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ORIGINAL ARTICLE

Endocrinological outcome in children and adolescents survivors of central nervous system tumours after a 5 year follow-up☆,☆☆

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KEYWORDS
Childhood brain tumours;
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Abstract
Introduction: Given the successful increase in survival rates with the current treatments for central nervous system tumours (CNST), survivors are at high risk for late adverse effects.
Purpose: To evaluate the endocrine sequelae in children with CNST according to the type of tumour and treatment received.
Patients and methods: A retrospective review of the clinical features, auxology, hormone determinations and imaging findings of 38 patients (36.8% females, 63.2% males) with CNST, with a minimum of 5 years follow-up, was performed.
Results: The mean age at diagnosis was 5.34±3.07 years, with 76.3% of the patients having at least one hormone deficiency, of which growth hormone (GH) (73.7% of all patients) was the most prevalent, followed by thyrotropin (TSH) (68.4%), corticotropin (31.6%), antidiuretic hormone (28.9%), and gonadotropin (LH/FSH) (21.1%) deficiency. Precocious puberty was found in 21.1% of patients. After 5 years of follow-up, 28.9% were obese. Craniopharyngioma had more hormone deficiencies, obesity and recurrence rates. The most frequently administered treatment was surgery + chemotherapy + radiotherapy, in 47.4% of the patients. Mean final height (20 patients) was -1.2 1.6 SDS, with a mean difference of -0.53 SDS regarding their target height.
Conclusions: 1) The type of tumour and treatment received influence the endocrinological sequelae. 2) The most frequent hormone deficiencies in all types of CNST, regardless of the

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treatment received, were GH and TSH. 3) Early diagnosis and prompt intervention of endocrine dysfunction can reduce the morbidity and improve quality of life over the long term.

PALABRAS CLAVE
Tumores cerebrales infantiles;
Secuelas endocrinas;
Eje hipotálamo-hipofisario;
Supervivientes de cáncer

Secuelas endocrinológicas en niños y adolescentes supervivientes de tumores del sistema nervioso central tras 5 años de seguimiento

Resumen
Introducción: Con las terapias actuales, la supervivencia de los tumores del sistema nervioso central (TSNC) es cada vez mayor y, con ello, las complicaciones a largo plazo.
Objetivo: Evaluar las secuelas endocrinológicas en niños con TSNC en relación con el tipo de neoplasia y el tratamiento recibido.
Sujetos y métodos: Se revisaron retrospectivamente los datos clínicos, auxológicos, analíticos y radiológicos de 38 pacientes (36,8% mujeres y 63,2% varones) con antecedente de TSNC y seguimiento mínimo de 5 años.
Resultados: La media ± desviación estándar de edad al diagnóstico fue de 5,34 ± 3,07 años. El 76,3% de los casos presentó al menos un déficit hormonal, siendo el más prevalente el de hormona de crecimiento (GH) (73,7%), seguido de los déficits de tirotropina (TSH) (68,4%), corticotropina (31,6%), hormona antidiurética (28,9%) y gonadotropinas (LH/FSH) (21,1%). El 21,1% de los pacientes presentaron pubertad precoz. A los 5 años de seguimiento, el 28,9% presentaba obesidad. El craneofaringioma fue el tipo tumoral que registró mayor número de casos con deficiencias hormonales, obesidad y tasa de recurrencia. El tratamiento más frecuentemente administrado fue la combinación de cirugía + quimioterapia + radioterapia, empleado en el 47,4% de los pacientes. La talla final media ± desviación estándar (20 pacientes) fue −1,2 ± 1,6; con una disminución media de −0,53 DE respecto de su talla diana.
Conclusiones: 1) El tipo tumoral y el tratamiento recibido influyen sobre las secuelas endocrinológicas; 2) las deficiencias hormonales más frecuentes en todos los tipos de TSNC, independientemente del tratamiento recibido, fueron GH y TSH; 3) el diagnóstico precoz y la intervención temprana sobre la disfunción endocrina, reducen la morbilidad y mejoran la calidad de vida a largo plazo.

Introduction

In childhood, central nervous system tumours (CNST) are the most frequent type of solid neoplasm and the second leading cause of malignancies (20-25% of the total[1]) following haematological malignancies.[2] The incidence of CNST in our environment is 3/100,000[1] in children below 15 years of age, with a male to female ratio of 1.2.[2]

In terms of location, CNST are predominantly supratentorial in the first two years of life; from then up to ten years, infratentorial, with the supratentorial location once again predominating during adolescence and adulthood.[2] The most common histologic types are astrocytoma (24%), glioma (22%), medulloblastoma/ primitive neuroectodermal tumours (10%), pituitary tumours and craniopharyngioma (10%), ependymoma (6%) and germinoma (4%).[1]

Treatment for most CNST includes surgery, except for poorly circumscribed or unresectable tumours. The surgical mortality rate for experienced surgeons is 1%[3] and morbidity varies according to tumour location and adjuvant therapy.[3] The indication of radiotherapy depends on tumour histology[2] and can be delivered focally (on the tumour itself) or to the whole brain and spine with a boost given at the tumour site.[3] CNST in children require high doses of radiation, typically > 30 Gy (frequently 50-60 Gy).[3] Age is a risk factor for developing long-term complications of radiotherapy, with profound intellectual disturbances appearing in children who receive radiation before 3 years of age.[4] The use of chemotherapy in the treatment of CNST has increased in recent years, and it has become the standard treatment to avoid radiotherapy in children younger than 3 years.[5] The agents used for chemotherapy depend on the sensitivity of each tumour type.

With the current treatment protocols, survival rates of CNST keep rising (73.3% at 5 years of age[6,7]) leading to long-term endocrine sequelae (43% of cases).[8] These effects are associated to the tumour's direct effect, its location, spread to and infiltration of other structures, treatment received, age at diagnosis, sex, and time elapsed since the end of treatment.[6] Due to the vulnerability and the limited restorative capacity of brain tissue, CNST survivors have a high risk of adverse effects.[9,3] A late effect is defined as any chronic physical, medical, cognitive, or psychosocial sequela occurring 5 years after the diagnosis of a tumour. The 5-year timeframe[10] is due to the fact that this is the time interval usually considered to define cancer survival.[11]

Objective

To evaluate the rates of endocrinological sequelae in children with CNST followed up at the Department of Endocrinology

of the Hospital Infantil Universitario Niño Jesús in Madrid, Spain, according to the type of neoplasm and the treatment received.

Subjects and methods

We performed a retrospective review of the medical records of patients with CNST with a follow-up period of at least five years between December 2011 and February 2012.

Endocrinological abnormalities were determined by the following evaluations:

Clinical and auxological

- Growth monitoring: weight, height and body mass index (BMI) at the time of diagnosis and every six months until adult height was reached.
- Physical examination: general, pubertal and thyroid at the time of diagnosis and at each visit until completion of pubertal development.

Laboratory and imaging studies

- Yearly assessment of insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), thyroid function (TSH and free T4), prolactin, morning cortisol and testosterone/estradiol (the latter depending on pubertal stage). In addition, stimulation tests were performed [for growth hormone (GH) (clonidine and insulin tolerance tests), gonadotropins (FSH, LH) (gonadotropin-releasing hormone test) and corticotropin (ACTH test)] when deficiency of these hormones was suspected.
- Imaging studies: annual bone age. Yearly thyroid ultrasound in case of cranial/spinal irradiation. Head magnetic resonance imaging as determined by the oncology team. Pelvic ultrasound to assess the onset/progression of puberty or in patients who had received spinal radiotherapy or gonadotoxic chemotherapy.

Results

The study included 38 patients with a mean age at diagnosis ± standard deviation (SD) of 5.34 ± 3.07 years. The distribution by sex was 36.8% female and 63.2% male.

Tumour type and frequency were medulloblastoma 26.3% (n = 10), craniopharyngioma 21.1% (n = 8), astrocytoma 18.4% (n = 7), germ cell tumour 10.5% (n = 4), ependymoma 10.5% (n = 4), glioma 2.6% (n = 1) and other 10.5% (n = 4). The four cases of "other tumour types" were 2 hamartomas and 2 rhabdomyosarcomas.

Among the studied patients, 76.3% had at least one hormone deficiency. The most prevalent deficiency was GH, found in 73.7% of cases, followed by TSH (68.4%), ACTH (31.6%) and LH/FSH (21.1%). Early puberty happened in 21.1% (n = 8) of these patients. At the five-year follow-up, 28.9% were obese (defined as BMI > 2 SDS in accordance with the references of Hernández et al., 1988). We found tumour relapse in 34.2% (n = 13) of cases and a secondary malignancy in 5.3% (n = 2), with no deaths during follow-up. One of the secondary neoplasms occurred in a male diagnosed with glioma, who was treated with surgery + cranial radiotherapy + chemotherapy, and years later was diagnosed with nodular basal cell carcinoma in the frontoparietal region. The other case was a male diagnosed with germinoma who

Table 1 Type of tumours and endocrinological sequelae recorded. Number and percentage of cases in parentheses. Mean time ± SD, expressed in years, elapsed between the start of treatment and the hormone disturbance.

Tumour type	GH deficiency	TSH deficiency	ACTH deficiency	ADH deficiency	LH/FSH deficiency	Early puberty
Medulloblastoma (n = 10; 26.3%)	(n = 9; 90%) 4.14 ± 1.80	(n = 10; 100%) 4.47 ± 3.60	(n = 1; 10%) 4.67 ± 0	(0)	(n = 1; 10%) 4.67 ± 0	(0)
Craniopharyngioma (n = 8; 21.1%)	(n = 8; 100%) 2.55 ± 2.99	(n = 8; 100%) 0.39 ± 0.57	n = 7; 87.5%) 0.52 ± 0.76	(n = 8; 100%) 0 ± 0	(n = 5; 62.5%) 5 ± 1.3	(0)
Astrocytoma (n = 7; 18.4%)	(n = 3; 42.8%) 7.7 ± 3.88	(n = 2; 28.6%) 4.54 ± 1.23	(n = 1; 14.3%) 12 ± 0	(0)	(n = 2; 28.6%) 12.21 ± 0.41	(n = 3; 42.8%) 5.55 ± 4.35
Germinoma (n = 4; 10.5%)	(n = 3; 75%) 1.32 ± 1.16	(n = 3; 75%) 0 ± 0	(n = 3; 75%) 0 ± 0	(n = 3; 75%) 0 ± 0	(0)	(n = 2; 50%) 8 ± 1.40
Ependymoma (n = 4; 10.5%)	(n = 2; 50%) 2.86 ± 1.21	(n = 1; 25%) 2 ± 0	(0)	(0)	(0)	(0)
Glioma (n = 1; 2.6%)	(n = 1; 100%) 7.92 ± 0	(n = 1; 100%) 13.92 ± 0	(0)	(0)	(0)	(n = 1; 100%) 8 ± 0
Other (n = 4; 10.5%)	(n = 2; 50%) 4.96 ± 1.71	(n = 1; 25%) 6 ± 0	(0)	(0)	(0)	(n = 2; 50%) 8.7 ± 1.35
Total (n = 38; 100%)	(n = 28; 73.7%)	(n = 26; 68.4%)	(n = 12; 31.6%)	(n = 11; 28.9%)	(n = 8; 21.1%)	(n = 8; 21.1%)

ACTH: adrenocorticotropic hormone or corticotropin; ADH: antidiuretic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone or thyrotropin; SDS: standard deviation score; n: number of cases.

Table 2 Type of tumour and cases with obesity (BMI > 2 SDS), relapse, and secondary malignancies. Number and percentage of recorded cases.

Tumour type	Obesity	Relapse	Secondary tumour
Medulloblastoma (n = 10; 26.3%)	n = 2; 20%	n = 2; 20%	0
Craniopharyngioma (n = 8; 21.1%)	n = 4; 50%	n = 6; 75%	0
Astrocytoma (n = 7; 18.4%)	n = 1; 14.3%	n= 3; 42.8%	0
Germinoma (n = 4; 10.5%)	n = 1; 25%	n = 1; 25%	n = 1; 25%
Ependymoma (n = 4; 10.5%)	0	n = 1; 25%	0
Glioma (n = 1; 2.6%)	N = 1; 100%	0	n = 1; 100%
Other (n = 4; 10.5%)	N = 2; 50%	0	0
Total (n = 38; 100%)	n = 11; 28.9%	n = 13; 34.2%	n = 2; 5.3%

SDS: standard deviation score; BMI: body mass index.

Table 3 Mean interval, expressed in years, between treatment and presentation of hormone deficiency.

Hormone deficiency	Years after surgery (mean ± SDS)	Years after radiotherapy (mean ± SDS)	Years after chemotherapy (mean ± SDS)
GH	3.9 ± 2.8	4.1 ± 2.1	4.4 ± 2.6
TSH	2.9 ± 3.4	3.4 ± 3.5	3.8 ± 3.7
ACTH	2.0 ± 3.9	3.6 ± 4.4	5.2 ± 5.5
LH/FSH	7.3 ± 3.7	8.1 ± 3.1	8.7 ± 3.6

ACTH: adrenocorticotropic hormone or corticotropin; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone or thyrotropin; SD: standard deviation.

received cranial radiotherapy + chemotherapy, and years later was diagnosed with papillary thyroid carcinoma. Tables 1 and 2 show the different tumour types, endocrinological sequelae, relapse, and secondary malignancies, as well as the time interval between treatment administration and hormone disturbance.

Due to its location, craniopharyngioma was the type of tumour with the highest number of cases of hormone deficiencies, obesity, and relapse rate. All craniopharyngioma cases (n = 8) presented GH, TSH, and ADH deficiency, 7 of them also presented ACTH deficiency, and 5 cases had hypogonadotropic hypogonadism.

Table 3 shows the mean time elapsed between treatment administration and the manifestation of each hormone deficiency. The emergence of pituitary hormone deficiencies (of all types) occurred sooner after surgery than after radiotherapy or chemotherapy. ADH deficiency was present from the start of treatment in all patients with this deficiency (11 cases of the total, consisting of 8 craniopharyngiomas and 3 germinomas).

The most frequently administered treatment was a combination of surgery + chemotherapy + radiotherapy, which was used in 47.4% of the patients; followed by surgery + radiotherapy in 24% of cases. The different types of treatment used and the endocrinological sequelae are shown in Tables 4 and 5. No patient received radiotherapy alone. Out of the 30 patients who were given radiotherapy (78.9% of the total), 28.9% (n = 11) received whole brain and spine irradiation, while 50% (n = 19) received cranial irradiation alone. Only one patient was treated with chemotherapy alone, a male with astrocytoma who had an early onset of puberty at 5.55 years of age, and who has not shown any endocrinological disturbance during follow-up, with a final height of +0.93 SDS, no relapse and no secondary neoplasms. One patient diagnosed with hypothalamic hamartoma at age 7.75 years was treated with GnRH analogues, and developed obesity during the 5-year follow-up.

Final height data were available for 20 patients, with mean −1.2 ± 1.6 SDS. This corresponds to a mean decrease of −0.53 SDS in relation to the target height.

Discussion

This study shows that after 5 years of follow-up for CNST, 76.3% of cases had one or more endocrinological abnormalities, a figure close to that reported in other series (80%)[12], although other groups have shown lower rates of 50%[1] or 43%.[8] Neuroendocrine effects can be caused by damage to the hypothalamus (GH deficiency) or specific organs (thyroid, gonads).[3]

In this study, the most frequent type of tumour was medulloblastoma (26.3%), which according to the literature is one of the most prevalent CNST histological types. Tumour histology alone is not an indicator for the emergence of late effects, but does play an indirect role as a sequelae indicator because treatment modality varies by tumour type.[3] Combined surgery + radiotherapy + chemotherapy was the treatment modality most used (47.4%). Currently, 25% of patients receive neurosurgery alone, 40% surgery + radiotherapy, and 30% surgery + radiotherapy + chemotherapy, depending on age, histology, and tumour site.[1,8] It is assumed that there

Table 4 Treatment received and endocrinological sequelae. Number of cases (in parentheses) and percentage.

Tumour type	GH deficiency	TSH deficiency	ACTH deficiency	ADH deficiency	LH/FSH deficiency	Early puberty
Surgery alone (n = 5; 13.15%)	(n = 4) 80%	(n = 3) 60%	(n = 2) 40%	(n = 3) 60%	(n = 2) 40%	(n = 1) 20%
Chemotherapy alone (n = 1; 2.6%)	0	0	0	0	0	(n = 1) 100%
Surgery + radiotherapy (n = 9; 24%)	(n = 7) 77.8%	(n = 7) 77.8%	(n = 5) 55.6%	(n = 5) 55.6%	(n = 3) 33.3%	(n = 1) 11.1%
Surgery + chemotherapy (n = 1; 2.6%)	0	0	0	0	0	0
Surgery + radiotherapy + chemotherapy (n = 18; 47.4%)	(n = 15) 83.3%	(n = 15) 83.3%	(n = 4) 22.2%	(n = 2) 11.1%	(n = 3) 16.7%	(n = 3) 16.7%
Chemotherapy + radiotherapy (n = 3; 7.9%)	(n = 2) 66.7%	(n = 1) 33.3%	(n = 1) 33.3%	(n = 1) 33.3%	0	(n = 1) 33.3%
Other (n = 1; 2.6%)	0	0	0	0	0	(n = 1) 100%
Total (n = 38; 100%)	(n = 28) 73.7%	(n = 26) 68.4%	(n = 12) 31.6%	(n = 11) 28.9%	(n = 8) 21.1%	(n = 8) 21.1%

ACTH: adrenocorticotropic hormone or corticotropin; ADH: antidiuretic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone or thyrotropin; n: number of cases.

Table 5 Therapeutic modalities and cases with obesity, relapse, and secondary tumours. Number of cases (in parentheses) and percentage.

Tumour type	Obesity	Relapse	Secondary malignancy
Surgery alone (n = 5; 13.15%)	(n = 1) 20%	(n = 2) 40%	0
Chemotherapy alone (n = 1; 2.6%)	0	0	0
Surgery + radiotherapy (n = 9; 24%)	(n = 4) 44.4%	(n = 6) 66.7%	0
Surgery + chemotherapy (n = 1; 2.6%)	0	0	0
Surgery + radiotherapy + chemotherapy (n = 18; 47.4%)	(n = 4) 22.2%	(n = 5) 27.8%	(n = 1) 5.6%
Chemotherapy + radiotherapy (n = 3; 7.9%)	(n = 1) 33.3%	0	(n = 1) 33.3%
Other (n = 1; 2.6%)	(n = 1) 100%	0	0
Total (n = 38; 100%)	(n = 11) 28.9%	(n = 13) 34.2%	(n = 2) 5.3%

BMI: body mass index; n: number of cases.

are few late effects in patients treated with surgery alone.[8] However, our study data differed in this respect, with high percentages of nearly all endocrinological alterations in these patients. It is believed that the risk for late effects is high for patients treated with radiotherapy and surgery, and even higher for those given adjuvant chemotherapy[8], and we also observed this in our study.

There is a strong correlation between hypothalamic-pituitary dysfunction and radiotherapy, which is dose-[13-15] and time-dependent.[16,17] The age at which radiation is administered influences some hormone deficiencies[1] (GH) but not others.[18] In CNST, the hypothalamic-pituitary region receives a mean dose of 53.6 Gy (40-70 Gy). It has been proposed that after cranial radiation, endocrinopathies emerge in the following sequence[19]: GH (4.5 years), LH/FSH (8 years), ACTH (9-10 years) and TSH (> 10 years).[18] Hyperprolactinaemia and diabetes insipidus usually occur afterwards. Chemotherapy potentiates the deleterious effects of radiotherapy on pituitary function, but there is no evidence that it causes neuroendocrine dysfunction on its own.[17,20]

GH axis. GH deficiency is the endocrinopathy most frequently associated to CNST in this and other studies.[3] We found evidence of GH deficiency in 73.7% of the patients, which is consistent with other studies (70%[6,13,14,21] or even 97%[12]), although in other series it was found in only 35.1%[1] or 21% of cases.[8] Some of these studies may have underestimated the rates of endocrinopathy because the diagnosis was based on patient/family self-reports[8], rather than on laboratory results as was the case in this and other studies.[12] Receiving treatment at an earlier age is associated with a higher prevalence of GH deficiency.[3]

GH deficiency is the most frequent, earliest[6] and most studied complication after cranial radiotherapy, as it develops in 52-100% of patients.[13] GH neurosecretory dysfunction is usually detected with doses ranging from 18-24 Gy, while total GH deficiency appears with doses > 30 Gy (and the higher the radiation dose, the earlier it develops). As was seen in our study, the risk for GH deficiency is high in medulloblastoma and optic glioma cases, because of the high radiation doses. GH deficiency is irreversible and can appear from 3 months to 6 years post-radiotherapy.[14] In our study it appeared after 4.1 ± 2.1 years (mean ± SDS). GH deficiency is caused by hypothalamus dysfunction from altered counterregulatory mechanisms controlled by the GHRH/somatostatin system, as the hypothalamus is more radiosensitive than the pituitary gland, the latter becoming damaged only with higher doses of radiation.[22] There is consensus that a failed GH stimulation test following hypothalamic-pituitary irradiation suffices to diagnose GH deficiency.[23] Published studies have employed different tests (stimulation or spontaneous secretion) with different sensitivities for the diagnosis, and may have underestimated its incidence depending on the test used.[18] In some patients with GH deficiency, the levels of IGF-1 and IGFBP-3 may be normal due to overweight and a nutritional regulation.[24]

Spinal axis irradiation diminishes the growth of the spinal growth cartilages and bone marrow, resulting in a short trunk in relation to disproportionately long limbs (sitting height more affected than standing height).[19,25] Medulloblastoma and ependymoma are treated in this way, and patients may lose up to 9-10 cm if they are irradiated in the first year of life, and 7 cm if they receive radiation at 5 years of age.

The effects of chemotherapy on growth plate cartilage are not well known.[20,26,27] One study demonstrated that the effect of chemotherapy on final height was as important as the effect of spinal radiotherapy in CNST survivors treated with GH.[26] Cytotoxic agents could amplify hypothalamic-pituitary damage caused by radiation[17] and affect hepatic production of IGF-1[24] and/or inhibit its action on the growth plate.

Final heights in our patients fell within normal parameters, with a mean difference from the target height of −0.53 SDS, whereas other studies have published final heights significantly shorter than the mid-parental heights[1], and even with 40% of the final heights below the 10th percentile.[26] Final heights below the target height could be due to GH deficiency, radiation-induced damage to the spine and the long bones, malnutrition due to reduced food intake, tumour relapse, chemotherapy, steroid therapy, early puberty, and other endocrinopathies.[18] There is an association between short stature in adulthood and younger age at diagnosis.[26,28]

TSH axis. Our series presented a high rate of hypothyroidism (68.4%) compared to figures of 28% in other cohorts.[15] A cranial radiotherapy dose > 30 Gy[16,27,29] can lead to central hypothyroidism, which is less frequent than primary hypothyroidism secondary to cervical radiotherapy or chemotherapy.[15] One study shows central hypothyroidism rates of 6%[30], while another study shows a rate as high as 14.9%.[1] Some studies[28,31] show a higher incidence rate of primary hypothyroidism in survivors who have received radiotherapy in combination with chemotherapy (70-75%) than in those who received radiotherapy alone (20-25%)[31], an association that has not been found in other studies.[32] There is controversy on whether cranial radiotherapy alone poses a lower risk of hypothyroidism[31] than craniospinal irradiation.[15] There is debate as to whether TSH and free T4 tests are sensitive enough to diagnose hypothyroidism, or whether a TRH test or a measurement of the nocturnal TSH surge should be performed.[18]

Gonadal axis. Early puberty is characteristic of hamartomas, optic gliomas, ependymomas, and astrocytomas. If the radiotherapy dose is > 18 Gy these tumours can cause early/accelerated puberty by interrupting the influence of cortical inhibition on hypothalamic GnRH neurons.[11] Paradoxically, doses > 30-50 Gy[18] are also associated to hypogonadotropic hypogonadism.[11,15] Our study and others show how, unlike GH and TSH deficiencies, which usually manifest 2-3 years post-treatment, GnRH deficiency will not be diagnosed until puberty or adulthood, making its incidence harder to quantify.[12] We observed that 21.1% of our cases, similar to what is reported in the literature (16-40%[33]), presented arrested or delayed pubertal development, or secondary amenorrhea. This is found more commonly in cases of craniopharyngioma, Langerhans cell histiocytosis, and germinoma. It is unclear whether chemotherapy alone can alter gonadotropin secretion.

Radiotherapy and chemotherapy may cause primary gonadal disorders.[6] One study found that spinal irradiation for CNST was associated to a 35% rate of ovarian dysfunction and a 3% rate of testicular dysfunction[12] (dispersed radiation reaches the ovaries more easily due to proximity).[4] Some chemotherapy agents can produce sex hormone deficiencies in both sexes.[34] These effects can result in reduced fertility.[34]

ACTH axis. We found a 31.6% rate of ACTH deficiency in CNST survivors, greater than the 3-7.9%[1] described in the literature. Transient suppression of ACTH production due to the prolonged use of corticosteroids in cancer treatment is found most frequently. It can also be due to the damage done directly by the tumour, surgical injury to the hypothalamus or pituitary gland, or to radiotherapy doses > 30-50 Gy.[27] The literature shows an ACTH deficiency incidence rate of 19-38% following radiotherapy for CNST, with a dose-effect relationship.[16] The reference test for diagnosing ACTH deficiency is the insulin tolerance test, but most healthcare sites use the short ACTH test or the glucagon stimulation test, which explains the variation in the diagnosis rate of this deficiency.[18]

Other endocrinopathies. ADH deficiency of ≥ 90% produces clinical manifestations of diabetes insipidus, which we diagnosed in 28.9% of our patients, as opposed to 10.5%[1] in other series. Diabetes insipidus appears more frequently in tumours affecting the infundibulum (craniopharyngioma, germinoma and optic glioma)[1], as well as following surgery. Although it is uncommon, it has also been described in association to radiotherapy doses > 45 Gy.[35]

Depending on the area and extent of hypothalamus that has been affected, different eating disorders will emerge, ranging from diencephalic cachexia in hypothalamic gliomas to severe obesity in craniopharyngiomas with hypothalamic involvement. We found obesity in 28.9% of patients, especially following the combination of surgery + radiotherapy and in craniopharyngiomas. This figure is higher than the 7% reported in other series[1] or even

in another study that found that BMI did not differ from BMI in age-matched controls.[36] Another study found that cranial radiotherapy doses > 20-50 Gy, especially in girls irradiated before 4 years of age, were significantly correlated with hypothalamic obesity.[10] For tumours that appear and/or are treated in the suprasellar region, obesity is of hypothalamic origin (40-50%), due to damage to the ventromedial area that integrates information from the peripheral hormones (leptin, ghrelin, and insulin). This disruption leads to hyperphagia. Other factors contributing to this type of obesity are glucocorticoids, GH deficiency (increased fat mass, decreased strength) and decreased physical activity.[10] Other hypotheses include vagally mediated hypothalamic hyperstimulation of pancreatic β-cells leading to hyperinsulinism and obesity, increased ghrelin secretion, decreased postprandial ghrelin suppression, and the potential role of α-melanocyte-stimulating hormone.[36]

Tumours secondary to CNST treatment are uncommon, but have potentially devastating consequences. They develop frequently in the CNS[11] (meningioma, malignant astrocytoma) but also in other locations (soft tissue sarcoma, thyroid carcinoma, skin carcinoma and lymphoma).[37] The risk for secondary malignancies is reported as 1-2% at 2-8 years[21] or 2.1% at 20 years following treatment of CNST.[38] One study showed that patients who received cranial radiation ≥ 50 Gy for CNST had a 7.1% incidence of secondary cranial tumour 25 years after initial diagnosis, compared to 1% in patients who had not been treated with radiation.[11] Cranial and/or spinal irradiation is a risk factor for the development of thyroid nodules, a large percentage of which are malignant.[18,35]

In adult survivors of childhood CNST, the mortality rate 30 years after diagnosis is 25.8% (13 times higher than that of age- and sex-matched controls in the USA), mostly due to recurrence and/or progression of the primary condition.[11] In our study, the recurrence rate was 34.2%, which was in a large extent, due to craniopharyngioma relapse.

In conclusion, tumour type and treatment modality determine endocrine sequelae. The most frequent hormone deficiencies following treatment of all types of CNST, regardless of treatment modality, were GH and TSH. Early diagnosis of endocrine dysfunction and prompt intervention reduce morbidity and can improve long-term quality of life. Life-long medical follow-up is needed, as complications can arise years after treatment.

Conflicts of interest

The authors declare having no conflicts of interest.

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