Pituitary deficiency after brain radiation therapy

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Insuffisance ante hypophysaire post-radique

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La radiothérapie cérébrale constitue une cause fréquente d’insuffisance ante hypophysaire, volontiers méconnue chez l’adulte, susceptible d’altérer la qualité de vie et l’état de santé de patients dont la survie s’est par ailleurs beaucoup améliorée au cours des dernières années. Ses conséquences ont été mieux étudiées chez l’enfant. La rapidité de survenue des déficits hormonaux est conditionnée par la dose absorbée par la région hypothalamo-hypophysaire mais leur fréquence et leur sévérité dépend également du fractionnement de la dose et de la durée de suivi. Le secteur somatotrope est le premier touché et 10 ans après radiothérapie 90 % des patients présentent une insuffisance en GH. Les autres secteurs sont atteints de manière moins fréquente et plus tardive. L’atteinte initiale hypothalamique s’accompagne dans 30-50 % des cas d’une hyperprolactinémie mais, paradoxalement, jamais de diabète insipide. Elle peut s’associer secondairement à une atteinte hypophysaire directe. Dans ce contexte, la réponse au test à l’ACTH ou GHRH-Arginine est longtemps conservée en cas d’insuffisance somatotrope ou cortico- drome démontrée par l’hypoglycémie insulinoïque. En cas d’irradiation cranio-spinale, incluant la région cervicale il existe un risque d’insuffisance thyroidienne primitive et la radiothérapie cervicale constituant un facteur de risque de cancer de la thyroïde, une surveillance morphologique de la thyroïde est nécessaire. L’atteinte du secteur gonadotrope peut se manifester à faible dose par des avances pubertaires alors qu’à forte dose on observe au contraire des retards pubertaires ou d’authentiques insuffisances gonadotropes. L’association à la radiothérapie d’une chimiothérapie conduit à des atteintes mixtes centrales et périphériques dont le diagnostic peut être difficile. Chez l’adulte, l’atteinte du secteur somatotrope est moins marquée mais la séquence des déficits est la même. Des études prospectives longitudinales sont nécessaires pour préciser les délais et la séquence de survenue des déficits, de manière à proposer aux patients un suivi adapté à leur cas.

Mots-clés : Insuffisance ante-hypophysaire, radiothérapie cérébrale, dépistage, traitement, exploration hormonale.

Pituitary deficiency after brain radiation therapy

Brain radiotherapy is a frequent and overlooked cause of pituitary deficiency in adults which may alter patients’ health and quality of life. Hormonal consequences have been better studied in children. The onset of hormonal deficiencies depends on the dose delivered to the pituitary-hypothalamic region while their incidence and severity depends on dose fractionating and follow-up duration. Somatotrophic function is the first affected, 90% of patients being GH deficient 10 years after radiotherapy. Other anterior pituitary functions are affected later and less frequently. While initial damage occurs in the hypothalamus, accounting for mild hyperprolactinemia in 30-50% of cases, diabetes insipidus is never observed. Direct pituitary deficiency may occur later. Responses to ACTH or GHRH-arginine tests may be normal for several years though an ACTH and/or GH deficiency has been demonstrated by an insulin tolerance test, which is considered as the gold standard. When the
A 21-year-old male was referred by his pediatric endocrinologist for adult follow up of pituitary deficiency (table I). Medical history started at age 9 when he was admitted to the hospital for vomiting and headaches. Cerebellar syndrome was observed associated with a papilledema. The MRI brought back images of a cerebellar tumor causing hydrocephaly. Surgical removal was subsequently performed and considered as complete. Pathology determined that it was an undifferentiated medulloblastoma. The treatment included chemotherapy and radiotherapy of the posterior cerebral fossa.

The size of the patient at age 9 was 1.34m (+1 SD), but his growth rate dropped early on in the follow up and the patient measured 1.38 m at age 11 (–0.5 SD). At age 12, GH secretion was explored by an ornithin test which proved to be normal (peak at 17 μg/l), ruling out a GH deficiency (GHD). TSH was elevated at 6.6mUI/l (N<5mUI/l) and the free thyroid hormones were at the lower limit of normal values. The TRH test brought back a delayed response, suggesting an hypothalamic deficiency (peak at 8mUI/l at the 2nd hour). A treatment with L-thyroxin was instituted.

Puberty onset was spontaneous at age 12.5. The patient measured 150cm and weighed 54kg. One year later, puberty reached the P4 stage, height gain was 6 cm while weight gain was 9kg. Combined arginine-insulin test, resulted in a GH peak at 8.5μg/l, suggesting partial GHD. Substitutive GH treatment was then proposed and not accepted by the family. At age 17.5, once puberty was over, the testicular volume reached 11ml, the patient measured 162cm and weighed 76kg (BMI: 29.3). He reported morning fatigue. Serum testosterone levels were normal (2.925pg/ml) while FSH reached 6 mU/l and LH 8mU/l. IGF-1 was low for the patient’s age at 206ng/ml (<–2 DS) and a complete GHD was proved by the response at 1.3 μg/l at the insulin tolerance test. The heart sonogram was normal. Osteodensitometry showed slight osteopenia with a rachidian T-score of –0.32 while the femoral T-score was 0.55. Recombined human GH treatment was introduced at the dose of 0.2mg per day, progressively increased to 0.4mg per day based on serum IGF-1 levels.

By the age of 19, the patient still reported fatigue despite normal levels of IGF-1. Patient’s size and weight were stable (162cm, 78kg), as was the testicular volume (10ml). Testosterone had decreased to 1.825pg/ml, while FSH and LH were at 2 and 4UI/l, respectively, denoting a partial gonadotrophic deficiency. Other hormonal tests were normal. A substitutive androgen treatment proved efficient on libido.

In summary, this young male patient irradiated on the posterior cerebral fossa at age 9 for a medulloblastoma first slowed his growth. Thereafter progressive hypothalamo-pituitary deficit developed, affecting first the thyreotropic function, then the somatotrophic function and finally the gonadotrophic function 10 years later (table I).

### COMMENTS

The recent improvements in the prognosis of hematological malignancies and brain tumors have triggered new interest in the impact of cerebral radiotherapy on hormones. Currently the life span of children with malignant brain tumors treated with a combination of sur-

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Time after radiotherapy (yrs)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>0</td>
<td>Medulloblastoma (surgery, chemotherapy, radiotherapy)</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>Thyreotropic deficiency</td>
</tr>
<tr>
<td>12.5</td>
<td>3.5</td>
<td>Partial somatotropic deficiency</td>
</tr>
<tr>
<td>17.5</td>
<td>8.5</td>
<td>Total somatotropic deficiency</td>
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<tr>
<td>19</td>
<td>10</td>
<td>Gonadotropic deficiency</td>
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gery, radiotherapy and/or chemotherapy is estimated to 65% at 5 years [13]. In adults treated for low grade glioma, life span ranges between 60 and 70% at 10 year follow up. Sequelae tend to be severe, particularly in the neurocognitive and psychosocial areas. Cancer therapy also causes medical disorders, including treatment-induced hormonal deficiencies and their potential impact on growth, fertility, body composition, cardiovascular risks and quality of life. Neurological sequelae need to be monitored and hormonal deficits, diagnosed and treated. In order to tailor adequate follow-up and hormonal substitution to patient needs, it is necessary to determine the sequence and delay of deficits onset, their relation to the parameters of the irradiation and more generally, to identify predictive factors of hormonal complications.

**Characteristics of Radiotherapy-Induced Anterior Pituitary Deficiencies**

**Age effect**

The pituitary-hypothalamic axis is classically considered to better withstand radiation in adults than a children. A supporting study has shown that adult pituitary-hypothalamic functions were normal 2.5 years after whole-body irradiation, whereas 50% of children had growth hormone deficits [19]. That is why the impact of brain radiotherapy on the endocrine system has mainly been investigated in young adults treated during childhood [13]. Yet several studies suggest that high dose treatments for brain tumors in adults might induce hypopituitarism as well [9]. These deficits are often undiagnosed, leading to altered quality of life [3]. In a recent, study, Agha et al. [2] showed that 1-15 years following irradiation for non-pituitary brain tumors, 41% of patients had hypopituitarism: 16% having a single deficit, 25% multiple deficits and 7% panhypopituitarism.

**Sequence of onset**

Cytotoxic irradiation of the pituitary-hypothalamic axis induces isolated or combined pituitary deficiencies [10-13, 19]. Studies unanimously report the somatotrophic function as being the first and the most constantly affected. The corticotrophic, gonadotrophic and thyrotophic functions are less often or later affected. Regardless of age and dose, diabetes insipidus is never found. Figure 1 illustrates the sequence of deficiencies after irradiation during childhood. It is reported that somatotrophic deficiency is present in 90% of children 10 years after brain radiotherapy [19]. The sequence of events in patients irradiated during adulthood is similar to that observed in children [2]. However, GH deficiency, the most often found disorder after radiotherapy is only reported in 32% of patients.

**Dose Effect**

Delay of onset is dose related, but the frequency and severity of deficiencies also depend on dose fractionating and follow-up duration [19].

In case of brain irradiation in childhood with a dose under 35 Gy, somatotrophic deficiency is isolated and occur 10 years later, on average (fig. 2). In Hata et al.’s work [16], children in total remission after prophylactic irradiation for acute lymphoblastic leukemia (mean dose=18Gy) only suffered from delayed growth without biologically proved GH deficiency 6 years after treatment. When doses range from 35 to 50Gy, GH deficiency occurs as early as 2 years after irradiation in over 50% of cases and is associated with another disorder in 5 to 10% of cases [13] (fig. 2). High-dose irradiation (60-70 Gy) used to treat tumors of the cerebellar fossa result in panhypopituitarism in 30 to 60% of cases [9]. The best index to measure the cytotoxic effects of radiation might be the Biological Effective Dose (BED) [23]. This index is based on a linear quadratic model, which takes into account the total dose received, fractionation of dose and tissue sensitivity to radiation. In a study of...
91 children with a mean age of 9 years at the time of radiotherapy and a 15 year follow up, the BED to the pituitary and hypothalamic was highly predictive of pituitary deficiency occurrence [23]. The mean BED was of 54Gy in the group of children with normal somatotropic explorations and of 77Gy in children with GH deficiency. The BED and GH peak during the stimulation test were well correlated. A multivariate analysis showed that the best predictors for the stimulated GH peak value were the BED and follow up duration.

In patients irradiated in adulthood, regression analyses revealed that predictive factors for a pituitary deficiency were the dose received and the duration of follow-up [2, 17]. The incidence of pituitary deficiencies is particularly elevated after nasopharyngeal radiotherapy performed with doses higher than 70Gy for a carcinoma, GH deficiency is systematically found after this radiation therapy while cortico-, thyreo- and gonadotrophic disorders are observed in 25-50% of cases [17].

Hypothalamic impact of radiation

Since early hyperprolactinemia is observed in 30-50% of patients, the impact of irradiation on the hypothalamus is commonly suggested, at least in the initial phases [2, 12, 13, 17]. However that diabetes insipidus is never observed. This might be due to differential radiosensitivity of the hypothalamic neurons. Pituitary cells are more radioresistant than hypothalamic cells and therefore require higher doses and more time to be affected. This explains why direct pituitary disorders can develop secondarily in patients with hypothalamic disorders. Consequently hormonal tests should be interpreted with great caution when exploring the pituitary-hypothalamic function: falsely reassuring results might be obtained when the stimulating test is mainly based on the direct stimulation of the pituitary gland [5, 11, 15]. The mechanisms of cytotoxicity induced by radiation are not fully understood. They are probably linked with nuclear DNA disorders that are beyond cell repair and that secondarily lead to apoptosis [13]. This explains the delayed cytotoxic effects of radiotherapy. As for the potentializing effects of chemotherapy, the debate is still open.

Somatotrophic Function

An estimated 90% of adult patients irradiated during childhood suffer from somatotrophic deficiency, while only 30% of patients irradiated during adulthood are affected. The 24-hour GH secretory profile illustrates the impact of radiation of the hypothalamus: it shows that the frequency and duration of peaks is comparable to those of controls but that peak amplitude is buffered and that the area under the curve is reduced. This suggests that hypothalamic control of GH secretion is qualitatively altered and this has been described as a neurosecretory dysfunction [12]. Responses to direct pituitary stimulation is normal for long periods of time. In Darzy et al.’s study [11] half the patients with severe somatotrophic deficiencies (insulin tolerance test, GH<3μg/l) responded above 9μg/l on the coupled GHRH-Arginine test (table II). Björk also demonstrated the low predictive value of the GHRH-Arginine test for diagnosing radiation-induced somatotrophic disorders [5] in 43 young adults treated with both chemo- and radiotherapy (18 to 30Gy) for lymphoblastic leukemia. When the threshold of the test is set at 7.5μg/l, the lack of response to the test is highly predictive of GH deficiency with a positive predictive value (PPV) of 95%, but the negative predictive value (NPV) is only 27%. When the threshold is set at 16.5μg/l, the NPV is barely better at 33% while the PPV is 90%. It has been suggested that the reliability of GHRH-Arginine test might improve in function of the time from irradiation [11]. Indeed the progressive decrease in GH response noted 5 to 10 years after irradiation might be indicative of a pituitary deficit due to a progressive atrophy by a direct effect of radiation or lack of stimulation [11]. However, discordant results have been reported in a recent study [15]: The mean GH response to the GHRH-Arginine test was 7.9μg/l in patients affected by severe somatotrophic deficiency as revealed by the insulin tolerance test (mean peak: 0.4μg/l) 14 years after radiotherapy for medulloblastoma. No correlation could be found between the GH peak and the time elapsed since radiotherapy. This highlights the caution with which GHRH tests should be interpreted, even in the long term. The IGF-1 is not discriminating since it is normal for age in 1/3 of deficient patients. The
insulin tolerance test is therefore considered as the Gold standard test to diagnose GH deficiency. But its practical implementation is not always possible since many patients suffer from persistent epileptic conditions. It has been suggested that the exploration of the GH axis may be carried out in 2 stages. First, a GHRH-Arginine test is performed. The insulin tolerance test will be carried out only in patients with a GH peak higher than 9 μg/l, in the absence of contraindication [15]. This is however, a theoretical suggestion, as the GHRH-Arginine test cannot currently be administered.

During prepuberty, the impact of GH deficiency on growth leads to systematic GH treatment. Results may prove disappointing when the spine has been irradiated, with radio-induced bone alteration. Once adulthood is reached, GH treatment may be considered to improve quality of life and body composition when the deficit is confirmed. Though this step might seem useless, especially when the deficiency is organic and irreversible, a recent study showed that the radiation induced GH deficiency diagnosed in childhood was not confirmed in 33% of children with a severe deficiency and in 56% of children with partial deficiency [14]. This could be explained by the difference in criteria used to diagnose GH deficit children and adults. The factors predicting the persistence of GH deficit include the severity of the deficit, the age at the time of radiotherapy and the dose received. This highlights the need to systematically re-evaluate the somatotropic function once adulthood is reached.

In adults, indications for GH treatment are limited by the potential risk of brain tumor recurrence. However, a pilot study of 50 consecutive patients (mean age 49) with a GH deficiency having occurred in adulthood, due to a malignant or non-malignant tumor of the parasellar region, and having received radiotherapy in 74% of cases, shows that the risk of tumor recurrence was not increased with substitutive GH treatment (median follow up: 3 years) [7]. However, prospective studies, with longer follow-up, are necessary in order to evaluate the rate of recurrences in patients that receive GH treatment.

**Corticotrophic Function**

Corticotrophic disorders are reported in 50-70% of patients irradiated during childhood and in 21% of patients irradiated at an adult age [2, 13]. Just as in GH deficiency, the insulin tolerance test is a more sensitive screening test than are the ACTH or the CRH tests since its impact is hypothalamic. Thus in Oberfield’s study, 5 years after radiotherapy, patient response to the ACTH test was inconclusive [20]. This was also true in Schmiegelow’s study [25], where 3% of patients that did not respond to the insulin tolerance test responded to the ACTH test. The insulin tolerance test is therefore the standard test. The multivariate analysis showed that the predictive factors of corticotrophic deficiency after childhood radiotherapy were the BED and the duration of follow up. There was no correlation with chemotherapy, age at radiation or sex [25]. Recently, 5 tests were compared in 22 children [27]: conventional ACTH (250 μg), low dose ACTH (0.2 μg/kg), metopirone, insulin tolerance test and basal serum cortisol (at 8 o’clock am). Results showed that low-dose ACTH was no more sensitive than conventional ACTH, and that metyrapone and insulin tolerance tests were comparable. The authors also found that children who responded poorly to the metyrapone test had low levels of morning cortisol. This simple determination is therefore a reliable means of screening and can be confirmed by a metopirone test when insulin tolerance test is contraindicated [27].

**Gonadotrophic Function**

The effects of brain radiotherapy on a child’s gonadotrophic function is highly dependent on the dose and the puberty status. Low doses (<30Gy) received by prepuberal
girls and 30 to 50 Gy doses received by either sex can cause precocious puberty, whereas strong doses result in delayed puberty and, in a limited number of cases, in true gonadotrophic deficiency [13].

This same phenomenon was reproduced in rodents by Sprague-Dawley [22], highlighting the radiosensitivity of the GnRH pulse generator: young female rats (12-16 days old) received 5-6Gy doses of radiation, causing precocious puberty in 20% of the animals. The mechanism is poorly understood but might involve lifting factors that inhibit puberty onset. In rodents having received doses above 9 Gy, sexual maturation was delayed and somatotrophic disorders were often associated.

In a dated paper, Constine [9] reported 61% of hypogonadism in post-puberal patients having received high doses of radiation during childhood. A more recent study showed that serum testosterone in adolescents having received brain radiotherapy was significantly lower than in controls [24]. But the gonadic function is mainly altered when chemotherapy is associated with radiation. When hormonal explorations are carried out to diagnose the disorder, partial or total gonadotrophic deficit can explain the apparently normal levels of FSH that conceal the associated primitive gonadotropic disorder. When this occurs, inhibine B assays may prove useful to diagnose seminiferous tubules that were altered by chemotherapy [24]. In patients who received adult radiotherapy, gonadic disorders are often overlooked. A recent study reported that 47% of patients having received radiotherapy suffered from erectile dysfunction, while 32% had an untreated gonadic deficiency [3]. Similar figures were reported by Agha [2], who found 27% of gonadotrophic disorders 1-15 years after tumor-related cerebral radiation.

**Thyreotrophic Function**

Thyreotrophic deficiency is the less frequent disorder in the list. In a recent study of 71 irradiated children followed up for 12 years, only 6% had thyreotrophic deficiency [26]. The multivariate analysis showed that TSH was correlated with T4L and follow up duration. When implemented, the TRH test finds an ample and prolonged TSH peak that argues for a hypothalamic disorder. In irradiated adults, thyreotrophic disorders were only found in 9% of patients, according to a recent study [2].

Primitive thyroid deficiency is the most frequently observed thyroid disorder, occurring in 24% of patients irradiated during childhood, among which 71% were irradiated in the cerebrospinal area, including the neck. In 3/4 of the cases the disorder was a compensated biological hypothyroidism with no consequence on the serum T3 or T4 levels but with elevated TSH. More generally, 30 to 50% of patients having received spinal radiation are affected with primitive thyroid disorders, regardless of their age at the time of radiotherapy [2, 13]. International guidelines recommend starting a substitution treatment when TSH levels exceed 10-12 mUI/l. In cases of combined central and peripheral disorders, substitution treatment should be implemented as soon as serum T3 and/or T4 are lower than their expected levels, regardless of the serum TSH. Regular cervical ultrasonicographic survey must be implemented, since patients are at higher risk for papillary thyroid cancer irradiation of the thyroid area.

**CONCLUSION**

Brain radiotherapy is a frequent cause of anterior pituitary deficiency, but is often underestimated in adults. It impacts the quality of life and health of patients. It is therefore crucial to explore pituitary function in all patients having received radiotherapy. The finding of isolated or multiple deficiencies should lead to hormone substitution, when possible. The impact of radiotherapy on the pituitary gland itself complicates the implementation and the interpretation of hormonal explorations. Longitudinal prospective studies are required to determine the time course and sequence of onset of deficiencies so as to tailor treatment to patients.

**REFERENCES**


