

Endocrinological late effects of oncologic treatment on survivors of medulloblastoma

Efectos endocrinológicos tardíos del tratamiento oncológico en supervivientes de medulloblastoma

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Abstract

Radiation therapy, chemotherapy, and surgery used to treat brain tumors have effects on the hypothalamic-pituitary-adrenal axis and can result in endocrine dysfunction in up to 96% of cases. **Patients and Method:** Retrospective and descriptive study in patients diagnosed with medulloblastoma who underwent treatment with chemo and radiotherapy in the last 20 years in a tertiary hospital. The variables analyzed were age, sex, weight, height, body mass index (BMI) at the end of follow-up, sexual maturity stage, serum levels of TSH and free T4, ACTH/cortisol and IGF-1, FSH, LH, estradiol, testosterone, lipid profile (total cholesterol), and growth hormone dynamic function test. **Results:** Total sample of 23 patients. Growth hormone deficiency is the most frequent sequelae (82%) followed by thyroid dysfunction (44.8%), and disorders of puberty (24.1%). Only one case of diabetes insipidus and two cases of corticotropin deficiency were diagnosed. **Conclusions:** Long-term follow-up of medulloblastoma survivors treated with chemo and radiotherapy reveals a very high prevalence of endocrine dysfunction, especially growth hormone deficiency and hypothyroidism. We believe that monitoring and long-term follow-up of these patients is necessary in order to ensure adequate therapeutic management of those treatable dysfunctions.

Keywords:

Childhood central nervous system tumors; endocrine system diseases; radiation therapy; growth hormone deficiency; hypothyroidism

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Introduction

Brain tumors are the most common solid neoplasms in childhood¹. The most frequent histological types include astrocytoma (24%), glioma (22%), medulloblastoma (MB)/primitive neuroectodermal tumor (PNET) (10%), pituitary and craniopharyngioma tumors (10%), ependymoma (6%), and germ cell tumors (4%)^{1,2}. Survival has improved substantially in recent decades, which reaches approximately 65% at 5 years, however, the improvement in prognosis is not without late adverse medical, neurocognitive, and psychosocial effects³.

Radiation therapy (RT), chemotherapy (CT), and surgery used to treat brain tumors have effects on the hypothalamic-pituitary-adrenal axis and could lead to endocrine dysfunction in up to 96% of cases⁴. These include growth hormone (GH) deficiency, hypothyroidism, disorders of pubertal development, central adrenal insufficiency, hyperprolactinemia, and diabetes insipidus. In addition, some adults with history of childhood central nervous system tumors often develop overweight or obesity, dyslipidemia, metabolic syndrome, and low bone mineral density^{3,5}. All these conditions require prolonged and close endocrinological follow-up in this type of patient⁶.

The objective of this study is to determine the frequency of endocrine disorders in children with MB undergoing CT and RT and to analyze the time of their development after completing the therapy.

Patients and Method

Study design

Descriptive and retrospective study. The inclusion criteria are patients diagnosed with MB during pediatric age (up to 14 years of age), treated with CT and RT at the Hospital La Fe in Valencia, between January 1997 and December 2016. According to the different treatment protocols, patients have received CT and RT, they do not present previous hormonal deficits, and are follow-up for at least 5 years in the pediatric endocrinology unit of the hospital.

The following patients are excluded: those who were not referred for follow-up in our unit, the deceased ones, those with hormonal deficiencies before tumor diagnosis, and those not treated with CT and RT according to our current protocols at the time of tumor diagnosis.

The first clinical and analytical assessment of patients by the pediatric endocrinology unit is carried out one year after the end of the oncological treatment. Subsequently, the follow-up is every 6 months until the age of 18.

The following variables are analyzed: age, sex, weight, height, body mass index (BMI) at the end of follow-up⁷, sexual maturation stage according Tanner-Whitehouse, serum thyroid-stimulating hormone (TSH) and free thyroxine (free T4) levels, adrenocorticotropic hormone (ACTH)/cortisol, insulin-like growth factor-1 (IGF-1), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), estradiol, testosterone, lipid profile (total cholesterol), and dynamic function test of growth hormone in those cases where it was required.

Definitions

Growth hormone deficiency: patients with a growth rate below the 25th percentile or growth rate below -1.5 SD (10th percentile) according to their sex, age, and pubertal stage plus a dynamic function/stimulation test (clonidine test or insulin hypoglycemia) with growth hormone peak <7 ng/ml. The GH deficiency diagnosis was based on growth rate data and low GH levels in two stimulation tests, or low GH levels in one stimulation test in those patients who were previously treated with RT and had some more associated pituitary hormone deficit⁸⁻¹⁰.

ACTH deficiency: serum cortisol levels do not increase above 18-20 µg/dl in a low-dose ACTH stimulation test (1 µg) or standard one (250 µg)^{11,12}.

Central hypothyroidism: free T4 levels are at the lower limit of normality or below the baseline range along with low, normal, or slightly elevated TSH levels and do not appear appropriate for free T4 levels.

Primary hypothyroidism: when there are elevated TSH levels and low T4 levels, and an elevated TSH level and a normal T4 level indicate subclinical hypothyroidism. The presence of goiter and/or positive thyroid antibodies levels, specifically antiperoxidase, is associated with an increased risk of progression to hypothyroidism (thyrotropin levels higher than 10 mUI/L)¹³.

Precocious puberty: the appearance of breast bud (grade II thelarche) in girls under the age of 8, and testicular volume higher than or equal to 4 ml in boys under 9 years of age, according to the Tanner-Whitehouse method of pubertal development assessment. If there is suspicion, the GnRH stimulation test is the gold standard for the diagnosis of precocious puberty with a maximum LH peak between 4 and 6 mUI/L or an LH/FSH ratio > 0.66^{14,15}. **Late puberty:** lack of grade II thelarche in girls over 13 years of age, and a testicular volume less than 4 ml in boys over the age of 14¹⁶. The physical examination was performed by a pediatric endocrinologist.

Hypogonadotropic hypogonadism: serum testosterone levels are undetectable, low or declining in men, or undetectable or low estradiol levels in women

in the context of low or inadequately normal levels of gonadotropins in girls over the age of 13 and over 14 years of age in boys¹². Low testosterone or estradiol levels in the presence of elevated gonadotropins are indicative of primary hypogonadism¹⁷. On the one hand, in the evaluation of gonadal function in men, inhibin B, produced mainly by the Sertoli cells of the testicle influenced by FSH, is a marker of spermatogenesis as it is positively correlated with sperm count and concentration in adulthood. On the other hand, in women, the anti-müllerian hormone (AMH) is produced by the granulosa cells of the preantral and small antral follicles in the ovaries and reflects the quantitative state of the ovarian reserve in adult women.

Although the determination of inhibin B has not been performed in our patients since it is not available in our laboratory, the usefulness of inhibin B and AMH in the fertility evaluation in patients undergoing oncological treatment has been demonstrated^{18,19}.

Hyperprolactinemia: the prolactin level is higher than 20 ng/mL²⁰.

Data analysis

A descriptive study is carried out in which quantitative variables are presented in mean and standard deviation, while qualitative variables are presented in absolute frequency and relative percentage.

This study was approved by the Clinical Research Ethics Committee of the Health Research Institute of the *Hospital Universitario and Politécnico La Fe*.

Results

Between January 1997 and December 2016, 267 children were treated at the Hospital La Fe due to central nervous system tumors, of which 53 were MB. Out of these, 30 patients were excluded since half of them (15) present recurrence or were in progression of the disease, 12 had not completed cancer treatment or were recently referred for follow-up in endocrine consultations (< 5 years), and the rest of them (3) were in follow-up in other centers. 23 children have been included in our work since they meet the inclusion criteria.

14 patients are male (60%) and 9 are female (40%). The mean age at tumor onset is 6.4 years (table 1).

Regarding the prognostic factors of the 23 patients, 11 correspond to high-risk MB (they present at least one of these characteristics: under 3 years of age, metastatic spread at the diagnosis, or post-surgical tumor remnant bigger than 1.5cm²), and the remaining patients correspond to standard risk (over the age of 3, no distant metastatic spread (M0), and with total or

almost total resection (tumoral remnant smaller than 1.5 cm)^{21,22}.

The treatment regimen used in these patients is HART (Hyperfractionated Accelerated Radiotherapy) for high-risk MB in 8 cases, PNET IV for standard risk MB in 8 cases, Head Start for children under 3 years of age in 2 cases, PNET III in 4 cases, and SIOP I in one case (Table 2).

The average duration of treatment until the end of RT is 8.4 months since diagnosis. The most frequent RT regimen is the HART one through linear accelerator with 6 MV photons, where craniospinal radiation therapy is the most used in all cases of MB. The mean cumulative dose of cranial RT (posterior fossa boost) is 55.7 Gy and craniospinal 29.2 Gy.

The most frequent endocrine sequel is GH deficiency, which occurs in 82 % of cases (19 patients). After radiation therapy finishes, the average time until growth rate is under -1.5 SD (less than 10th percentile) was 37.7 months. The mean value of maximum GH after the stimulation test is 2.9 ng/mL (range from 0.05 to 8.9). Out of the 19 cases with GH deficiency, 11 (57%) of them received treatment with recombinant human GH. All patients at the time of the deficiency

Table 1. Characteristics of patients according to sex, age, tumor histology, therapeutic regimen received, late endocrinological effects and average time until the onset of the complication

Characteristics	n (%)	
Sexo	Boys	14 (60%)
	Girls	9 (40%)
Age at diagnosis (years)	3-12	
Follow-up time (years)	5-13,5	
Risk group	High-risk MB	11
	Low-risk MB	12
Late effects	n (%)	Time until onset (months)
GH Deficiency	19 (82%)	37,7
Central hypothyroidism	6 (26%)	63,1
Primary hypothyroidism	4 (17%)	
Precocious Puberty	2 (8,6%)	ND*
Hypergonadotropic hypogonadism	1 (4,3%)	
Hypogonadotropic hypogonadism	3 (13%)	
ACTH deficiency	2 (8,6%)	
Overweight	15 (65%)	
Obesity	2 (8,6%)	

Not determined (ND)*: Given the short follow-up of these patients, many will probably be diagnosed with some type of pubertal dysfunction in adulthood.

diagnosis presented IGF-1 levels in normal range according to their age and sex. The average treatment duration is 12.1 months (range from 2.9 to 73.9 months). The mean height at the time of the deficiency diagnosis is -1.6 SD (range from -3.5 to 0.6 SD) (Table 3).

Final height is available in 11 patients of the sample, 4 treated with GH (Table 3), and 7 untreated (Table 4). Only a patient with GH deficiency reaches a final

height according to her target height. The difference in final height regarding target height is similar between both groups with deficiency of male patients untreated and those treated with GH.

The second most frequent endocrine deficiency is the thyroid dysfunction present in up to 10 cases (43.4%). The onset occurs with an average of 63.1 months after finishing RT therapy. Central hypothyroidism

Table 2. Treatment scheme according to protocol

Type	N	Therapeutic regimen
HART for High Risk Medulloblastoma	8	High-dose CT (methotrexate, vincristine, etoposide, cyclophosphamide, carboplatin) + HART RT + double megatherapy (thiotepa) and Autologous Bone-marrow Transplantation.
HIT- SIOPI PNET IV MB standard risk	8	Surgery + RT + 8 CT cycles (cisplatin, lomustine, vincristine)
Schema HEAD Start I/II	2	QT 3 cycles (vincristine, etoposide, cyclophosphamide, cisplatin +/- methotrexate +/- RT + 3 cycles megatherapy (thiotepa, carboplatin) con Autologous Bone-marrow Transplantation
SIOPI PNET III	4	Standard risk Medulloblastome: surgery +/- CT (vincristine, carboplatin, etoposide, cyclophosphamide) + RT High risk Medulloblastome: surgery + CT (vincristine, carboplatin, etoposide, cyclophosphamide) + RT
SIOPI 1	1	Surgery + RT +/- CT (lomustine, vincristine).

CT: Chemotherapy; RT: radiotherapy. MB: medulloblastome; HART: Hyperfractionated Accelerated Radiotherapy; PNET: Primitive neuroectodermal tumor.

Table 3. Target height and Final height in patients with Growth Hormone Deficiency treated with GH

Boys	Target height (cm) (SDS)	Final height (cm) (SDS)	Comparison of Target height with Final height (SDS)
1	163.1 (-2.24)	151.5 (-4)	1.76
2	165.8 (-1.79)	159.9 (-1.06)	-0.73
3	167.6 (-1.37)	163.8 (-1.11)	-0.26
Average height	165.5 (± 2.26 cm)	158.4 (± 6.28)	
Girls	Target height (cm) (SDS)	Final height (cm) (SDS)	Comparison of Target height with Final height (SDS)
1	155.8 (-1.23)	147 (-1.91)	0.68

Table 4. Target height and Final height in patients with Growth Hormone Deficiency NOT treated with GH

Boys	Target height (cm) (SDS)	Final height (cm) (SDS)	Comparison of Target height with Final height (SDS)
1	179.7 (0.32)	164.5 (-0.91)	1.23
2	185 (1.21)	173 (0.44)	0.77
3	164.7 (-2.02)	159 (-2.88)	0.86
4	177.3 (-0.07)	154 (-1.7)	1.63
Average height	176.67 (± 8.60 cm)	162.62 (± 8.13 cm)	
Girls	Target height (cm) (SDS)	Final height (cm) (SDS)	Comparison of Target height with Final height (SDS)
1	160.1 (-0.69)	158.8 (-0.66)	-0.03
2	157.4 (-1.19)	159.3 (-0.6)	-0.59
3	158.3 (-0.6)	157.9 (-0.6)	0
Average height	158.6 (± 1.37 cm)	158.66 (± 0.70)	

dism is the most frequent, present in 6 cases (26%), and Primary hypothyroidism in 4 cases (17%). One patient presented hypothyroidism after thyroidectomy due to papillary thyroid carcinoma. In another patient, a thyroid nodule was detected which, after fine-needle aspiration biopsy, was compatible with colloid cyst. None of the patients developed thyrotoxicosis.

Pubertal dysfunction was detected in 6 cases (26%). Hypogonadotropic hypogonadism was the most frequently present in 3 patients (13%), followed by early puberty in 2 cases (8.6%), and finally, hypergonadotropic hypogonadism in one case (4.3%).

Secondary adrenal insufficiency was present in 2 cases (8.6%). There is no case of hyperprolactinemia, and only one case with central diabetes insipidus at the time of diagnosis.

Regarding body mass index, 4 patients are in normal weight (17%), 2 are underweight (8%), 2 are obese (8%), and 15 are overweight (65%). A patient with obesity which was related to metabolic syndrome followed treatment with statins and metformin.

Discussion

The results of this work include some of the endocrinological late alterations that may appear in children with MB when undergoing oncological treatment.

There is a strong correlation between total radiation dose and the development of hormonal deficiencies, therefore, low radiation doses (18-24 Gy) could cause isolated GH deficiency, while higher doses (> 60 Gy) cause multiple pituitary hormones deficiency. Pituitary atrophy secondary to radiation triggers an increased frequency and severity of longer-term hormonal deficiency after RT treatment²⁴.

GH deficiency was the main deficiency found in our work. Current evidence suggests that up to almost 100% of children treated with radiation doses higher than 30 Gy at some point present a partial GH deficiency². Most studies were conducted within 10 years after diagnosis, thus it is possible that after a longer-term follow-up, a higher incidence of GH deficiency may be detected^{3,5,23}.

In our series, the GH deficiency is also the first one to establish an average of 37.7 months. Several studies have shown that most patients treated for brain tumors present a deficiency between 3 months and 5 years after RT²⁴. Clinical observations reveal that GH-secreting cells are the most radiosensitive, followed by gonadotropin- and adrenocorticotropin-secreting cells. Thyrotrophin is usually the last hormone affected, although variations may occur in this order³. It is recommended to perform the same stimulation tests in case of suspected GH deficiency in children

who have not previously undergone oncological treatment, however, the GH-releasing hormone plus arginine test (GHRH+ARG) may present false negatives^{8,12}. Since GH deficiency is the first to appear, it is possible to diagnose without a stimulation test in patients who do not have adequate linear growth according to their age and pubertal stage, and there are also three more associated pituitary hormones deficiencies¹². In our series, all patients with stunted growth and suspected deficiency underwent stimulation tests since none of them had another pituitary deficiency previously associated.

Some authors make the GH deficiency diagnosis based on the IGF-1 value decrease for the age range and pubertal stage⁵, however, the patients in our sample do not present very low IGF-1 values. Normal IGF-1 values have also been detected in other studies of patients with MB and stunted growth²³. Both IGF-1 and IGFBP-3 have advantage over GH since they present relatively constant serum concentrations throughout the day, allowing random measurements rather than a stimulation test. On the one hand and in relation to IGF-1, a high specificity (>90%) but also a low sensitivity (50-70%) has been suggested, especially in children aged under 5 years, therefore, a low IGF-1 concentration is highly predictive of GH deficiency, however, normal levels do not exclude this entity^{12,25}. On the other hand, although the IGFBP-3 concentration is less affected by nutritional status and age, predictive values similar to those of IGF-1 have been suggested and do not present major diagnostic advantages^{25,26}.

In our series, both patients with GH deficiency untreated and those treated reach a final height below their target. These findings along with the normal IGF-1 values in these patients demonstrate that the suboptimal growth of the survivors of these tumors has a multifactorial origin. Although there are some unknown factors that may affect the final height and also the GH deficiency of these patients, it has been suggested that radiation on the spinal axis delay the growth of vertebral plates and the spinal cord, resulting in a short trunk in relation to disproportionately long limbs (sitting-height ratio more affected than foot size), thus CT could affect the liver production of IGF-1 and/or prevent its action on the growth plate^{27,28}. On the other hand, the precocious puberty diagnosis in these patients may negatively influence the final height by limiting the duration of the pubertal growth spurt and the premature closure of the growth plates.

The second most common endocrine deficiency is thyroid dysfunction. The appearance of both primary and central hypothyroidism may occur after RT, especially when the hypothalamic-pituitary-adrenal axis is within the radiation fields^{4,24}. Also, craniospinal irra-

diation radiates the thyroid gland if the gland is within the radiation fields or as scattered radiation. However, exclusive cranial radiation can also cause a small scattered dose to the thyroid gland, which impact has been less documented³.

In 6 patients, alterations in pubertal development were observed. This disorder occurs most often due to radiation damage in the hypothalamic-pituitary-gonadal axis, and less frequently due to the CT used^{2,3}. The most frequently detected alteration was the hypogonadotropic hypogonadism, followed by precocious puberty, which was observed in 4 women and 2 men. Some cytotoxic drugs used in treatment regimens such as lomustine, busulfan as well as high doses of cisplatin have gonadotoxic effects²³.

It is believed that precocious puberty after RT is caused by the loss of inhibition exerted by the cerebral cortex on the hypothalamus. With low and high radiation doses (25-50 Gy) some authors describe a higher incidence of precocious puberty in girls than in boys, although for other authors the incidence is similar between men and women^{3,23}.

Diabetes insipidus appeared only in one case and it did at the diagnosis of the tumor. In general, central diabetes insipidus often occurs in the presence of tumors in the pituitary or hypothalamus region or after surgical treatment in these regions, and in addition, it is rarely reported after cranial irradiation.

Obesity is caused by hypothalamic damage, either by direct intervention of the tumor or by the effect of surgery and RT³. The ventromedial hypothalamus damage can cause hyperphagia and obesity due to a direct effect on appetite control centers or due to the vagal tone disinhibition at the pancreatic beta-cell level, leading to insulin hypersecretion and obesity. Insulin hypersecretion has been observed in patients with obesity caused by a brain tumor or cranial irradiation²⁹.

It has been shown that ACTH deficiency requires high doses of radiation (above 30-40 Gy) and doses under 24 Gy are infrequent. In addition, its presentation is also time-dependent, thus when it is suspected, there are usually other associated pituitary deficiencies. For this reason, no stimulation test was performed in the two patients with suspected stimulation deficiency. However, regardless of the underlying cause of the ACTH deficiency, there is consensus in the performance of diagnostic tests¹². Currently, the low-dose ACTH stimulation test (250 µg) has a high validation degree. Another variation uses a low dose of 1 µg for adrenal stimulation but, according to the available data, the

latter does not present better diagnostic accuracy than the test with 250 µg¹¹.

Conclusions

Long-term follow-up of central nervous system tumor survivors treated with CT and RT shows a high prevalence of endocrine dysfunction. The frequency and severity of hormonal deficiencies increase with the time elapsed since the end of the treatment, especially the GH deficiency which is the first one that usually occurs, although it is possible that there is a multifactorial origin of the stunted growth of these patients. Since our sample size is small, no conclusions can be drawn regarding the final height related to GH treatment in those patients with deficiencies. However, given the known high prevalence of pituitary hormone deficiencies in patients undergoing CT and RT, we consider that long-term follow-up is crucial given the complications that may arise.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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Authors state that no economic support has been associated with the present study.

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