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Growth and endocrine disorders in optic glioma

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Abstract. Hypothalamo-pituitary function in children with optic glioma may be impaired by the tumour itself and by the high cranial radiation doses used in treatment. This study evaluates the effect of optic glioma and its treatment on patient growth and pubertal development. Twenty-one patients (13 boys, 8 girls), treated for optic glioma by cranial irradiation (45–55 Grays) at a mean age of 5.4 years, were evaluated before ($n = 10$) and/or after ($n = 21$) irradiation. Growth hormone (GH) deficiency was present in only 1 patient tested before irradiation and in all patients after irradiation. Precocious puberty occurred in 7/21 cases, before irradiation in 5 patients and after irradiation in 2 patients. The cumulative height loss during the 2 years after irradiation was 0.2 ± 0.2 SD (m ± SEM) in 7 patients with precocious puberty and 1.1 ± 0.2 SD in 14 prepubertal patients ($P < 0.01$). The corresponding bone age advance over chronological age, evaluated 1–3 years after irradiation, was 1.1 ± 0.5 and -0.7 ± 0.3 year in the two groups ($P < 0.01$). The mean height loss between time of irradiation and the final height was 2.3 ± 0.6 SD ($n = 6$). Primary amenorrhoea, associated with low oestradiol levels, occurred in two of the three girls of pubertal age. These data indicate that the high dose of cranial radiation used to treat optic glioma invariably results in GH deficiency within 2 years and that hGH therapy is required when GH deficiency is documented. Precocious puberty, resulting in apparently normal growth velocity in spite of GH deficiency, should be treated with luteinizing hormone-releasing hormone analogues because of the risk of accelerated bone maturation and reduced final height.

Key words: Growth hormone – Precocious puberty – Growth – Optic nerve diseases – Radiotherapy

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Abbreviations: AITT = arginine-insulin tolerance test; FSH = follicle-stimulating hormone; GH = growth hormone; hGH = human growth hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone; PP = precocious puberty; SDS = standard deviation score; TSH = thyroid-stimulating hormone

Introduction

Children with optic glioma frequently exhibit a precocious puberty (PP) in association with growth hormone (GH) deficiency. The optic glioma itself may be associated with the development of PP, which appears to be gonadotropin-dependent [8], while the irradiation delivered to the hypothalamo-pituitary area during treatment causes GH deficiency [16]. The combination of these two endocrine abnormalities may result in reduced final stature [1].

The present study examines the growth and the course of endocrine disturbances in patients with optic glioma in order to provide an improved rationale for endocrine treatment following radiation therapy. The results show that the optic glioma itself is rarely responsible for endocrine disorders, except for inducing PP, and that the radiation dose used in its treatment invariably produces GH deficiency.

Patients

Twenty-one children (13 boys, 8 girls) treated for optic glioma were evaluated at the Paediatric Endocrinology unit, Hôpital Malades, Paris, between 1971 and 1987. Informed consent had been obtained from patients and their parents. Eleven children had cutaneous neurofibromatosis lesions. The optic glioma was detected by the presence of visual (13 patients) or neurological (6 patients) abnormalities or PP. Diagnosis of optic glioma was made on the basis of the neuroradiological characteristics of the tumour [6] and confirmed histologically in six cases (biopsy in one patient and partial surgical removal of the optic tumour in five patients). All patients were irradiated with fractionated doses of 45–55 Grays (1 Gray = 100 rad) delivered over 5–6 weeks. The mean age at irradiation was 5.4 ± 0.7 years (m ± SEM, range 1.5 to 10.3 years). No patient received chemotherapy.

In ten patients, endocrine evaluation was performed just before irradiation. Two of them who underwent surgery were evaluated immediately after surgery and before irradiation. All 21 patients, including the 10 evaluated before irradiation, also underwent endocrine evaluation after irradiation. The mean time between irradiation and the last clinical evaluation was 5.1 ± 0.8 years (1 to 14.3 years). Final height was achieved in six patients. Five of them received human growth hormone (hGH) treatment.

Methods

The diagnostic criteria for true PP were: in girls, breast and pubic hair development before the age of 8 years and, in boys, an increase in testicular volume and testosterone secretion (plasma testosterone > 3.5 nmol/l) before the age of 10 years [18]. Height changes were expressed as standard deviation score (SDS) based on chronological age. Heights were compared to the French national standards [15]. Bone age was assessed by the Greulich and Pyle method [5]. Pubertal stages were rated according to Tanner [19]. Final height was considered to be reached when the height gain during the preceding year was below 2 cm at bone age greater than 14 years in girls and 16 years in boys.

Spontaneous growth was studied during the 2 years following irradiation. At least 2 yearly growth measurements were made. This longitudinal growth study was performed according to pubertal development: 14 patients remained prepubertal and 7 patients had PP with plasma testosterone > 3.5 nmol/l in boys or oestradiol > 92 pmol/l in girls over the 2 years following irradiation.

GH secretion was evaluated by the GH peak response to the arginine-insulin tolerance test (AITT, [10]). Diagnosis of GH deficiency was based on a GH peak response to AITT below 8 µg/l and was confirmed by a second test. The hypothalamo-pituitary-gonadal axis was investigated by measuring the basal plasma levels and luteinizing hormone-releasing hormone (LHRH, 100 µg/m^2 i.v.)-stimulated plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and by determining plasma testosterone in boys and oestradiol in girls. Other pituitary functions were evaluated as previously described [3]. The plasma free thyroxine, basal and stimulated cortisol levels were normal in all ten patients evaluated before irradiation. The thyroid stimulating hormone (TSH) response to thyrotropin-releasing hormone, which was evaluated in two patients, was also normal. The post-irradiation TSH response to thyrotropin-releasing hormone was low (< 10 mU/l) in 11 out of 21 patients. Plasma free thyroxine was normal. These 11 patients were given L-thyroxine replacement therapy (100 µg/m^2 per day). The concomitant plasma and urine osmolalities indicated a normal urinary kidney concentrating capacity in all 21 patients tested after irradiation. The only patient with corticotropin deficiency was given replacement therapy (hydrocortisone 15 mg/m^2 per day). Human GH treatment was at a dose between 0.3 and 0.4 IU/kg per week given twice a week. The interval between irradiation and the onset of hGH treatment was greater than 2 years in all cases.

Results are expressed as mean ± SEM and statistical comparisons were made by Student's *t*-test.

Results

Growth changes in relation to pubertal development

Height changes during the first 2 years after irradiation were expressed according to pubertal development (Fig. 1). The mean height SDS did not change in the patients with PP (0.7 ± 0.5 SD, before; 0.7 ± 0.1 SD at 1 year; 0.5 ± 0.5 SD at 2 years, NS). In contrast, the mean height SDS decreased significantly in the prepubertal patients (−0.1 ± 0.4 SD before, −0.7 ± 0.4 SD at 1 year, $P < 0.01$; −1.2 ± 0.4 at 2 years, $P < 0.01$ compared to 1 year). The cumulative height changes over 2 years were −0.2 ± 0.2 SD (0.2 to −1 SD) in the group with PP and −1.1 ± 0.2 SD (0.2 to −2 SD) in the prepubertal group ($P < 0.01$). Only one patient in the prepubertal group showed no reduction in height gain over the 2 years. Mean bone age advancement over chronological age, evaluated 1–3 years after radiation, was 1.1 ± 0.5 years in the group with PP and −0.7 ± 0.3 years in the prepubertal group ($P < 0.01$). This corresponded to mean bone age progression of 3.5 ± 0.7 and 1.7 ± 0.4 years ($P < 0.01$), respectively.

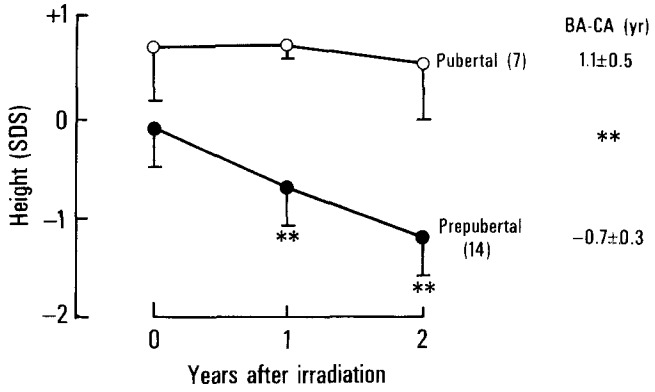

Fig. 1. Height changes (m ± SEM) in children treated by cranial irradiation for optic glioma, according to their pubertal development. The mean height SDS over 2 years did not change in the patients with precocious puberty and decreased significantly in the prepubertal patients (** $P < 0.01$ compared to time 0). The bone age advancement over chronological age *(BA-CA)* was evaluated 1 to 3 years after irradiation

Growth hormone secretion

Growth hormone secretion was normal before irradiation in all but one patient who had a large optic tumour. The mean GH peak response to AITT was 21.0 ± 4.1 ng/ml (8.4 to 40 ng/ml) in the other nine patients. All patients had GH deficiency after irradiation. The mean GH peak response to AITT was 4.2 ± 0.4 ng/ml (0.9 to 7 ng/ml). Patients were tested at different intervals after radiation, with a mean post-irradiation interval of 2.5 ± 0.6 years (1–9 years). In the group having a normal peak GH response to AITT just before irradiation, the mean interval between irradiation and the first test showing GH deficiency was 1.5 ± 0.2 years (1–2.3 years).

Pubertal changes

Seven patients had a history of PP (Table 1). This PP was recognized prior to radiation in five patients (cases 1, 2, 5–7) and after radiation in two (cases 3, 4). Their plasma testosterone and oestradiol levels were in the pubertal range (plasma testosterone between 5.5 and 26.3 nmol/l in boys and plasma oestradiol at 220 pmol/l in the girl). The LHRH-stimulated LH peak values were higher than the FSH peak values in three out of seven patients.

The evolution of pubertal development after irradiation was different in boys and girls. Pubertal age boys ($n = 6$) had plasma testosterone levels which remained in the normal pubertal range (8.5 to 25.5 nmol/l) over an interval of 4–14.3 years after irradiation. In contrast two out of three girls aged over 15 years had primary amenorrhoea. The plasma oestradiol levels of these two girls were low (37 and 55 pmol/l), with normal plasma prolactin values, and their response to LHRH stimulation indicated gonadotropin deficiency (plasma peak LH values of 0.7 and 3.2 units/l respectively).

Table 1. Endocrine evaluation in patients with precocious puberty secondary to optic glioma

Patients	Sex	Time since irradiation (years)	CA	Pubertal stage	Testosterone (nmol/l)	Oestradiol (pmol/l)	LH peak (units/l)	FSH peak (units/l)
1	M	1.4	8.2	P2 35×20	7.3		9.0	5.1
2	M	1.5	11.8	P4 50×30	11.7		7.7	8.6
3	M	1.4	11.0	P2 40×20	17.3		4.3	7.1
4	M	2.2	7.0	P2 45×25	26.3		7.9	7.6
5	M	2.0	12.0	P2 40×20	11.7		9.0	4.2
6	M	2.1	9.8	P3 30×15	5.5		–	–
7	F	2.2	8.5	P1 B2		220	7.1	20.0

CA = chronological age at time of evaluation; LH and FSH peak after LHRH; pubertal stage according to Tanner [19] with B breast and P pubic hair development, testicular dimensions in mm

Final height

Final height was achieved in seven cases, one had PP. All received hGH therapy for more than 2 years. Mean height loss between the time of irradiation and final height was 2.3 ± 0.6 SD (range 1.5 to 6 SD).

Discussion

Growth is a major problem in children irradiated for optic glioma because of the combination of central PP secondary to the tumour itself and radiation-induced GH deficiency. Premature secretion of steroids in these patients, which maintains a normal growth velocity despite the GH deficiency and excessive bone maturation, may lead to ultimate short stature.

Optic glioma is a tumour frequently associated with neurofibromatosis [9]. It is the most frequent cause of organic PP [18]. This PP is not accompanied by other hypothalamo-pituitary dysfunction. The present data show that, with the exception of PP, all pituitary functions were normal in the majority of patients prior to irradiation. The sole patient with GH deficiency prior to irradiation had a large tumour. PP has been reported in neurofibromatosis with and without optic glioma [4, 7, 17]. Other lesions associated with neurofibromatosis, including hypothalamic hamartoma and hydrocephalus, may be associated with central PP. None of the patients in this study presented with these lesions. Likewise none of them had vertebral lesions, which can also impair growth [14]. The way in which optic glioma causes PP is not known, but it appears to be gonadotropin dependent [8]. The mean peak LH response to the LHRH test was elevated (36 units/l) in the seven cases described by Laue et al. [8]. This differs from our findings and may perhaps be explained by the fact that only four of the seven cases in that study were irradiated, two of them very shortly before testing. The relatively low peaks of LH observed in the present study may be partly due to the high dose of radiation used, which can itself induced gonadotropin deficiency [12].

Optic glioma is currently treated with high doses of conventional voltage cranial radiation. Endocrine disorders secondary to such irradiation have been extensively described [11, 16]. It was previously shown that high doses of cranial irradiation resulted in GH deficiency in almost all patients, and, less frequently, in TSH deficiency and gonadotropin deficiencies. Adrenocorticotropin deficiency rarely occurs and no posterior pituitary deficiency has resulted from cranial irradiation. In the present study, GH deficiency occurred within 2 years after the radiation. The high frequency of GH deficiency observed in the present study after such a short interval is greater than we reported previously with doses of 31–42 Grays [2]. This difference is probably due to the high radiation dose delivered to the hypothalamo-pituitary area. A comparison of these data with those previously reported after lower cranial doses suggests that the frequency of GH deficiency and the speed of its onset are related to the hypothalamo-pituitary radiation dose [11]. The decrease in growth rate induced by GH deficiency in children irradiated for optic glioma was also more rapid than previously reported [2], suggesting that high doses of radiation induce more severe GH deficiency than do low doses. The growth velocity of the GH-deficient patients is determined by their pubertal development. Growth retardation occurred during the 2 years following radiation in all but one of the prepubertal cases. Growth velocity remained normal for chronological age when precocious puberty was present, but significant bone age acceleration occurred in this group, indicating that growth was not appropriate for the advancement of bone maturation. In spite of the precocious secretion of sex steroids, growth velocity remained in the prepubertal range because of the associated GH deficiency [13].

This study provides useful guidelines for the management of children irradiated for optic glioma. The maintenance of a normal-for-age growth rate should not be considered to be a sufficient index for normal GH secretion after cranial irradiation. It may be obtained at the cost of accelerated bone maturation secondary to precocious puberty. Therefore, as almost all children irradiated for optic glioma are likely to develop GH deficiency, their GH secretion should be evaluated every 6 or 12 months. In children with precocious puberty, a decreased reponse to a stimulation test requires hGH replacement therapy even if the growth velocity is at a normal prepubertal level. LHRH analogue therapy

might also be considered, depending on the age of the patients, to avoid the risk of reduced final height secondary to precocious puberty. Because of the possibility of gonadotropin deficiency in this group of patients having received high cranial radiation dose, the need for sex steroid replacement therapy should also be considered according to the clinical status. This type of carefull follow up and treatment of patients irradiated for optic glioma should result in an improved final stature.

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