Hypothalamic-Pituitary Dysfunction in Survivors of Childhood Brain Tumors in Prasat Neurological Institute

Apasri Lusawat MD*,
Kanlaya Dhiravibulya MD*, Sasipa Thammongkol MD*,
Somlak Vanavanan MSc**, Pat Mahachoklertwattana MD***

** Department of Pediatric Neurology, Prasat Neurological Institute, Bangkok, Thailand*
*** Biochemical laboratory of Department of Pathology, Ramathibodi Hospital, Bangkok, Thailand*
**** Pediatric endocrinology unit of Department of Pediatrics, Ramathibodi Hospital, Bangkok, Thailand*

Objective: *To assess hypothalamic-pituitary dysfunction in childhood brain tumor survivors in Prasat Neurological Institute.*
Material and Method: *Between October 2007 and September 2008, 19 brain tumor survivor children in Prasat Neurological Institute without recurrence at least 2 years after complete treatment were included in the present study. The patients were categorized according to brain tumor location into directly (DHPA) (9 cases) and indirectly (IDHPA) (10 cases) involving hypothalamic-pituitary axis. All patients were treated by surgery. Furthermore, six cases were combined with radiation and chemotherapy and 10 cases were combined with radiation therapy only. Growth Hormone (GH) stimulation test by clonidine and/or L-Dopa, ACTH stimulation test and thyroid function test (TFT) were done.*
Results: *The mean age at diagnosis was 9.9 $\pm$ 4.6 years old and the interval from diagnosis to study was 5.8 $\pm$ 2.2 years. Seven DHPA (77%) and seven IDHPA patients (70%) had low peak GH with significant lower level in the former group ($p < 0.05$). Six of seven DHPA (85%) and one IDHPA patients (10%) had low response to ACTH stimulation test. All DHPA (100%) and 10% IDHPA patients had central hypothyroidism. By ACTH stimulation test in DHPA patients, hypocortisolism was detected in five and excluded in one who later stopped prednisolone after prolonged continuation. The central hypothyroidism was newly detected in two DHPA patients and replacement therapy was initiated. GH deficiency (GHD) was detected by GH stimulation test in 73% of overall brain tumors. Growth hormone therapy would be considered in the appropriate GHD patients.*
Conclusion: *With effective therapy and improving survival rates of brain tumor children, hypothalamic-pituitary dysfunction in either DHPA or IDHPA group should be regularly monitored to prevent further morbidity and improve quality of life.*

Keywords: *Brain tumor, Children, Hypothalamic-pituitary dysfunction*

J Med Assoc Thai 2010; 93 (1): 38-47
Full text. e-Journal: *http://www.mat.or.th/journal*

Brain tumors, the second most frequent childhood cancers, constitute about 25% of all types of cancers in children and are the most common solid tumors in children[1]. Survival after diagnosis of brain tumors has improved substantially over the last few decades. Five-year relative survival probability for all childhood brain malignancies is approximately 65%[2-4]. Neurosurgery is the main treatment for most childhood brain tumors, followed by RT about 55%, while the role of chemotherapy remains unsettled[5]. Endocrine disorders are prominent among the spectrum of long-term conditions that may afflict brain tumor survivors; in one survey, 43% had a self-reported endocrine condition[6]. These may affect growth, body composition, fertility, quality of life, morbidity, and mortality. Long-term follow-up programs and services are essential in order to address the unique needs of the growing population of childhood cancer survivors

Correspondence to: Lusawat A, Department of Pediatric Neurology, Prasat Neurological Institute, Rajavithi Rd, Bangkok 10400, Thailand. Phone: 0-2644-7333 ext 3157, Fax: 0-2354-7085. E-mail: lusawat@hotmail.com

as they navigate the challenges of today's healthcare system. Prevention and/or early identification of complications is crucial in order to decrease the long-term health risks associated with curative treatment for childhood cancer. The objective of the present study was to assess the hypothalamic-pituitary dysfunction in childhood brain tumor survivors, which is one of the parts for developing the long-term follow-up service in our hospital.

Hypothalamic-pituitary dysfunction can occur by tumor itself, by cranial radiation therapy, by chemotherapy, or by any surgery to remove a tumor in the hypothalamic-pituitary region if it is not already present[7,8]. The radiation required to cure the child's tumor may damage normal surrounding tissue. When hypopituitarism ensues in this situation, it is usually the result of radiation-induced damage to the hypothalamus, as the pituitary gland is relatively resistant to radiation. Different hypothalamic-pituitary axes have different sensitivities to radiation. These patients were compared with regard to the growth hormone, thyroid, and adrenal axes because these axes had been tested in all of them.

Serum GH levels is one of the data to diagnosis GH deficiency that must be integrated with clinical, auxological (growth), and biochemical data. Because most of the body's GH is made during sleep, with several significant peaks linked to deep sleep (stage III-IV EEG), the first cycle usually occurs at approximately 60 to 90 minutes after falling sleep. Random GH measurements during the day, even in tall individuals, are frequently low and thus potentially misleading[9]. Several physiologic and pharmacologic methods are used to test GH. The more common approach is stimulation testing (also referred to as provocative testing) with medications known to activate the physiologic regulation of GH secretion, notably the α-adrenergic pathway (*e.g.*, Clonidine), the dopaminergic system (*e.g.*, L-dopa combined with Inderal (propranolol)) and hypoglycemic stimulus to GH secretion by using glucagon or insulin (insulin tolerance test (ITT))[10-13]. These stimulation tests must be performed in the fasting state (early in the morning), because glucose intake suppresses GH secretion. Hypoglycemia results in uncomfortable adrenergic manifestations such as sweatiness, excessive hunger, and shakiness, and may cause neuroglycopenic manifestations such as loss of consciousness or seizures. Seizure is common in brain tumor and may be easily induced by hypoglycemia from ITT/glucagon test in these patients. The present study chose clonidine and L-dopa for GH stimulation tests to avoid seizure although ITT/glucagon tests can also be used to assess cortisol production, thus eliminating the need for an additional stimulation test either on the same day or on a different day[13].

The mode of assessment of the HPA axis remains controversial[14-16]. Insulin tolerance test (ITT) has been considered the golden standard when assessing the HPA axis[17,18]. Blood glucose level of 2.2 mmol/liter or less results in neuroglycopenia, which activates the hypothalamus with secretion of CRH, resulting in secretion of ACTH from the pituitary gland. The ITT in adults is regarded as a safe test in experienced hands[19,20], however case reports have demonstrated potential risks in children[21,22]. Therefore, in children and in patients with cardiac disease or epilepsy, ACTH test is safer. The present study chose the low dose ACTH test using synthetic corticotropin to assess the function of the adrenal cortex.

Material and Method

A prospective study was conducted at the Pediatric Neurology clinic of Prasat Neurological Institute between October 2007 and September 2008. Nineteen patients, 14 boys and five girls with diagnosis of brain tumors under 15 years of age were included in the present study. All patients were treated with surgery. Some patients followed by cranial or craniospinal RT and some patients also received chemotherapy. These patients were in remission more than 2 years from the end of treatment. The patients were divided into two groups based on tumor location with directly or indirectly involving the hypothalamic-pituitary axis (DHPA vs. IDHPA). The DHPA group consisted of nine patients including two craniopharyngioma, three germ cell tumor (1 suprasellar and pineal, 2 suprasellar), one parasellar meningioma, one suprasellar ganglioglioma, one hypothalamic harmatoma, and one clivus chordoma (some part of the tumor invading into sellar region). The IDHPA group consisted of 10 patients including three supratentorial tumors (germ cell tumor at 2 pineal and 1 thalamus) and seven posterior fossa tumors (5 medulloblastoma, 1 ependymoma and 1 brain stem astrocytoma) (Table 1). The mean age of the patients at the time of diagnosis was 11.5 ± 3.65 years old for the DHPA group and 8.4 ± 5.06 years old for the IDHPA group (Table 2). The treatment in the DHPA group consisted of surgery only (n = 3) and surgery and cranial irradiation (n = 6). The treatment in the IDHPA group consisted of surgery and cranial irradiation (n = 5) and surgery,

Table 1. Brain tumor diagnosis

Brain tumor (cases)	19
Direct involving HP axis (DHPA)	9
Germinoma/suprasellar	3
Craniopharygioma	2
Hypothalamic harmatoma	1
Meningioma/parasellar	1
Ganglioglioma	1
Chordoma/clival	1
Indirect involving HP axis (IDHPA)	10
Posterior fossa tumors	7
Medulloblastoma	5
Astrocytoma/brainstem	1
Ependymoma/4th ventricle	1
Supratentorial tumors	3
Immature teratoma/pineal	2
Mixed germ cell tumor/thalamus	1

Table 2. General data of patients in both DHPA and IDHPA groups

	DHPA	IDHPA
Patients (n)	9	10
Radiation therapy (n)	6	10
Chemotherapy (n)	0	6
Age at onset (mean ± SD) (y)	11.5 ± 3.65	8.4 + 5.06
Age at assessment (mean ± SD) (y)	16.6 ± 3.21	14.9 ± 4.5
Interval from diagnosis to study (y)	4.2 ± 1.96	5.6 ± 2.23

cranial and spinal irradiation (n = 5). The range of cranial/craniospinal irradiation dose was 24 to 60 Gy for 28 to 60 days. For those children with medulloblastomas and ependymoma, the cranial radiation was directed to the whole brain as well as_a posterior fossa boost of radiation and for all other tumors, was localized to the area of the tumor. Six patients in IDHPA group received combined chemotherapy.

History reviewing, physical examination, and informed consent were performed in all patients at the time of the present study by pediatric neurologists in the clinic. Height was measured and pubertal status assessed clinically by the method of Tanner. Patients were considered postpubertal if they had mature secondary sexual characteristics (Tanner stage 5). In prepubertal children aged more than 10 years old, estrogen was prescribed with the dosage of 0.3 mg twice daily for three days before growth hormone stimulation test. If steroid was maintained previously without definite abnormal basal cortisol level before, steroid was stopped 2-4 weeks before ACTH stimulation test. In case of previous thyroid hormone replacement therapy with borderline low level of thyroid function, thyroid hormone was withheld 2-4 weeks before test. They were appointed to admit to Pediatric Neurology ward one day before or early in the morning of study. Venous blood samples were obtained after an over-night fast (12 hours), at 9 AM for GH, basal cortisol and thyroid function test at the first time of study. Serum concentration of GH was measured after stimulation with clonidine (4 μg/kg) at 60, 90 and 120 minutes. Value above 7.0 ng/ml was considered normal response. When value was below 7.0 ng/ml, second GH stimulation test was performed on the next day with L-dopa (Sinemet® (250/25) at the following dosage according to body weight: ¼ tablet for body weight less than 15 kg, ½ tablets for 15.1 to 30 kg, 1 tablet for more than 30 kg) combined with propanolol 1 mg/kg (maximum of 40 mg). Blood samples were drawn in the time intervals as clonidine stimulation test. The diagnosis of GH deficiency was made based on serum GH value less than 7.0 ng/ml on both pharmacologic tests. Following GH stimulation test with clonidine, ACTH stimulation test was performed by using intravenous ACTH (Cortrosyn®) in a dosage of 0.5 μg/1.73 m^2 on the same day. Blood samples were drawn at 30 and 60 minutes after ACTH injection. A peak cortisol response of 18 μg/dl or more was considered adequate response in the ACTH test. The normal values of thyroid function were as follow: T4: 6.09-12.23 μg /dL, FT4: 0.58-1.64 ng/dL, TSH: 0.34-5.6 IU/ml. When serum T4 and free T4 level were below normal values while TSH was not elevated, central hypothyroidism was diagnosed.

The statistical analysis used in the present study included calculation of the mean, standard deviation (SD) and percentage. Height was expressed as a standard deviation score (SDS) according to the method of Tanner et al[23] to compare heights at different ages and gender as well as the HV (height velocity) in centimeters per year. Height SDS, height velocity, and peak GH of growth hormone deficient patients were compared between DHPA and IDHPA group by using Mann Whitney U-Test. The significance level was set at 0.05.

Results

The mean time of hormonal study after diagnosis of brain tumor for the total study group of

Table 3. Summary of details of all 19 patients

	Sex	Age study	Age onset	Tumor	Surgery	RT	CT	Pubertal stage	HT-SDS	HV cm/y	Status before study							Abnormal	
											Low cortisol	On steroid	TFT	On eltroxin	DI	On ADH	GH	ACTH/ cortisol*	TFT
1	M	21.1	14.8	Germinoma/ Suprasellar	Partial	Local 36 Gy	No	Delayed	-0.5	0.33	Normal range w/o stimulation	Yes	Normal	No	Yes	Yes	Yes	Yes	Yes
2	M	11.9	8.1	Craniopharyngioma	Gross total	No	No	Delayed	-1.7	4.67	Abnormal	Yes	Low normal	Yes	Yes	Yes	Yes	Yes*	Yes**
3	M	17.0	10.8	Meningioma Lt.parasellar area	Subtotal	Local 54 Gy	No	Delayed	-1.2	4.50	Normal range w/o stimulation	No	Abnormal	Yes	No	No	Yes	Yes	Yes
4	M	19.8	14.9	Germinoma Suprasellar	Partial	Local 54 Gy	No	Delayed	-0.9	3.38	Abnormal	Yes	Abnormal	Yes	Yes	No	Yes	Yes*	Yes
5	M	17.3	13.9	Hypothalamic Harmatoma	Gross total	No	No	Normal	0.8	4.15	Normal range w/o stimulation	No	Abnormal	Yes	No	No	No	Yes	Yes
6	M	15.5	12.7	Germinoma Suprasellar, Pineal	VP-shunt	Local 36 Gy	No	Delayed	-2.3	1.00	High level during on hydrocortisone	Yes	Abnormal	Yes	Yes	Yes	Yes	Yes	Yes
7	M	15.0	11.4	Ganglioglioma Suprasellar	Near total	No	No	Normal	-0.5	2	Low cortisol, during on pred and dexa	Yes	Low normal	Yes	No	No	No	Yes	Yes**
8	F	19.6	12.1	Craniopharyngioma	Partial V-Pshunt	Local 36 Gy	No	Normal for age, 2'amenorrhea	-2.3	0.25	Normal range w/o stimulation	Yes	Low normal	Yes	Yes	No	Yes	No	Yes**
9	F	12.6	3.9	Clivus chordoma	Subtotal x2	Local 36 Gy	No	Normal	-1.5	3.00	No test	No	No test	No	No	No	Yes	No	Yes
10	F	8.5	2.3	Medulloblastoma	Gross total	CSI 24, PF 55 Gy	Yes	Normal	-0.1	7.50	No test	No	No test	No	No	No	No	Yes	No
11	M	17.7	12.3	Astrocytoma Brain stem	Subtotal	Local 60 Gy	No	Normal	-0.6	2.80	No test	No	No test	No	No	No	No	No	No
12	F	19.5	12.5	Medulloblastoma	Gross total	CSI 24, PF 55, TB 60 Gy	Yes	Normal	-2.5	1.3	No test	No	No test	No	No	No	Yes	No	No
13	F	9.7	2.1	Ependymoma 4th ventricle	Gross total	WB 54 Gy	No	Premature puberty	1.2	6.60	No test	No	No test	No	No	No	Yes	No	No
14	M	17.0	5.1	Medulloblastoma	Near total	CSI 36, PF 55, TB 60	No	Delayed	0.6	5.77	No test	No	No test	No	No	No	Yes	No	No
15	M	10.6	4.4	Medulloblastoma	Gross total	CSI 24, PF 55 Gy	Yes	Normal	-1.	4.65	No test	No	No test	No	No	No	Yes	No	No
16	M	18.3	12.7	Medulloblastoma	Gross total	CSI 24, PF 55 Gy	Yes	Delayed	-1.7	1.44	No test	No	No test	No	No	No	Yes	No	No
17	M	19.8	14.9	Mixed germ cell tumor/Lt.thalamus	Subtotal	Local 50 Gy	Yes	Normal	-1.8	1.33	No test	No	Abnormal	Yes	No	No	No	No	Yes
18	M	10.1	4.8	Immature teratoma Pineal	Gross total	Local 50 Gy	No	Normal	-1.4	3.92	No test	No	No test	No	No	No	Yes	No	No
19	M	17.2	12.4	Immature-mature teratoma/Pineal	Gross total	Local 50 Gy	Yes	Delayed	-2.5	4.5	Normal	No	Normal	No	No	No	Yes	No	No

RT = radiation therapy, CT = chemotherapy, CSI = craniospinal irradiation, PF = posterior fossa boost, TB = tumor boost, WB = whole brain irradiation, HT-SDS = height standard deviation scores, HV = height velocity, DI = diabetes inspidus, TFT = thyroid function test, ADH = antidiuretic hormone drug (Minirin^{R})

* Abnormal basal cortisol before study - no ACTH stimulation test, ** Low normal TFT before study-off eltroxin 2-4 weeks before repeat TFT

19 children was 5.8 ± 2.16 years. The mean age of diagnosis was 9.9 ± 4.6 years old.

Table 3 summarizes detailed data of all 19-brain tumor patients.

GH stimulation test

GH stimulation test with clonidine were done in all 19 patients, while 16 patients had additional L-dopa stimulation. As regards GH, seven patients in both the DHPA and IDHPA group (77% vs. 70%) had GH deficiency. The mean peak GH level of GHD patients in both groups were 0.5 ± 1.19 and 2.79 ± 1.55 ng/ml respectively. There was no difference in height SDS at assessment and height velocity but significant difference in peak GH of GHD patients between groups (Table 4).

One patient with premature puberty (Pt 13) and high height velocity (6.6cm/year) was found to have GH deficiency as well. One craniopharyngioma (Pt 2) with height SDS -1.7 and age of 11.9 years old at study was considered to receive growth hormone therapy.

ACTH stimulation test

ACTH stimulation tests were done in all patients except two patients in the DHPA group who already had definite low basal cortisol level and had been taking prednisolone since diagnosis. Four patients in the DHPA group had no definite abnormal basal cortisol level before the present study but received prednisolone since diagnosis, so prednisolone was stopped 2 weeks before ACTH test. No patients in IDHPA group had been tested for cortisol level before the present study. Peak cortisol was lower than 18 μg/dl in five and one patients in DHPA and IDHPA group respectively. The mean peak cortisol levels were 10.32 ± 5.54 and 16.71 μg/d in abnormal ACTH test patients of the DHPA and IDHPA group respectively (Table 5).

After study, in the DHPA group, the diagnoses of cortisol deficiency were confirmed in three patients, newly detected in one patient (Pt 3). Replacement therapy with prednisolone in all of them was done. However, this condition was excluded by ACTH test in one patient (Pt 8) who could later stop the drug. Subtle abnormal ACTH stimulation test was found in two cases (one in each group: Pt5 and 10 respectively), yearly monitoring of cortisol and ACTH test is considered.

Thyroid function test

Eight of nine patients in the DHPA group had ever been tested before for thyroid function and having definite abnormal, borderline abnormal, and normal in four, three, and one patients respectively. Three patients of borderline abnormal thyroid function had stopped eltroxin 2-4 weeks before repeating test. One patient in the IDHPA group had definite central hypothyroid. Fourteen patients (5 of DHPA group and 9 in IDHPA) group were tested for thyroid function. Central hypothyroidism was newly detected and confirmed in two and three patients in DHPA group respectively.

In conclusion, all patients in the DHPA group (100%) were found to have central hypothyroidism. The mean value of T4, free T4 and TSH were 3.56 ± 0.73 μg/dL, 0.49 ± 0.15 ng/dL and 2.59 ± 2.09 IU/ml respectively. No patient in the IDHPA group was additionally detected with abnormal thyroid function.

After study, eltroxin for replacement therapy was given in 10 patients (9 in DHPA, 1 in IDHPA).

Table 4. Height SDS, Height velocity and peak GH in GHD patients

Parameter	GHD patients		p-value
	DHPA	IDHPA	
Height SDS			
Mean ± SD	-1.48 ± 0.7	-1.05 ± 1.46	
Median	-1.48	-1.43	0.949
Range	-2-0	-3-1	
HV (cm/y)			
Mean ± SD	2.45 ± 1.90	4.03 ± 2.02	
Median	3.00	4.50	0.125
Range	0.25-4.67	1.3-6.6	
Peak GH (ng/ml)			
Mean ± SD	0.50 ± 1.19	2.79 ± 1.55	
Median	0.00	2.70	0.08*
Range	0.00-3.20	0.60-5.10	

Table 5. Peak cortisol after ACTH stimulation test

ACTH stimulation (n = 17)	Abnormal (n)	Normal (n)
Peak cortisol	<18 μg /dl	≥18 μg /dl
DHPA (mean ± SD) (n = 7)	10.32 ± 5.54 (5)	23.03 ± 3.35 (2)
IDHPA (mean ± SD) (n = 10)	16.71 (1)	23.44 ± 2.60 (9)

Sexual development

In the DHPA group, five patients had delayed secondary sex characteristics, and one had secondary amenorrhea after treatment of craniopharygioma (Pt8). In the IDHPA group, three patients had delayed puberty and one patient had premature puberty.

Diabetes insipidus

Five patients in the DHPA group previously had diabetes insipidus (2 craniopharygiomas, 3 supra-sellar germinomas). Three of these patients are still on ADH (Minirin^{R}) for symptomatic treatment of diabetes inspidus.

Discussion

Nineteen brain tumor survivors who were diagnosed since aged under 15 years old were recruited. Mean follow-up time was 5.8 $\pm$ 2.16 years. To avoid recurrence of tumor during the present study, the authors chose patients who were free of tumor recurrence for more than 2 years because several studies in brain tumor found that the recurrence rate for many tumors decreases significantly at 2 years from completion of therapy[24,25]. The patients were divided into two groups according to whether brain tumor location involved hypothalamic-pituitary axis. Brain tumors in each group can cause HP axis dysfunction by different pathophysiology. The directly involving HPA group may have direct effect to HPA by tumor invasion or surgical removal while the other group may cause hormonal dysfunction by radiation or chemotherapy.

It is common in brain tumors directly involving the hypothalamic-pituitary axis (DHPA) to have abnormal pituitary hormones. All patients in the present study also had at least two hormones, which were lower than normal level. Cortisol insufficiency is the most important parameter to consider in view of its role in regulating vital functions during stressful situations in every patient with tumors in this region. Interestingly, hypocortisolism were later detected in two patients in this group (Pt 3 and 5), on the other hand, one patient (Pt 8) diagnosed with craniopharyngioma had normal ACTH stimulation test and could later stop medication. Moreover, two patients (Pt 6 and 7) had been confirmed abnormal reserved adrenal function by ACTH stimulation test. This implied that ACTH stimulation test is useful and should be routinely set to detect, confirm, and exclude cortisol insufficiency in any patient with tumor in this region that had normal basal cortisol level before prescribing lifelong steroid replacement therapy for this condition. The benign brain tumors in this group with total surgical removal without radiation therapy could also have normal GH function as shown in two patients (Pt 5 and 7) with normal GH peak. This implies that patients with this condition should be screened for GHD by stimulation test only once, if GH function is normal. Serially GH stimulation test is not necessary. Serially neurological, physical examination and neuroimaging after surgery for tumor recurrence are reasonable practice. All patients in this group had central hypothyroidism and two were detected later in the present study, so serially monitoring of thyroid function is recommended for a brain tumor in this region in spite of previously being normal.

In the IDHPA group, all patients who had the primary brain tumor not directly involving the HP axis, were treated with surgery and cranial/craniospinal irradiation with 60% combined chemotherapy and mean follow-up time interval of 5.6 $\pm$ 2.23 years. Endocrine dysfunctions after cranial irradiation have been documented in many studies. The pituitary gland was considered to be resistant to the effects of external irradiation[26], while it was speculated that the hypothalamus was more sensitive to irradiation[27]. In the 1970s it was suggested that patients were at risk of developing anterior pituitary hormone deficiencies if the HP region was within the treatment field, and that the damage of irradiation was of hypothalamic origin[28] with growth hormone deficiency (GHD) as the first and frequently the only manifestation of radiation-induced hypopituitarism during childhood[24,29,30]. The difference in the development of anterior pituitary hormone deficiencies, with growth hormone (GH) being most frequently affected, suggests that selective hypothalamic neuronal and pituitary cell damage by direct radiation occurs.

Current evidence suggests that nearly 100% of children treated with radiation dosage more than 30 Gy will have blunted GH responses to an insulin tolerance test (ITT), whilst 35% of those receiving less than 30Gy still show a normal peak GH response to the ITT between 2 and 5 years after radiotherapy[31]. Prospective studies also suggest that impaired GH responses to provocative tests can occur as early as 3 months and certainly in the first 12 months post-irradiation for brain tumors[32,33]. When the RT consists of one set of fields covering the whole brain, the HP region lies within these fields and thus receives the full-prescribed dose. If the RT consists of two sets of fields, a primary set covering the whole brain and a set

of boost fields covering for instance the posterior fossa, the total dose to the HP region depends on whether this region is totally or partially included in the boost fields. Since the delimitation of the HP region is difficult to delineate it was not apparent how much of the volume of the HP model would provide the best description of the dose received by the HP region. All patients in the IDHPA group had received cranial irradiation/cranial-spinal irradiation ranged from 24 to 60 Gy, whilst the average risk medulloblastoma patients in the present study received dosage radiation of HP region lower than other type of brain tumor, which received at least 36 Gy. However, it has been claimed that irradiation of the hypothalamus with focal RT of the posterior fossa, *e.g.* in children with medulloblastoma cannot be avoided due to the very close relation of the anterior limit of the posterior fossa radiation field extending to the posterior clinoid, and hence encompassing the posterior part of the hypothalamus[33,34]. Therefore, this can be explained for the medulloblastoma patients who received lower dosage of RT but still had GHD. However, one medulloblastoma (Pt 10) who had an average risk and received cranial spinal irradiation of 24 Gy with posterior fossa boost of 55 Gy still had normal GH after clonidine test which might be explained by interindividual differences in the degree of irradiation to the HP region, and the fact that there is a steep dose gradient on the border of the radiation field underlines the necessity of very precise planning of the treatment fields as in the study of Schmiegelow M which observed huge interindividual differences in time to onset of GHD in children presumably equally treated[5]. Moreover, one brain stem glioma (Pt 11) and one mixed germ cell tumor of thalamus (Pt 7) still had normal GH even 4.5-5.4 years after completion of high dosage local brain irradiation (60, 50 Gy respectively), this could be explained by effectively avoiding the HP region from radiation in both cases. Consequently, while GHD is prevalent in brain tumor survivors, other pituitary hormone deficits occurred in only 2-6% after almost 10 years following 40-50 Gy[29,35].

Clinical observations revealed that GH is the most radiosensitive followed by gonadotrophin, adrenocorticotrophin (ACTH) and thyrotrophin (TSH) the last hormone to be affected, although variations in this order can occur. Compared to the present study, GHD was found in 70% of the patients in the IDHPA group while cortisol deficiency and central hypothyroidism were found in only 10% of each. Schmiegelow et al (2006) found central hypothyroidism in 6% and primary hypothyroidism in 24% of the cohort (73% mild or compensated hypothyroidism 27% overt primary hypothyroidism) with a median length of follow-up of 12 years (range: 2-28 years)[5]. In contrast to previous study, the authors found only 10% of central hypothyroidism without primary hypothyroidism with a median time interval of follow-up of 5 years (range: 3.3-11.3 years). Previous studies of Livesey et al (1990), Constine et al (1993), Oberfield et al (1997) and Spoudeas et al (2003) based on less than 12 years follow-up demonstrated only subtle abnormalities of ACTH insufficiency suggesting that the hypothalamic-pituitary-adrenal axis might be affected relatively late by irradiation[8,36,37]. Schmiegelow et al (2003) found dysfunction of the HPA axis in 19%, who demonstrated insufficiency of their HPA axis with basal cortisol levels below 500 nmol/liter and which did not respond with a peak cortisol above the cut-off level to neither an ACTH test (30 or 60 min.) nor an ITT[18]. The present study demonstrated 10% of IDHPA group (Pt10) with a subtle low response to ACTH stimulation test with peak cortisol less than 18 μg/ml at 30 and 60 minutes (16.7 and 13.7 μg /ml respectively).

Endocrinological late effects of chemotherapy in the treatment of brain tumors have only been investigated in a few studies[38]. The effect of chemotherapy on growth has been suggested to potentiate the deleterious effects of RT. In the cohort study, Schmiegelow et al (2000) investigated the possible influence of chemotherapy on peak GH by an ITT/arginine stimulation test in 73 children who were treated with CIR or CSI and 29 children were treated pre- and/or postoperatively with adjuvant chemotherapy in addition to RT, and concluded that chemotherapy did not have a significant impact on GH secretion[39]. Because of the limited number of patients in the present study, the authors could not conclude whether chemotherapy potentiated the RT effects or not. Hypothalamic-pituitary dysfunction secondary to radiation is also time dependent. There is an increase in the frequency and severity of hormonal deficits with a longer time interval after radiotherapy. The progressive nature of the hormonal deficits following radiation damage to the hypothalamic-pituitary axis can be attributed to the delayed effects of radiotherapy on the axis or the development of secondary pituitary atrophy following previous hypothalamic damage[34,40,41]. This necessitates prolonged follow-up with serially testing of pituitary function in patients treated with cranial irradiation for brain tumors.

Conclusion

As the overall cure rate of children treated for a brain tumor has increased during the last three decades, the number of long-term survivors is increasing. The improvement in prognosis has been achieved at the expense of serious late effects, including endocrine problems. The recognition and prompt management of these are essential to prevent further morbidity and impairment of quality of life. From the present study, the authors will further develop endocrinological monitoring protocol for childhood brain tumor survivors in our hospital. Future research for endocrinological problems in the brain tumor patients should be designed to direct the better method of treatment that can reduce these problems in childhood brain tumor survivors.

Acknowledgements

The authors would like to express our thanks for the funding from Prasat Neurological Institute Foundation, the statistical analysis by Miss. Pimchanok Puthkhao BPA, BSc, MSc (statistician of Prasat Neurological Institute), supporting data of radiation therapy from Dr. Sakpisid Wongpiyabovorn (radiotherapist of National Cancer Institute) and the contribution from all nurses and personnel in the Pediatric Neurology Unit of Prasat Neurological Institute.

References

1. Gurney JG, Davis S, Severson RK, Fang JY, Ross JA, Robison LL. Trends in cancer incidence among children in the U.S. Cancer 1996; 78: 532-41.
2. de Nully BP, Olsen JH, Hertz H, Carstensen B, Bautz A. Trends in survival after childhood cancer in Denmark, 1943-87: a population-based study. Acta Paediatr 1995; 84: 316-24.
3. Bleyer WA. Epidemiologic impact of children with brain tumors. Childs Nerv Syst 1999; 15: 758-63.
4. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al., editors. SEER Cancer statistics review, 1975-2006 [homepage on the Internet]. Bethesda, MD: National Cancer Institute. 2009 [cited 2009 Nov 15]. Available from: http://seer.cancer.gov/csr/1975_2006/
5. Schmiegelow M. Endocrinological late effects following radiotherapy and chemotherapy of childhood brain tumours. Dan Med Bull 2006; 53: 326-41.
6. Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 2003; 97: 663-73.
7. Geffner ME. Hypopituitarism in childhood. Cancer Control 2002; 9: 212-22.
8. Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993; 328: 87-94.
9. Preece MA. Making a rational diagnosis of growth-hormone deficiency. J Pediatr 1997; 131: S61-4.
10. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000; 85: 3990-3.
11. Lanes R, Recker B, Fort P, Lifshitz F. Low-dose oral clonidine. A simple and reliable growth hormone screening test for children. Am J Dis Child 1985; 139: 87-8.
12. Martinez AS, Domene HM, Ropelato MG, Jasper HG, Pennisi PA, Escobar ME, et al. Estrogen priming effect on growth hormone (GH) provocative test: a useful tool for the diagnosis of GH deficiency. J Clin Endocrinol Metab 2000; 85: 4168-72.
13. Vanderschueren-Lodeweyckx M, Wolter R, Malvaux P, Eggermont E, Eeckels R. The glucagon stimulation test: effect of plasma growth hormone and on immunoreactive insulin, cortisol, and glucose in children. J Pediatr 1974; 85: 182-7.
14. Abdu TA, Elhadd TA, Neary R, Clayton RN. Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 1999; 84: 838-43.
15. Hurel SJ, Thompson CJ, Watson MJ, Harris MM, Baylis PH, Kendall-Taylor P. The short Synacthen and insulin stress tests in the assessment of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol (Oxf) 1996; 44: 141-6.
16. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Lancet 1988; 1: 1208-10.
17. Clayton RN. Short Synacthen test versus insulin stress test for assessment of the hypothalamo [correction of hypothalmo]-pituitary - adrenal axis: controversy revisited. Clin Endocrinol (Oxf) 1996; 44: 147-9.

18. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Lange M, Poulsen HS, Muller J. Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. J Clin Endocrinol Metab 2003; 88: 3149-54.
19. Lange M, Svendsen OL, Skakkebaek NE, Muller J, Juul A, Schmiegelow M, et al. An audit of the insulin-tolerance test in 255 patients with pituitary disease. Eur J Endocrinol 2002; 147: 41-7.
20. Jones SL, Trainer PJ, Perry L, Wass JA, Bessser GM, Grossman A. An audit of the insulin tolerance test in adult subjects in an acute investigation unit over one year. Clin Endocrinol (Oxf) 1994; 41: 123-8.
21. Burke CW. The pituitary megatest: outdated? Clin Endocrinol (Oxf) 1992; 36: 133-4.
22. Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. BMJ 1992; 304: 173-4.
23. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. Arch Dis Child 1966; 41: 613-35.
24. Darendeliler F, Livesey EA, Hindmarsh PC, Brook CG. Growth and growth hormone secretion in children following treatment of brain tumours with radiotherapy. Acta Paediatr Scand 1990; 79: 950-6.
25. Sulmont V, Brauner R, Fontoura M, Rappaport R. Response to growth hormone treatment and final height after cranial or craniospinal irradiation. Acta Paediatr Scand 1990; 79: 542-9.
26. Kelly KH, Feldsted ET, Brown RF, Ortega P, Bierman HR, Lowbeer BV, et al. Irradiation of the normal human hypophysis in malignancy: report of three c cases receiving 8,100-10,000 r tissue dose to the pituitary gland. J Natl Cancer Inst 1951; 11: 967-83.
27. Arnold A. Effects of x-irradiation on the hypothalamus: a possible explanation for the therapeutic benefits following x-irradiation of the hypophysial region for pituitary dysfunction. J Clin Endocrinol Metab 1954; 14: 859-68.
28. Larkins RG, Martin FI. Hypopituitarism after extracranial irradiation: evidence for hypothalamic origin. Br Med J 1973; 1: 152-3.
29. Duffner PK, Cohen ME, Voorhess ML, MacGillivray MH, Brecher ML, Panahon A, et al. Long-term effects of cranial irradiation on endocrine function in children with brain tumors. A prospective study. Cancer 1985; 56: 2189-93.
30. Brauner R, Rappaport R, Prevot C, Czernichow P, Zucker JM, Bataini P, et al. A prospective study of the development of growth hormone deficiency in children given cranial irradiation, and its relation to statural growth. J Clin Endocrinol Metab 1989; 68: 346-51.
31. Shalet SM, Beardwell CG, MacFarlane IA, Jones PH, Pearson D. Endocrine morbidity in adults treated with cerebral irradiation for brain tumours during childhood. Acta Endocrinol (Copenh) 1977; 84: 673-80.
32. Livesey EA, Hindmarsh PC, Brook CG, Whitton AC, Bloom HJ, Tobias JS, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 1990; 61: 622-5.
33. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr 1991; 118: 226-8.
34. Shalet SM, Beardwell CG, Morris-Jones PH, Pearson D. Pituitary function after treatment of intracranial tumours in children. Lancet 1975; 2: 104-7.
35. Duffner PK, Cohen ME. Long-term consequences of CNS treatment for childhood cancer, Part II: Clinical consequences. Pediatr Neurol 1991; 7: 237-42.
36. Oberfield SE, Nirenberg A, Allen JC, Cohen H, Donahue B, Prasad V, et al. Hypothalamic-pituitary-adrenal function following cranial irradiation. Horm Res 1997; 47: 9-16.
37. Spoudeas HA, Charmandari E, Brook CG. Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumours. Med Pediatr Oncol 2003; 40: 224-9.
38. Olshan JS, Gubernick J, Packer RJ, D'Angio GJ, Goldwein JW, Willi SM, et al. The effects of adjuvant chemotherapy on growth in children with medulloblastoma. Cancer 1992; 70: 2013-7.
39. Ogilvy-Stuart AL, Shalet SM. Growth and puberty after growth hormone treatment after irradiation for brain tumours. Arch Dis Child 1995; 73: 141-6.
40. Spoudeas HA, Hindmarsh PC, Matthews DR, Brook CG. Evolution of growth hormone neurosecretory disturbance after cranial irradiation for childhood brain tumours: a prospective study. J Endocrinol 1996; 150: 329-42.
41. Schmiegelow M, Lassen S, Poulsen HS, Feldt-Rasmussen U, Schmiegelow K, Hertz H, et al. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. Clin Endocrinol (Oxf) 2000; 53: 191-7.

ภาวะฮอร์โมนต่อมใต้สมองบกพร่องในผู้ป่วยเด็กโรคเนื้องอกสมองที่รอดชีวิตในสถาบันประสาทวิทยา

อาภาศรี ลุสวัสดิ์, กัลยาณ์ ธีระวิบูลย์, ศศิภา ธรรมมงคล, สมลักษณ์ วนวนานต์, พัฒน์ มหาโชคเลิศวัฒนา

วัตถุประสงค์: *เพื่อศึกษาภาวะฮอร์โมนต่อมใต้สมองบกพร่องในผู้ป่วยเด็ก โรคเนื้องอกสมองที่รอดชีวิตของสถาบันประสาทวิทยา*

วัสดุและวิธีการ: *ตั้งแต่ตุลาคม พ.ศ. 2550 ถึง กันยายน พ.ศ. 2551 ได้ทำการศึกษาผู้ป่วยเด็กโรคเนื้องอกสมองในสถาบัน ประสาทวิทยาที่ไม่มีการกลับเป็นซ้ำของเนื้องอกอย่างน้อย 2 ปี จำนวน 19 ราย โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม ตามตำแหน่งเนื้องอกที่อยู่ใกล้เคียง และตำแหน่งที่ไม่เกี่ยวข้องกับไฮปธาลามัส และต่อมใต้สมองโดยตรง (DHPA และ IDHPA) จำนวน 9 และ 10 ราย ตามลำดับ ทุกรายได้รับการผ่าตัด 10 ราย ได้รับรังสีรักษาร่วมเท่านั้น และ 6 ราย ได้เคมีบำบัดร่วมกับรังสีรักษา ผู้ป่วยที่เข้าร่วมการวิจัยจะได้รับการตรวจฮอร์โมนการเจริญเติบโตด้วยการกระตุ้นโดยใช้ยาโซลนิดีน และ/หรือ แอลโดปา ตรวจคอร์ติซอลด้วยการกระตุ้นด้วยยา ACTH และตรวจไธรอยด์ฮอร์โมน (TFT)*

ผลการศึกษา: *อายุผู้ป่วยเมื่อวินิจฉัย เฉลี่ย 9.9 $\pm$ 4.61 ปี ระยะเวลาตั้งแต่รักษาจนกระทั่งได้เข้าร่วมวิจัยเฉลี่ย 5.8 $\pm$ 2.16 ปี ผู้ป่วยในกลุ่ม DHPA 7 ราย (ร้อยละ 77) และ IDHPA 7 ราย (ร้อยละ 70) พบภาวะขาดฮอร์โมนการเจริญเติบโต และพบว่าระดับฮอร์โมนการเจริญเติบโตในกลุ่ม DHPA ต่ำกว่ากลุ่ม IDHPA อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) ร้อยละ 85 และร้อยละ 10 ของผู้ป่วยกลุ่ม DHPA และ IDHPA ตามลำดับ มีค่าคอร์ติซอลต่ำกว่าปกติหลังจากกระตุ้นด้วย ACTH ผู้ป่วยร้อยละ 100 และร้อยละ 10 ของกลุ่ม DHPA และ IDHPA ตามลำดับ มีภาวะไธรอยด์บกพร่องจากต่อมใต้สมอง จากการกระตุ้นด้วย ACTH ในผู้ป่วยกลุ่ม DHPA พบว่ามีความผิดปกติ 5 ราย และปกติ 1 ราย ซึ่งต่อมาสามารถหยุดยาสเตียรอยด์ที่ได้รับมาเป็นเวลานานได้ พบผู้ป่วยกลุ่ม DHPA 2 ราย ที่ไม่เคยตรวจพบ TFT ผิดปกติมาก่อนมีภาวะไธรอยด์บกพร่องจากต่อมใต้สมอง ซึ่งต่อมาได้รับยาไธรอยด์ฮอร์โมนทดแทน จากการใช้การกระตุ้นด้วยยาโคลนิดีน และแอลโดปาในการศึกษานี้ สามารถตรวจพบภาวะฮอร์โมนการเจริญเติบโตบกพร่องร้อยละ 73 ของผู้ป่วยทั้งหมด การรักษาภาวะฮอร์โมนการเจริญเติบโตบกพร่อง ได้รับการพิจารณาตามความเหมาะสมของผู้ป่วยแต่ละราย*

สรุป: *เนื่องจากการรักษาที่มีประสิทธิภาพมากขึ้นในปัจจุบันทำให้อัตราการรอดชีวิตของผู้ป่วยเด็ก ที่เป็นเนื้องอกสมองมีจำนวนเพิ่มมากขึ้น จึงควรมีการเฝ้าระวังภาวะฮอร์โมนต่อมใต้สมองบกพร่องอย่างต่อเนื่องเพื่อลดภาวะแทรกซ้อนและเพิ่มคุณภาพการรักษาผู้ป่วยในกลุ่มนี้*