

ORIGINAL ARTICLE

## Addressing the post-irradiation hypothalamic-pituitary endocrine abnormalities of brain tumors in pediatric patients

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### Summary

**Purpose:** Hypothalamic-pituitary axis is susceptible to radiotherapy, causing endocrine disorders to childhood cancer survivors. We conducted a systematic review in order to assess the radiation-induced toxicity that leads to hormone secretion abnormalities and their severity in children with brain tumors.

**Methods:** The data were collected by relevant studies on PubMed and EMBASE. Articles up to December 2016 were included. We selected studies which focused on children patients (<18 yr old) with brain tumors treated with radiotherapy and the consequences for their endocrine system.

**Results:** Growth hormone (GH) deficiency was the most common post-irradiation abnormality among children cancer survivors, followed by gonadotrophin (GT), thyroid stimulating hormone (TSH), corticotropin (ACTH) and prolactin (PRL) disorders.

**Conclusions:** The age of the patient, total radiotherapy dose, number of fractions, fraction size and the duration of treatment seem to determine the severity of these disturbances.

**Key words:** brain, endocrine abnormalities, pediatric, radiotherapy, tumors

### Introduction

The central nervous system (CNS) tumors represent the second most frequent childhood malignancy [1]. More specifically, low grade gliomas (LGG) are the CNS malignancies most diagnosed in children, representing a percentage of 35% [2]. Survival rates (5-year survival is almost 80%) appear to be improved over the past years due to the remarkable progress in diagnosis and treatment of children with brain tumors [3].

Although surgical approach represents the gold standard in therapeutic management of these patients, radiotherapy can be selected as the primary treatment when the tumor has central location and multifocal appearance. The radiation field can include the tumor itself or the whole brain and spine. A boost dose is given at the tumor site [4,5].

The most common childhood brain tumors treated with radiotherapy (mostly combined with

surgery) according to the International Classification of Childhood Cancer are the following: ependymomas, choroid plexus tumor, astrocytomas, intracranial and intraspinal embryonal tumors (including medulloblastomas, PNET, medulloepithelioma, atypical teratoid/rhabdoid tumor), other gliomas (including oligodendrogliomas, mixed and unspecified gliomas, neuroepithelial glial tumors of uncertain origin), other specified intracranial and intraspinal neoplasms (including pituitary adenomas and carcinomas, craniopharyngiomas, pineal parenchymal tumors, neuronal and mixed neuronal-glial tumors, meningiomas) and unspecified intracranial and intraspinal neoplasms [6]. Except for the primary brain tumors, radiotherapy is also delivered for the treatment of head and neck tumors, nasopharyngeal and skull base tumors or prophylactically in cases of acute lymphoblastic leukemia (ALL) and after total-body irradiation before bone marrow transplant.

Radiotherapy schedule for the treatment of childhood CNS tumors include doses >30 Gy (usually 50-60 Gy) whereas prophylactic irradiation doses for ALL range from 18 to 24 Gy [5]. When the hypothalamic-pituitary axis (H-P axis) is involved in the radiation field, multiple endocrine disturbances may occur due to its radio-sensitivity. Almost the 43% of the children treated with radiotherapy for brain tumors will develop at least one endocrine insufficiency. In the Childhood Cancer Survivor Study [9] (CCSS), 43% of children treated for cerebral tumors had one or more endocrinopathies. Consequently, structured follow-up programs for childhood cancer survivors include endocrine assessments. The total dose of radiation, the fraction size, the number of fractions and the total duration of treatment determine the biological impairment of the H-P axis and as a result the appearance of abnormalities in the hormonal secretion by the anterior pituitary. H-P axis' dysfunction is more vulnerable when a hypofractionated schedule is applied (large fraction size in a short period of time) instead of a schedule with small fraction size and long duration [7].

## Methods

A systematic literature review was performed based on database search in PubMed/MEDLINE and EMBASE and included articles up to December 2016. The terms used for the search were 'Brain Tumors', 'Radiotherapy', 'Irradiation', 'hypothalamus', 'hypophysis', and synonyms combined with one or more of the following: 'endocrine disorders', 'pediatric patients'. Furthermore, these terms were combined with the respective key words for each paragraph. Publications mentioned in the reference list found in the database

search and considered suitable were manually searched for. Clinical phase I, II, randomized phase III and IV studies, reviews, meta-analyses and abstracts of important meetings were analyzed. Only articles published in English were included.

## Evidence synthesis

The pituitary gland lies in the sella turcica, a cavity of the sphenoid bone in the base of the skull. It is connected anatomically with the hypothalamus through the connecting stalk. The pituitary consists of two lobes that have not only different embryological origin but also a different physiological function: the anterior lobe or adenohypophysis and the posterior lobe or neurohypophysis. The ectoderm and more specifically Rathke's pouch gives rise to the adenohypophysis whereas the neurohypophysis is derived from the neuroectoderm. The anterior lobe is responsible for the secretion of the following hormones: GH, TSH, the gonadotrophins, including luteinizing hormone (LH) and follicle stimulating hormone (FSH), ACTH and PRL. It produces also the endorphin, a polypeptide which inhibits the perception of pain and the beta-lipotropin, a fat-mobilizing protein hormone. Stimulated hypothalamic neurons secrete either stimulating or inhibiting hormones which are transferred through the hypophyseal portal system to the anterior lobe regulating the release of hormones by the adenohypophysis. The neurohypophysis could be considered as a hypothalamus' extension. Neurons originating at the supraoptic and paraventricular nuclei of the hypothalamus produce the hormones vasopressin and oxytocin which are transferred through the hypothalamic-hypophyseal tract to the posterior pituitary, where they are stored in axon terminals and are released to the systematic circulation [8,9].

## Growth hormone disorders

GH is the first hormone to be affected by brain irradiation for the treatment of tumors and infiltrative diseases such as histiocytosis, sarcoidosis, hemochromatosis, tuberculosis and lymphocytic hypophysitis [4,5,10-15,16]. Children with ALL can also receive CNS prophylactic radiotherapy, including the spine. Considering GH's important physiological function during childhood, GH deficiency has major clinical consequences for the children treated with radiotherapy including short stature, diminished quality of life, slow muscular development, increased subcutaneous fat and reduced bone density. Furthermore, GH deficiency persisting throughout adulthood appears to aggra-

vate cardiovascular risk profile [17]. Post-irradiation GH abnormalities appear to be both dose- and time-dependent [5,10-12,15]. Total doses of 18 Gy to the hypothalamic-pituitary region cause significant deviation from the normal spontaneous GH secretion as far as quality and quantity are concerned. After a dose of 24 Gy or more, spontaneous secretion is decreased but provoked GH level can be normal and after 27 Gy or more both spontaneous GH secretion and responses to provocative stimuli become progressively less [16]. Although the total dose of radiation is strongly connected with GH abnormalities, there are other factors such as the duration of treatment, fraction size, number of fractions and the age of the patient which are considered to be crucial. GH deficiency may not appear for ten or more years when low doses (18-24 Gy) are used, whereas with higher doses (>30 Gy), GH deficiency can be noticed within 5 years [11,13]. For children treated with radiotherapy to the hypothalamus-pituitary region, the diagnosis of GH deficiency remains a controversial subject. The failure of one stimulation test (Insulin tolerance test or GH-releasing hormone/arginine test) which assesses the maximum secretion of GH after the administration of a secret-analogue, is diagnostically useful. False negative results are possible, rendering stimulation tests unreliable and inaccurate when low doses of radiation have been used [12]. The frequent measurement of serum GH levels (every 20 min for 12-24 hrs), especially during sleep, is an exacting but more accurate process. Peak GH response after a stimulation test (Insulin tolerance test or GH-releasing hormone/arginine test) less than 10µg per liter implies GH deficiency but when the serum concentration is less than 5µg per liter, shows severe deficiency [15]. Insulin growth factor 1 (IGF1) and insulin growth factor binding protein 3 (IGFBP3) serum levels are usually normal despite the presence of post-irradiation GH deficiency and cannot be used as diagnostic criterion to establish the diagnosis [12,15]. Clinical findings which are of great diagnostic importance include stature at least 2.5 standard deviations below the mean normal height for children of the same age, delayed skeletal maturation, growth velocity less than the 25<sup>th</sup> percentile and eventual height considerably less than parental [18]. GH replacement therapy with recombinant human GH (rhGH) since 1980s is widely used and targets to normalize linear growth and body composition. A probable side effect is impaired glucose tolerance and hyperglycemia, thus measurements of serum glucose levels are required, especially for patients who are most prone to develop insulin resistance [19]. Despite the fact that there is no evidence that

GH triggers the development of new malignancies, replacement therapy is usually administered one year after radiotherapy for the majority of tumors and ALL and after two years in case of ependymomas or medulloblastoma [16].

### **Luteinizing hormone/follicle-stimulating hormone disorders**

LH's/FSH's secretion by the anterior pituitary is triggered by gonadotrophin-releasing hormone (GnRH), a hormone produced by the hypothalamus. Eventually, the unimpaired H-P axis will result in the maturation of germ cells, production of testosterone and estradiol and reproductive capability. Both early and delayed puberty are reported as common complications after radiotherapy used to treat childhood CNS tumors, due to H-P axis' exposure [4,5,13,14,20,21]. After spinal radiotherapy, the scattered radiation dose is possible to cause primary gonadal disorders. Ovaries are more susceptible to damage than testes due to their anatomical proximity to the spine [4,5]. Precocious puberty is explained by the following pathophysiological mechanism: radiation disrupts the cortical stimulus which normally inhibits the production of GnRH by the hypothalamus during pre-pubertal period [4]. In girls, precocious puberty is characterized by menarche before 10 years of age and breast development before 8 years of age (Tanner's stage B2), whereas late menarche is described as the onset of menstrual cycles at 16 years or greater. Testicular development (volume >3 ml or length >25mm) before 9 years of age in boys who have not undergone testicular radiotherapy or alkylating chemotherapy is an important clinical finding suggesting precocious puberty (Tanner's stage G2) [13,20,21]. Secondary sexual characteristics, such as pubic hair are also assessed. Female patients are more vulnerable to central precocious puberty than male patients treated with brain radiotherapy with doses of 18-24 Gy but no difference between the two genders is stated when doses of 25-30 Gy are used [10]. Doses of 18-24 Gy are used as a CNS prophylaxis for patients with ALL, causing early sexual development and menarche [20]. Survivors who experience precocious puberty are more likely to develop hypogonadotropic hypogonadism during adulthood which is also correlated with brain radiotherapy doses >30-50 Gy [4,13]. Apart from the clinical findings, the investigation of central precocious puberty requires the measurement of estradiol/testosterone serum levels and the evaluation of LH/FSH secretion after a stimulation test with GnRH or GnRH agonist [13]. Elevated estradiol/testosterone levels and abundant LH response

are supportive findings of early pubertal development. On the other hand, reduced testosterone, LH/FSH levels in males and prolonged amenorrhea combined with low estradiol levels in females imply gonadotrophin deficiency [13]. Children patients who experience early puberty as a result of radiotherapy are at great risk of growth failure and short stature whereas patients with delayed puberty will probably experience fertility disorders as adults and reduced bone mineral density. As far as treatment is concerned, a LH-releasing hormone analogue is administered to patients who experience precocious puberty while in the setting of delayed puberty replacement treatment with testosterone to males and ethinyl estradiol or 17  $\beta$ -estradiol to females is recommended [10,13,21].

### TSH disorders

Post-irradiation TSH disorders occur less frequently than GH and LH/FSH ones. Hypothalamus produces TRH, an hormone which is responsible for the secretion of TSH which causes the synthesis of T3 and T4 by the thyroid gland. These hormones are crucial for the regulation of multiple physiological functions including bone growth, reproduction, muscular and cognitive development [22]. Central hypothyroidism, characterized by low free thyroxin (fT4) and reduced (or sometimes normal) TSH serum levels, occurs to a percentage of 23% of patients 4 years after brain radiotherapy with doses >42 Gy [1,5,10,22]. Normal TSH levels after TRH stimulation test indicate hypothalamic dysfunction whereas no response to TRH suggests damage in the anterior pituitary. Almost 20-30% of patients who have received cervical radiation will develop primary hypothyroidism within 5 years after radiotherapy [22]. Primary hypothyroidism (low fT4 and increased TSH levels) is caused by the direct parenchymal and vascular radiation damage to the gland which usually receives not only 70-80% of the posterior spinal field exit dose but also a part of the craniocervical radiation dose [23]. TSH deficiency occurs when doses >30-40 Gy are delivered [4,10]. The relatively low incidence of central hypothyroidism (compared to GH and gonadotrophin deficiency) is attributed to three factors: First, the primary damage of the thyroid gland may obscure central malfunction for a long period of time. Secondly, high TSH and low fT4 serum levels could falsely suggest primary hypothyroidism, although they are caused by post-irradiation TSH's reduced biological activity, a phenomenon called serum alteration. In conclusion, TRH producing cells in the hypothalamus and TSH producing cells in the pituitary are generally not affected by irradiation

at least in the short-term, leading to delayed appearance of post-irradiation central hypothyroidism [24]. It is of great importance to mention that doses of 20-29 Gy to the gland increase the risk of secondary carcinoma, usually of papillary type, whereas doses >30 Gy diminish that risk [10]. Recent trials applied the hyperfractionated craniospinal radiotherapy (HFRT) as an alternative to conventionally fractionated craniospinal radiotherapy (CFRT) to children with medulloblastoma. In HFRT, radiation fractions of 1-1,1 Gy are used more than once in the day but the total dose and time of treatment remain the same as CFRT. It was shown that HFRT applies higher doses of radiation to tumor cells than healthy ones and as a result acts protectively and decreases the risk of possible late thyroid dysfunction [24]. Hormone replacement therapy with thyroxine is strongly recommended in order to reinstate hormones' serum levels and prevent the impact of hypothyroidism on children's development and cognitive abilities [5,22].

### ACTH disorders

Radiation-induced ACTH deficiency leads to low synthesis of cortisol and adrenal androgens by the adrenal glands whereas the synthesis of mineralocorticoids is mostly ACTH-independent. Thereby, aldosterone, sodium and potassium serum levels remain normal. Clinical manifestations of adrenal deficiency include weakness, weight loss, poor appetite, nausea, vomiting, abdominal pain, hypotension, hypoglycemia, vascular collapse, low fight or flight response and even adrenal shock. However, partial ACTH deficiency due to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is often asymptomatic, but during stressful stimuli, failure to mount a biologically sufficient cortisol response may lead to deleterious consequences and endanger survival.

Radiotherapy with low doses (18-24 Gy) used for the treatment of hematologic malignancies, such as ALL, is not proven to impair the production of ACTH by the pituitary but doses >24 Gy administered for the treatment of brain tumors can cause ACTH deficiency [25]. For the diagnosis of ACTH deficiency, multiple tests are used in clinical practice such as Synacthen test and ITT. Although the ITT has been considered the gold standard when assessing the HPA axis, case reports have demonstrated potential risks using the ITT in children [26]. Therefore, the ACTH test is used in children. The conventional ACTH test using synthetic corticotropin assesses the function of the adrenal cortex. Chronic ACTH deficiency results in atrophy of the adrenal cortex and failure

to respond to exogenous corticotropin. The ACTH test is thus an indirect measurement of the function of the pituitary gland. Brain irradiation may cause ACTH secretory abnormalities if the HP axis has been irradiated. According to a study, 24% of children treated with brain irradiation for CNS or brain tumors were diagnosed with ACTH deficiency [25]. Although ACTH deficiency is not as common as other post-irradiation endocrine disorders, lifelong follow-up is recommended because it may emerge later in life causing life-threatening conditions, if left untreated.

### Hyperprolactinemia

Hyperprolactinemia is a rare post-irradiation complication, causing usually insignificant clinical problems. Despite the fact that only 5% of children and adults treated with low radiation doses will develop hyperprolactinemia, adult women radiated with doses >40 Gy appear to be more vulnerable [7]. Elevation in prolactin levels reveals hypothalamic dysfunction which is not inhibited by dopamine.

### Pathophysiological mechanism of post-irradiation damage

Hypothalamus-pituitary axis' hormonal failure can be explained by the direct effect of radiation to the DNA of hypothalamic and pituitary's cells, causing irreparable damage and diminished functionality [7]. In addition, neuroglia cells degenerate and vascular damage occurs, including endothelial loss, blood-brain barrier disruption, edema, hypoxia, vasa vasorum inflammation, thrombosis, hemorrhage and rupture, subsequent fibrosis and thickening of the base membrane [27].

### Conclusions

According to the International Classification of Childhood Cancer, brain tumors account for the 23% of malignancies under the age of 15 years, rendering them the first type of childhood solid neoplasms and the second most common oncological disease after hematological malignancies. Although radiotherapy is thriving in the last few years and has substantially contributed to the improvement in prognosis of CNS pediatric tumors, the appearance of post-irradiation complications can be proved devastating for patients' quality of life. The spectrum of these complications includes learning disabilities, memory and perceptual deficits and hormone deficiencies which are attributed

to the impairment of the H-P axis and depend on numerous factors related not only to parameters of radiotherapy (total radiation dose, fraction size, organ/tissue volume) but also to the host (gender, age, developmental status). The appropriate assessment and early confrontation of endocrine failure are considered requisites for the normal development of childhood cancer survivors and thus long-term follow-up guidelines have been published [4,9,13,20,25] in order to be applied in everyday clinical practice. As far as the GH is concerned, follow-up includes the evaluation of nutritional status, height and weight every six months and yearly after the growth completion, the Tanner staging every six months until complete pubertal development and the control of thyroid function. Weight below the 3<sup>rd</sup> percentile in growth chart and retarded bone age in an x-ray of the wrist are signs of poor growth velocity. Physical examination, evaluation of pubertal progress (Tanner staging, testicular volume by Prader orchimeter) every year and measurements of LH/FSH, testosterone and estradiol serum levels are recommended for the evaluation of precocious puberty and gonadotrophin deficiency. The follow-up of thyroid function requires yearly physical examination (weight, height, hair and skin) and measurement of TSH and fT4 but more frequent screening is proposed during periods of rapid growth. Finally, for patients irradiated in the H-P axis with doses  $\geq 30$  Gy yearly evaluation for ACTH insufficiency is suggested. The sudden mental derangement could possibly imply primary tumor recurrence or appearance of secondary tumor and thus clinical assessment and imaging of the region should be performed. The applied treatment strategy (extent of surgical resection, RT doses and radiation field, possible administration of chemotherapeutic agents), the histological type and location of the tumor should be meticulously registered in the patients' medical history which constitutes a crucial asset during the long-term follow-up. In the past few years, 3-dimensional imaging techniques have been proven veritably valuable to the more precise H-P axis dosimetric estimation and consequently to the proper evaluation of potential hormone deficiencies. In addition, recently applied hyperfractionated radiotherapy techniques reduce the radiation exposure of the normal brain parenchyma but meanwhile maximize the dose which the tumor itself receives.

The constant progress in brain tumors treatment strategies enhances the survival rates and triggers the need for early diagnosis of post-irradiation late effects and immediate therapeutic intervention. H-P axis dysfunction numbers among

the most serious abnormalities for childhood brain tumors survivors and requires more thorough understanding of the pathophysiology of the damage in order to achieve not only timely diagnosis but also to organize an individualized long-term follow up program for each patient. Collaboration of multiple medical specialties, such as pediatrician,

radiation oncologist and endocrinologist is crucial for the best confrontation of the challenges posed to the children patients and their families.

### Conflict of interests

The authors declare no conflict of interests.

### References

- Ramanauskienė E, Labanauskas L, Verkauskienė R et al. Early development of endocrine and metabolic consequences after treatment of central nervous system tumors in children. *Medicina (Kaunas, Lithuania)* 2014;50:275-280.
- Bergthold G, Bandopadhyay P, Bi WL et al. Pediatric low-grade gliomas: how modern biology reshapes the clinical field. *Biochim Biophys Acta* 2014;1845:294-307.
- McGregor LM, Metzger ML, Sanders R et al. Pediatric cancers in the new millennium: dramatic progress, new challenges. *Oncology (Williston Park)* 2007;21:809-820; discussion 820, 823-824.
- Güemes Hidalgo M, Muñoz Calvo MT, Fuente Blanco L et al. Endocrinological outcome in children and adolescents survivors of central nervous system tumors after a 5 year follow-up. *An Pediatr (Barc)* 2014;80:357-364.
- Anderson DM, Rennie KM, Ziegler RS et al. Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. *Cancer* 2001;92:2709-2719.
- Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev* 2010;36:277-385.
- Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metabol* 2009;5:88-99.
- Scocciati S, Detti B, Gadda D et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol* 2015;114:230-238.
- Kahle W, Frotscher M (Eds): *Color Atlas of Human Anatomy, Vol. 3: Nervous System and Sensory Organs (5th Edn)*. Thieme, Stuttgart, 2003.
- Toogood AA. Endocrine consequences of brain irradiation. *Growth Horm IGF Res* 2004;14: 118-124 (Suppl A:S118-124).
- Sklar C, Wolden S. Therapy for Pediatric Brain Tumors and the Risk of Growth Hormone Deficiency. *J Clin Oncol* 2011; 29:4743-4744.
- Mulder RL, Kremer LC, van Santen HM et al. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. *Cancer Treat Rev* 2009;35:616-632.
- Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. *Endocr Relat Cancer* 2010;17:141-159.
- Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. *Pediatr Clin North Am* 1997;44:489-503.
- Merchant TE, Rose SR, Bosley C et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol* 2011;29:4776-4780.
- Shalet M. Radiation and Pituitary Dysfunction. *N Engl J Med* 1993;328:131-133.
- Thomas JD, Monson JP. Adult GH deficiency throughout lifetime. *Eur J Endocrinol* 2009;161:97-106 (Suppl 1:S97-S106).
- Vance ML, Mauras N. Growth hormone therapy in adults and children. *N Engl J Med* 1999;341:1206-1216.
- Bramnert M, Segerlantz M, Laurila E et al. Growth hormone replacement therapy induces insulin resistance by activating the glucose-fatty acid cycle. *J Clin Endocrinol Metab* 2003;88:1455-1463.
- Armstrong GT, Whitton JA, Gajjar A et al. Abnormal timing of menarche in survivors of central nervous system tumors: A report from the Childhood Cancer Survivor Study. *Cancer* 2009;115:2562-2570.
- Dunkel L, Quinton R. Transition in endocrinology: induction of puberty. *Eur J Endocrinol* 2014;170:229-239.
- Jereczek-Fossa BA, Alterio D, Jassem J et al. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev* 2004;30:369-384.
- Ricardi U, Corrias A, Einaudi S et al. Thyroid dysfunction as a late effect in childhood medulloblastoma: a comparison of hyperfractionated versus conventionally fractionated craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;50:1287-1294.
- Laughton SJ, Merchant TE, Sklar CA et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol* 2008;26:1112-1118.
- Rose SR, Danish RK, Kearney NS et al. ACTH deficiency in childhood cancer survivors. *Pediatr Blood Cancer* 2005;45:808-813.
- Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. *Br Med J* 1992;304:173-174.
- Murphy ES, Xie H, Merchant TE et al. Review of brain radiotherapy-induced vasculopathy. *J Neurooncol* 2015;122:421-429.