawn to determine cortisol and GH 30 and 15 min before and 15, 30, 45, 60, 90 and 120 min after an intravenous injection of 0.15 U insulin/kg body weight (Actrapid, Novo Nordisk AS, Bagsvaerd, Denmark).

At the second assessment, blood samples were obtained to determine basal levels of follicle stimulating hormone (FSH) and luteinising hormone (LH) 15 min before, and 15, 30, 45, 60, 90 and 120 min after 0.1 mg gonadotropin-releasing hormone (GnRH) (Relefact LHRH, Hoechst, Frankfurt am Main, Germany). Thyroid-stimulating hormone (TSH) was measured 15 min before, and 20, 60 and 120 min after 0.4 mg thyrotropin-releasing hormone (TRH) (Relefact TRH, Hoechst).

Basal plasma levels of insulin-like growth factor-1 (IGF-1), tri-iodothyronine (T3), total thyroxine (T4), free thyroxine (FT4), prolactin, testosterone (in men), oestradiol and progesterone (in women) were also determined.

Hormone assays. Cortisol was determined by fluorescence polarisation immunoassay on a TDx analyser (Abbott, Amstelveen, The Netherlands), GH and IGF-1 by immuno radiometric assay (IRMA) (Nichols Institute Diagnostics, San Juan Capistrano, U.S.A. and Diagnostic Systems Laboratories, Webster, U.S.A., respectively). Prolactin was determined using an immunofluorometric assay (Delfia, Turku, Finland), LH and FSH were determined by radioimmunoassay (RIA;

Table 1. *Characteristics of* 20 *adult patients treated for childhood medulloblastoma*

Patient no. and sex		Age at treatment (years)	Post-treatment interval (years)	Dose of cranial radiation therapy and boost (Gray)	Chemotherapy	Substitution treatment or concomitant medicine use
1	M	7	25	37 (25)	–	thyroxine 0.1 mg
2	F	11	17	34.5 (20)	–	–
3	F	8	17	35 (15)	ster, mtx, vcr	–
4	F	8	18	35 (20)	ster, mtx, vcr	OC
5	F	8	19	35 (17)	ster, mtx, vcr	–
6	F	5	16	36 (19)	ster, mtx, vcr	GH 4IU 2/weekly, OC
7	M	13	16	35 (17)	ster, mtx, vcr	–
8	M	13	10	35 (20)	ster, mtx, pro, vcr	–
9	M	8	15	35 (20)	mtx, vcr, pro	GH 4IU 2/weekly, thyroxine 0.1 mg
10	M	4	20	35 (20)	ster, mtx, vcr	–
11	M	7	21	40 (17)	–	–
12	M	5	23	35 (20)	–	–
13	M	11	9	25 (30)	–	–
14	M	8	14	35 (20)	pro, mtx, vcr	–
15	M	17	9	35 (20)	–	–
16	M	10	14	35 (15)	ster, mtx, pro, vcr	–
17	M	5	14	35 (22)	pro, vcr, mtx	–
18	M	15	8	35 (20)	ster, mtx, vcr	
19	F	6	15	35 (15)	mtx, vcr, pro	OC
20	M	14	19	42 (20)	–	–

mtx, methotrexate; vcr, vincristine; ster, steroids; pro, procarbazine; OC, oral contraceptive; GH, growth hormone.

Johnson and Johnson, Amersham, U.K.). Testosterone, oestradiol and progesterone were also determined by RIA (respectively, in-house; Diagnostic Products Corporation, Los Angeles, California, U.S.A.; Orion Diagnostica Espoo, Finland). T4 and T3 were determined by in-house RIA, FT4 by a two-step fluoroimmunoassay and TSH by immunofluorometric assay (both Delfia, Turku, Finland). Antithyroid peroxidase (TPO) was measured by chemiluminescence immunoassay (BRAHMS, Berlin, Germany).

References values

Reference values of GH and cortisol responses to insulin-induced hypoglycaemia and of LH and FSH responses to GnRH stimulation were adapted from Becker [9]. A peak plasma GH concentration > 18.9 mU/l (> 7 ng/ml) was considered a normal response. An absolute GH deficiency was defined as a response < 6.75 mU/l and a subnormal response as a peak response between 6.75 and 18.9 mU/l. The cortisol response was considered normal if the peak plasma cortisol concentration was above 0.55 μmol/l or if the absolute increase in plasma cortisol was above 0.28 μmol/l. Normal LH and FSH responses to GnRH were defined as a 2–3-fold increase in plasma LH concentration over basal levels and a more than 1.5-fold increase in plasma FSH over basal levels, respectively. Reference values for the TSH response to TRH were obtained from the Laboratory of Clinical Chemistry, Academic Medical Centre, University of Amsterdam, defining a normal response of TSH to TRH as a peak plasma concentration of TSH between 2.8 and 22.5 mU/l.

Statistical analysis

Statistical comparisons were made by logistic regression (SPSS, 1996), considering *P* values less than 0.05 as statistically significant.

RESULTS

Growth hormone

All subjects were tested, except 2 who received GH substitution. The results are shown in Table 2. 14 subjects (70%) had an impaired GH response. All these subjects except 1 (no. 3) had signs or symptoms compatible with GH deficiency, with lack of energy as the major complaint. 7 subjects (35%) had an absolute GH deficiency. In 2 subjects, this had been diagnosed previously (nos 6 and 9, 13 and 3 years after treatment, respectively). 7 subjects (35%) showed a subnormal GH response. IGF-1 was decreased in only 6 subjects. Therefore, IGF-1 as a diagnostic test for GH deficiency yielded a sensitivity of 40% and a specificity of 85%.

Hypothalamus–pituitary–gonadal (HPG) axis

All subjects had mature secondary sexual characteristics (Tanner V). All women had a normal menstrual cycle. 3 women were excluded from the GnRH test because of the use of an oral contraceptive. Thus, in 17 subjects (14 men, 3 women) the HPG axis was studied. The results are shown in Table 3. 3 subjects showed central hypogonadism. Testosterone was decreased in 2 men, 1 (no. 1) in combination with a low peak response of LH to GnRH and 1 (no. 11) with a decreased basal LH. 1 man (no. 9) showed a low peak response of FSH after GnRH stimulation. In 3 men, basal FSH was elevated (nos 8, 12 and 18). All these subjects had received combination chemotherapy including procarbazine.

Table 2. Cortisol and peak growth hormone (GH) response to insulin-induced hypoglycaemia, insulin-like growth factor-1 (IGF-1) concentration basal and peak cortisol responses to hypoglycaemia

Patient no. and sex	GH (mU/l)*	IGF-1 (nmol/l)	Cortisol (μmol/l)*	
	Peak		Basal	Peak
Reference values	> 18.9	See below†		> 0.55 or delta 0.28
1 M	5.0	28	0.53	0.88
2 F	0.5	10	0.53	0.66
3 F	9.1	36	0.62	0.81
4 F	8.4	19	0.87	1.34
5 F	2.6	6	1.21	1.64
6 F	s	s	1.01	1.74
7 M	20.5	19	0.59	0.89
8 M	18.3	39	0.51	0.78
9 M	s	s	0.30	0.69
10 M	9.1	46	0.34	0.75
11 M	0.5	12	0.24	0.51
12 M	6.0	19	0.53	1.43
13 M	16.8	34	0.26	0.87
14 M	33.5	21	0.36	0.76
15 M	56.0	37	0.37	0.79
16 M	11.9	64	0.48	0.77
17 M	25	24	0.28	0.75
18 M	59	42	0.40	0.71
19 F	7.9	13	0.58	1.27
20 M	30	35	0.40	0.72

*Maximal concentration after insulin-induced hypoglycaemia.
†Reference values, IGF-1: men 20–30 years 21–84 nmol/l, 30–40 years 17–53 nmol/l; women 20–30 years 16–66 nmol/l, 30–40 years 13–52 nmol/l.
s, substitution therapy.

Testicular volume was normal in all except 2 subjects (in nos 11 and 17, testicular volume was 14 and 10 ml, respectively).

Hypothalamus–pituitary–thyroid (HPT) axis

None of the investigated subjects had clinical signs of hypothyroidism. 2 had been diagnosed previously as having subclinical primary hypothyroidism on the basis of a slightly elevated TSH and normal T4 (nos 1 and 9, 9 and 8 years post-treatment, respectively) and had been treated with thyroxine. Data are summarised in Table 4. Of the 18 tested subjects, 1 subject (no. 18) had a decreased total plasma T4 concentration, but otherwise normal thyroid hormone concentrations, compatible with marginal central hypothyroidism. 1 subject (no. 12) showed a decreased FT4, a slightly elevated TSH and an exaggerated response of TSH to TRH, compatible with primary hypothyroidism. 5 subjects (nos 2, 6, 10, 16 and 19) with an exaggerated response of TSH to TRH and normal FT4, T4 and T3 were considered as having subclinical primary hypothyroidism. Anti-TPO antibodies were absent in all these subjects (< 5 KU/l).

Hypothalamus–pituitary–adrenocortical (HPA) axis

Data are summarised in Table 2. All 4 subjects showed a normal cortisol response to insulin-induced hypoglycaemia.

Prolactin

Plasma concentrations of prolactin were within normal limits in all subjects.

Table 3. Gonadal function in patients treated for medulloblastoma

Patient no. and sex	E2 (nmol/l)	P (nmol/l)	T (nmol/l)	FSH (U/l)		LH (U/l)	
				Basal	Peak	Basal	Peak
Reference values	f 0.04–0.73 l 0.22–0.95	f < 1–3.0 l 12–60	11–35	1–10	> 1.5 over basal	5–15	> 2–3 over basal
1 M			9.9	1.5	3.0	5.5	10.0
2 F	0.45	4.2		5	12	6.5	42
3 F	0.2	1.2		4.5	9	15	55
4 F	OC	OC		OC	OC	OC	OC
5 F	0.31	14.5		3	5	4.5	27
6 F	OC	OC		OC	OC	OC	OC
7 M			12	2	4	6	19
8 M			18.3	23	50	9	63
9 M			29.2	2.5	3	5	21
10 M			18	4	9	6	22
11 M			10.2	2.5	6	3	17
12 M			12.9	12	37	8	63
13 M			20	5.5	12	6.5	22
14 M			36	3.0	10.5	6.5	21
15 M			12	4.0	nd	7.0	nd
16 M			15.5	3	6.5	4	27
17 M			22	2.5	4	5.5	18
18 M			21	14	28	7.0	45
19 F	OC	OC		OC	OC	OC	OC
20 M			11.0	4.0	nd	5.2	nd

E2, oestradiol; P, progesterone; T, testosterone; FSH, follicle-stimulating hormone; LH, luteinising hormone; f, follicular phase; l, luteal phase; peak, maximum levels of FSH or LH found after 100 μg gonadotropin-releasing hormone (GnRH); nd, not determined; OC, oral contraceptive.

Summary of endocrine abnormalities

5 of 20 subjects had normal hormonal profiles (nos 7, 14, 15, 17 and 20). 7 subjects had absolute GH deficiency; in 2, this was combined with both central hypogonadism and primary hypothyroidism (nos 1 and 9), in 1 (no. 11) with central hypogonadism and in 1 (no. 12) with primary hypothyroidism. An additional 7 subjects showed subnormal responses of GH without impairment of the HPG or HPT axis. 1 subject (no. 18) showed marginal central hypothyroidism without impairment of the other axes. GH deficiency showed a negative correlation with age at treatment ($P = 0.014$). There was no significant correlation between neuro-endocrine abnormalities and post-treatment interval or the use of chemotherapy.

DISCUSSION

Detailed studies of endocrine function in adult, long-term survivors of childhood medulloblastoma have not been reported previously. In this study, long-term follow-up after treatment was achieved (median 16 years). The localisation of the medulloblastoma was the fossa posterior in all subjects, making the site of the surgical procedure very unlikely to have produced central endocrine impairment. Furthermore, surgically induced deficiencies usually manifest shortly after surgery, whereas radiation-induced damage manifests only months to years after irradiation [10, 11]. In this study, 13 subjects had been treated with combination chemotherapy. Since this group did not differ in hypothalamus–pituitary function as compared with patients without chemotherapy, chemically induced hypopituitarism is a very unlikely cause of the observed endocrine effects.

From studies of children with ALL, it is known that hormonal deficiencies can occur after radiation doses as low as 18 Gy, especially when treated at a young age [12]. In a detailed study by Crowne and colleagues, low dose cranial irradiation was shown to cause subtle pertubations of the GH axis during the pubertal growth spurt, but not prepubertally [13]. Patients with brain tumours receive much higher radiation doses. Our subjects received a mean dose of 35 Gy to the hypothalamus–pituitary region and showed a high proportion (75%) of endocrine abnormalities. The predominant deficiency was GH impairment; in 7 subjects (35%) an absolute GH deficiency was present, while 7 additional subjects (35%) showed a subnormal GH response to ITT. IGF-1 did not prove to be a reliable diagnostic test for GH deficiency, which is in accordance with other studies [14]. Several studies have shown that the majority of patients treated for brain tumours become GH deficient 3 months to 5 years after radiation therapy [15]. As most studies were performed within 10 years after diagnosis, it was postulated that after a lengthier interval even more hypothalamus–pituitary deficiencies would gradually become apparent, as a result of slowly progressing radiation-induced changes [16]. On the contrary, Shalet and associates postulated that the occurrence of radiation damage to the hypothalamus–pituitary axis is predominantly dependent on young age at treatment and the dose received [17], rather than on the post-treatment interval. Our study supports this hypothesis, as the presence of GH deficiency was associated with treatment at a young age and not with post-treatment interval. No conclusion could be drawn about the dose of radiation as a determinant of endocrine failure, since in our study population the range of radiation doses given was only very small.

Only 3 subjects (18%) showed central hypogonadism in our study. Rappaport and colleagues reported that isolated central impairment of gonadotrophins does not occur as a

Table 4. Thyroid function in patients treated for medulloblastoma

Patient no. and sex	T4 (nmol/l)	FT4 (pmol/l)	T3 (nmol/l)	TSH (mU/l)	
				Basal	Peak
Reference values	70–150	10–23	1.3–2.7	0.4–4.0	2.8–22.5
1 M	s	s	s	s	s
2 F	100	12.1	1.85	2.7	23.3
3 F	105	16.9	2.1	2.2	16.4
4 F	155	16	2.3	1.4	15.8
5 F	110	13.1	2.6	2.6	15
6 F	115	11	2.1	1.2	23.6
7 M	90	12.9	1.8	2.3	16.4
8 M	135	15.7	2.4	1.9	11
9 M	s	s	s	s	s
10 M	100	15.1	1.7	2.8	23.6
11 M	90	10.8	2.1	2.6	12.5
12 M	75	7.6	2.1	4.3	28.6
13 M	120	15.7	2.1	1.9	16.2
14 M	105	13.3	1.8	1.8	12.8
15 M	85	9.3	1.35	4.0	nd
16 M	100	13.2	2.8	3.9	29.5
17 M	95	16.6	2.3	2.4	13.4
18 M	60	10.1	1.9	1.5	14.0
19 F	140	14.2	2.3	2.5	28.0
20 M	115	21.4	2.15	2.6	15.4

T4, thyroxine; FT4, free T4; T3, tri-iodothyronine; TSH, thyrotrophin; peak, maximum levels of TSH after 400 µg thyrotrophin-releasing hormone; nd, not determined; s, substitution.

consequence of cerebral irradiation, but is always associated with GH deficiency [18]. We confirmed this, as central impairment of the HPG axis was associated with GH deficiency in all cases. In addition, we identified 3 men with raised basal plasma FSH levels. All these men had received procarbazine as part of the adjuvant chemotherapy, which is known for its cytotoxic effect on the germinal epithelium [19]. Although we did not perform semen analyses, the raised FSH levels are probably due to primary gonadal insufficiency due to damage to the germ cells.

In our study population, 1 case of central hypothyroidism was found and 3 cases of primary hypothyroidism. The TRH stimulation test, amplifying minor abnormalities in basal TSH secretion, revealed 5 subjects with an exaggerated response of TSH to TRH. Since T4, FT4 and T3 concentrations were normal, this reflects subclinical primary hypothyroidism. Auto-immune hypothyroidism as a possible cause of primary hypothyroidism was ruled out in this group by the absence of anti-TPO antibodies. Thus, the exaggerated response of TSH to TRH is most probably due to primary hypothyroidism caused by damage to the thyroid gland as a result of irradiation of the craniospinal axis. This is in accordance with other studies [6]. Chemotherapy has so far not been associated with damage to the thyroid. The possible interaction of radiotherapy and chemotherapy in the development of primary hypothyroidism has not been investigated so far. Radiation-induced central cortisol deficiency is uncommon, but has been described incidentally. Since this impairment can be life-threatening, it is important to know the long-term incidence of this deficiency. Determining the adrenocorticotrophic hormone (ACTH) reserve by an ITT is regarded as a reliable instrument for diagnosing cortisol deficiency [20, 21]. Our results demonstrated that no subjects had such a deficiency.

Hyperprolactinaemia is a common finding after cranial irradiation [22]. It is assumed to result from injury to the hypothalamus, leading to disruption of the dopaminergic inhibition of prolactin secretion [23]. Although we expected elevated levels of prolactin to occur in some subjects, all subjects had normal prolactin.

In this study, the frequency of GH deficiency was in accordance with earlier findings in the literature. By contrast, impairment of the gonadal and thyroid axis due to irradiation damage of the hypothalamic–pituitary region in our material was less frequent than the expected rate in view of the long post-treatment interval. A striking feature of this study was the observation that after a long follow-up period, the cortisol reserve in patients remained normal. The assessment of the exact localisation of the radiation-induced damage is a matter of debate in the literature. Deficiency of the pituitary gland may occur at any level of the pituitary gland or may originate in the hypothalamus. Differentiation between hypothalamic and pituitary endocrine dysfunction is difficult [24, 25]. Our results suggest highly selective damage according to hypothalamic and/or pituitary cell type, rather than according to topography.

In conclusion, the current study shows late endocrine sequelae after cranial irradiation for childhood medulloblastoma. GH deficiency is common and is inversely related to age at treatment. Impairment of the HPG and HPT axes is observed much less frequently. There were no subjects with impairment of the HPA axis or with hyperprolactinaemia. In view of the high prevalence of GH deficiency and the potential benefit from GH replacement therapy in terms of well being [26, 27], long-term endocrine surveillance after craniospinal irradiation appears mandatory.

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