Clin Pediatr Endocrinol 2007; **16**(1), 1-9

Original Article

Prevalence of Obesity, Hyperlipemia and Insulin Resistance in Children with Suprasellar Brain Tumors

Masanori Adachi[1], Takayoshi Tsuchiya[1], Koji Muroya[1], Yumi Asakura[1], Ken-ichi Sekido[2], and Hironobu Sato[2]

[1]*Department of Endocrinology and Metabolism, Clinical Research Institute, Kanagawa Children's Medical Center, Yokohama, Japan*

[2]*Department of Neurosurgery, Kanagawa Children's Medical Center, Yokohama, Japan*

Abstract. Weight gain is a common sequela of suprasellar tumors, referred to as hypothalamic obesity. We undertook an evaluation of obesity and metabolic aberrations among patients treated at our institute. During the 12 mo from Apr. 2005, 23 patients (10 males and 13 females) with remitted suprasellar tumors attended our clinic: 10 patients with craniopharyngioma, 7 with germinoma, 4 with optic nerve glioma and others. Of these, 12 patients (52%) were found to have obesity on the basis of percent overweight and/or percent body fat. Elevated cholesterol and/or triglyceride (TG) was found in 9 patients (39%), and insulin resistance was suspected in 7 patients (30%). Three patients exhibited strikingly elevated postprandial TG levels. All 6 patients with the growth without GH phenomenon had at least one metabolic aberration. In conclusion, the prevalence of hypothalamic obesity was nearly half in our series, and hyperlipemia and insulin resistance were also frequently found. The increased risk for metabolic aberration in growth without GH patients was suggested.

Key words: craniopharyngioma, hypothalamic obesity, metabolic syndrome, hypertriglyceridemia, growth without GH

Introduction

Brain tumors located in the suprasellar region are frequently found in childhood, and include craniopharyngioma, germinoma, optic nerve glioma and histiocytosis (1). Following the extension of the tumor or intervening procedures, such as surgery, chemotherapy and radiation, considerable damage to the hypothalamic pituitary axis is almost inevitable. Accordingly, most children with suprasellar tumors suffer from endocrinological sequelae, even after the original lesion has been cured (2). In addition, these children have been shown to have a high risk of developing morbid obesity, which has recently been referred to as hypothalamic obesity (3–6). In this report, we studied the prevalence of obesity among children with suprasellar tumors who had been treated at our institute. Additionally, we evaluated metabolic aberrations in these patients, and tried

Received: June 12, 2006
Accepted: September 6, 2006
Correspondence: Dr. Masanori Adachi, Department of Endocrinology and Metabolism, Clinical Research Institute, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama 232-8555, Japan
E-mail: madachi@mars.sannet.ne.jp

Table 1 Profiles of 23 patients with remitted suprasellar tumors

	Sex*	Current age	Pathology[∀]	Age at surgery[#]	Chemotherapy	Radiation therapy[Δ]	Note
1	f	3 yr	CP	0y (T)	–	–	
2	f	4 yr	CP	2y (T)	–	–	
3	f	9 yr	CP	7y (P)	–	Local 54.4Gy	
4	f	10 yr	CP	6y (T)	–	–	
5	m	11 yr	CP	7y (T),10y (T)	–	–	
6	m	11 yr	CP	3y (T)	–	–	
7	f	12 yr	CP	1y (T)	–	Local 50.0Gy	
8	m	14 yr	CP	3y (T)	–	–	
9	f	15 yr	CP	6y (P), 7y (P), 12y (T)	–	γ-knife	
10	m	17 yr	CP	6y (T), 7y (P), 14y (T)	+	γ-knife	
11	f	13 yr	G	7y (P)	+ (BMT)	WB 19.8Gy, Local 25.2Gy	germinoma with STGC[@]
12	m	16 yr	G	13y (b)	+	WB 20.0Gy, Local 14.0Gy	
13	m	16 yr	G	13y (b)	+	WB 34.2Gy	
14	f	19 yr	G	6y (b)	+	WB 27.0Gy, Local 18.0Gy	dysgerminoma
15	m	21 yr	G	15y (b)	+	WB19.8Gy, Local 16.2Gy	
16	f	21 yr	G	11y (P)	+	WB 36.0Gy, Local 55.0Gy	malignant germinoma
17	m	22 yr	G	14y (b)	+	WB 21.6Gy, Local 19.8Gy	
18	f	10 yr	OP	1y (P)	+	Local 45.0Gy	diencephalic syndrome
19	m	14 yr	OP	1y (b)	+	Local 59.2Gy	diencephalic syndrome
20	f	14 yr	OP	6y (b), 9y (P)	+	Local 50.4Gy	
21	f	15 yr	OP	2y (b)	+	Local 57.4Gy	
22	m	11 yr	INF	3y (b)	+	–	grade 1 astrocytoma
23	f	14 yr	HIS	1y (b)	+	–	

* f: female, m: male. [∀]CP: craniopharyngioma, G: germinoma, OP: optic glioma, INF: infundibuloma, HIS: Langerhans histiocytosis, [#]T: total or near-total resection, P: partial resection, b: biopsy. [Δ]WB: whole brain irradiation, Local: local irradiation. [@]syncytiotrophoblastic giant cells.

to correlate them with clinical features and endocrinological alterations of the patients.

Patients and Methods

Patients with remitted suprasellar tumors, who had been diagnosed and treated at our institute and had attended our endocrinological unit more than once from April 2005 to April 2006, were enrolled in this study. Those with Rathke's cleft cyst or hypophysitis were excluded. In addition, a 28-yr-old male with craniopharyngioma, who had been subjected to long-term bed rest because of a serious neurological sequela, was also excluded. As depicted in Table 1, a total of 23 patients (10 males and 13 females) met the enrollment criteria, including 10 patients with craniopharyngioma (43%), 7 patients with germinoma (30%), 4 with optic nerve glioma (17%), and single cases of infundibuloma and Langerhans cell histiocytosis. The current ages of the patients were distributed from 3 to 22 yr old, the median of which was 14 yr old. All craniopharyngioma patients had near-total or total tumor removal for the first line treatment, followed by additional radiotherapy or chemotherapy in cases of incomplete resection or tumor recurrence. Some cases were forced to undergo repetitive operations. In patients with germinoma and optic nerve glioma, radiotherapy and chemotherapy

were the mainstay of the treatment, following biopsy or partial resection. One case of germinoma with syncytiotrophoblastic giant cells underwent autologous peripheral stem cell transplantation.

With each patient, a retrospective review regarding the contents of therapies and the extent of endocrinological dysfunction was carried out. For the assessment of metabolic alteration, the degree of overweight (%-overweight) was determined and body fat mass was estimated for each patient. The percent overweight was expressed as the quotient of the excess weight to the ideal weight. In female patients less than 15 yr of age and males less than 18, ideal weight was based on the auxological data from normal Japanese children (7). For the remaining patients, the weight compatible with a body mass index of 22 was regarded as ideal. Body fat mass was measured by whole-body bioelectrical impedance analysis (TBF-310, Tanita Corp. Tokyo, Japan). In addition, blood pressure, total cholesterol level, triglyceride (TG) level and the homeostatic model assessment of insulin resistance (HOMA-R: fasting IRI (μU/mL) × fasting glucose (mg/dL)/405) was determined.

The diagnosis of GH deficiency followed the consensus guideline of the Growth Hormone Research Society (8) as well as the national guidelines for the diagnosis of GH deficiency. In brief, the GH responses to exogenous GH secretagogues less than 3 ng/mL indicated severe GH deficiency (SGHD) whereas GH responses between 3–6 ng/mL were considered to be moderate GH deficiency (MGHD).

Obesity was defined according to the criteria made by national experts (9) as follows: more than 20% overweight and/or %-body fat exceeding 25% in males, 30% in females younger than 11 yr, and 35% in females older than 11 yr.

Hyperlipemia was defined as either an elevated fasting total cholesterol level above 220 mg/dL or fasting TG level above 140 mg/dL (10). Presence of insulin resistance was suggested when HOMA-R exceeded 2.5, according to the guidelines from the Japan Diabetes Society (11).

Statistical analysis was performed using ystat2000.xls. For the comparison among groups according to tumor pathology, the Yates χ^2-test and non-parametric statistical methods (Kruskal Wallis-H-test) were applied because of the relatively small samples and skewed distribution of the data. For the comparison between groups with or without GH administration, the Yates χ^2-test or Fisher's test was applied as necessary. P values less than 0.05 were taken as statistically significant.

Results

Endocrinological dysfunction

Table 2 shows the endocrinological status of the patients at the time of study. All patients with craniopharyngioma suffered from panhypopituitarism with diabetes insipidus except case 1, in whom the tumor was identified by chance through evaluation for head injury. All patients with germinoma also had more than one defect of the pituitary hormones. On the other hand, none of the patients with optic nerve glioma showed adrenal insufficiency or diabetes insipidus, but they had been treated for precocious puberty. The condition of so-called growth without GH, normal or accelerated linear growth despite GH deficiency, was observed in 6 patients. Of these, 3 patients had chosen to take GH supplementation, expecting the effect to improve their metabolic aspects.

Metabolic aberrations

In Table 3, the results of investigation for the metabolic aspects of the patients are summarized. Obesity, judged from either the %-overweight or %-body fat, was found in 12 out of 23 patients (7 males, 5 females). No patients were hypertensive at the time of investigation. Fasting blood samples in the morning could be obtained in all but one patient. In those samples, an elevated total

Table 2 Endocrinological status of 23 patients

	Growth hormone (GH)*	L-thyroxine[#]	Hydrocortisone[∀]	Gonadal state[Δ]	DDAVP[@]	Growth without GH
1	MGHD, GH (–)	(–)	(–)	?	(–)	–
2	SGHD, GH (–)	55 μg	5 mg	?	(+)	–
3	SGHD, GH (–)	50 μg	10 mg	?	(+)	–
4	SGHD, on GH	100 μg	on demand	?	(+)	+
5	SGHD, on GH	100 μg	5 mg	?	(+)	+
6	SGHD, on GH	100 μg	21 mg	?	(+)	+
7	SGHD, on GH	100 μg	16 mg	HH	(+)	–
8	SGHD, on GH	100 μg	15 mg	HH	(+)	–
9	SGHD, GH (–)	100 μg	10 mg	HH	(+)	+
10	SGHD, on GH	150 μg	24 mg	HH	(+)	–
11	SGHD, on GH	100 μg	10 mg	HH	(+)	–
12	MGHD, GH (–)	200 μg	10 mg	N (compensated)	(+)	–
13	SGHD, on GH	100 μg	10 mg	HH	(+)	–
14	SGHD, off GH	50 μg	(–)	PP	(+)	–
15	MGHD, GH (–)	125 μg	15 mg	HH	(+)	–
16	SGHD, GH (–)	100 μg	10 mg	HH	(–)	+
17	SGHD, GH (–)	100 μg	(–)	N	(–)	–
18	SGHD, on GH	(–)	(–)	PP	(–)	–
19	SGHD, on GH	75 μg	(–)	PP → HH	(–)	–
20	N	50 μg	(–)	PP	(–)	–
21	SGHD, off GH	75 μg	(–)	PP	(–)	–
22	SGHD, on GH	25 μg	(–)	?	(+)	–
23	SGHD, GH (–)	100 μg	(–)	HH	(+)	+

*SGHD: severe GH deficiency, MGHD: moderate GHD. 'GH (–)' denotes that the patient has never taken GH replacement, whereas 'on GH' means that the patient took GH at the time of evaluation. 'off GH' means the patient had taken GH replacement previously. [#]Dose of thyroid hormone (L-T4) supplementation. [∀]Dose of hydrocortisone supplementation. [Δ]N: normal function, HH: hypogonadotropic hypogonadism, PP: precocious puberty, ?: too young for evaluation. [@]Presence (+) or absence (–) of DDAVP usage.

cholesterol level (>220 mg/dL) was identified in 4 patients. Elevated TG (>140 mg/dL) was found in 6 patients, including 2 patients (cases 5 & 13) who exhibited strikingly elevated postprandial TG levels of more than 1,200 mg/dL. In addition, another patient (case 16) also had postprandial hypertriglyceridemia, as much as 1,029 mg/dL, despite a normal fasting TG level. This patient was labeled to have hyperlipemia. HOMA-R exceeding 2.5 was found in 7 patients (3 males, 4 females) including one (case 9) whose fasting glucose was 101 mg/dL.

Collectively, out of 23 patients, 16 patients had at least one metabolic aberration, such as obesity, hyperlipemia and insulin resistance, which accounted for two thirds of all the patients. Of these, obesity was most frequently found, and 9 out of 12 obese patients had either accompanying hyperlipemia or insulin resistance. The relationship between obesity, hyperlipemia and insulin resistance is summarized in Table 4, with categorization according to the tumor pathology.

Table 3 Metabolic status of 23 patients

	Height [cm] (SD score)	Weight [kg]	%-overweight*	%fat*	Blood pressure [mmHg]	Total cholesterol# [mg/dL]	Triglyceride# [mg/dL]	Fasting BS [mg/dL]	IRI [μIU/mL]	HOMA-R#
1	91.2 (–1.0)	14.8	+13.8	NT	98/58	NT	NT	NT	NT	NT
2	92.3 (–3.0)	13.8	+4.5	18.2	106/62	170	62	57	1.5	0.21
3	120.0 (–2.0)	27.4	+18.6	23.0	90/58	206	20	77	1.0	0.19
4	141.9 (+0.8)	47.7	+31.8	33.1	98/60	198	58	82	8.0	1.62
5	146.4 (+0.2)	54.6	+35.7	25.5	112/54	214	428 (1,207)	71	16.9	2.96
6	147.6 (+1.0)	68.3	+65.8	40.5	128/54	252	36	76	32.1	6.02
7	139.6 (–2.0)	32.6	–5.9	12.8	100/50	165	114	77	5.8	1.10
8	149.2 (–2.1)	41.5	–2.2	25.8	80/50	151	50	81	7.6	1.52
9	159.8 (+0.5)	68.9	+22.6	38.9	118/68	156	150	101	105.7	26.4
10	158.5 (–2.1)	60.6	+22.7	37.2	110/76	201	127	80	3.5	0.69
11	142.1 (–2.4)	39.8	+9.8	27.6	74/38	163	80	77	21.7	4.13
12	176.5 (+1.1)	83.7	+22.1	38.6	128/48	292	39	97	6.2	1.48
13	160.6 (–1.6)	72.7	+43.0	32.5	122/64	253	288 (1,285)	81	12.0	2.40
14	146.3 (–2.2)	50.3	+6.8	37.6	112/64	314	288	89	7.0	1.54
15	170.1 (–0.1)	56.9	–10.8	19.2	118/70	203	175	98	8.7	2.11
16	159.9 (+0.3)	50.5	–10.1	25.6	118/80	206	74 (1,029)	82	4.9	0.99
17	159.0 (–2.0)	38.8	–30.2	15.4	102/68	151	33	78	2.9	0.56
18	123.5 (–2.5)	25.9	+4.2	21.2	86/46	198	25	84	3.8	0.79
19	158.1 (–0.7)	47.6	–3.2	32.3	124/88	194	52	93	50.3	11.55
20	141.1 (–2.9)	51.2	+44.2	40.7	108/66	188	67	90	28.9	6.42
21	158.3 (+0.2)	70.7	+28.2	41.6	120/78	196	31	88	19.0	4.13
22	135.2 (–1.4)	34.0	+4.9	19.1	108/80	177	29	91	3.8	0.85
23	150.6 (–1.2)	50.7	+16.6	28.6	90/46	186	175	92	10.9	2.48

*Underlined figures denote the patients who were categorized as obese. #Underlined figures denote the elevated values indicating hypercholesterolemia, hypertriglyceridemia or insulin resistance. In parentheses, extremely elevated postprandial triglyceride values are provided. NT: not tested.

Relationship between tumor pathology, endocrinological dysfunction and metabolic aberration

Among the 3 major groups of tumor pathology (craniopharyngioma, germinoma and optic nerve glioma), the incidence of obesity was not significantly different: 60% craniopharyngioma, 43% germinoma and 75% in optic nerve glioma (P=0.90). In addition, the %-overweight in each group did not differ significantly (P=0.66). Hyperlipemia was most frequently observed in germinoma (71%), followed by craniopharyngioma (30%), and optic nerve glioma (0%). This order was reversed in insulin resistance: optic nerve glioma 75%, craniopharyngioma 30% and germinoma 14%. These differences showed no statistical significance (P=0.22 and P=0.38, respectively).

Among the GH deficient patients, 11 patients were on GH replacement therapy, whereas 11 patients were not at the time of evaluation. In each group, the incidence of obesity was similar (7/11 vs. 4/11, P=0.39). Likewise, the incidences of hyperlipemia and insulin resistance were not significantly different (3/11 vs. 6/11, P=0.39; 4/11 vs. 2/11, P=0.64, respectively). These results did not change fundamentally, when 2 patients with previous GH usage were added to the GH

Table 4 Summary of the relationship between obesity, hyperlipemia and insulin resistance (n=22)

	HL (+)	HL (–)	IR (+)	IR (–)	HL (+) or IR (+)	HL (–) and IR (–)
obesity (+)	6 CP 3 G 3 OP 0	6 CP 3 G 0 OP 3	6 CP 3 G 0 OP 3	6 CP 3 G 3 OP 0	9 CP 3 G 3 OP 3	3 CP 3 G 0 OP 0
obesity (–)	3 CP 0 G 2 OP 0	7 CP 3 G 2 OP 1	1 CP G 1 OP	9 CP 3 G 3 OP 1	4 CP 0 G 3 OP 0	6 CP 3 G 1 OP 1

HL: hyperlipemia, IR: insulin resistance. CP: craniopharyngioma, G: germinoma, OP: optic glioma.

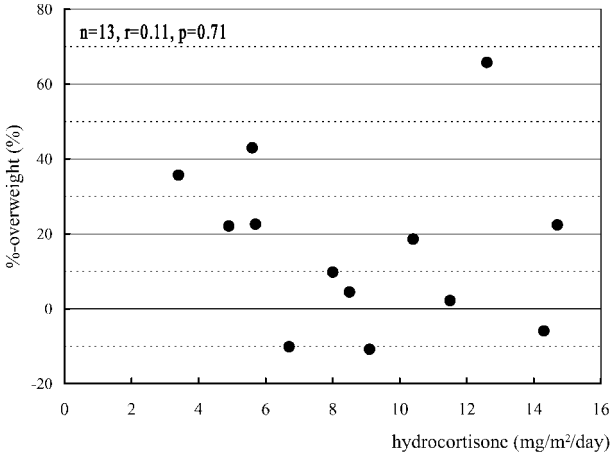

Fig. 1 The relationship between supplemented hydrocortisone doses (mg/m^2/day) and the degree of overweight (%) in patients with ACTH deficiency.

treatment group.

The dose of supplemented hydrocortisone (mg/m^2/day) did not correlate with the degree of overweight, as shown in the Fig. 1.

All 6 patients with growth without GH had at least one metabolic aberration: obesity in 4, hyperlipemia in 5 and insulin resistance in 3. Conversely, all 3 patients with combined obesity, hyperlipemia and insulin resistance had accompanying growth without GH.

Discussion

Hypothalamic obesity refers to intractable weight gain following hypothalamic damage, which has been described in both children and adults (3–6). This complication has been most frequently observed after treatment for craniopharyngioma, accounting for 50 to 70% of children with craniopharyngioma (4, 6). Dietary modification tends to fail, leaving these patients at high risk of developing morbid obesity. Because obesity is a primary risk factor for morbidity in the general population, hypothalamic obesity may be a serious complication both in physical fitness and in psychological aspects.

The mechanism for the development of hypothalamic obesity has not been fully elucidated. Excessive hunger due to a disturbed satiety center was once postulated (12, 13). However, it was demonstrated that the energy intake in children with hypothalamic obesity is not always increased (14). Insulin hypersecretion from pancreatic beta cells resulting from diminished vagal tone due to a damaged ventromedical hypothalamus is a promising hypothesis (15, 16). In addition, increased 11-beta-hydroxysteroid dehydrogenase activity was demonstrated in hypothalamic obesity patients (17), which may play an additional role in its

pathogenesis.

In assessing obesity, we evaluated both the degree of overweight and the %-body fat. Three patients (case 8, 14, 19) showed adequate weight despite their increased %-body fat, highlighting the importance of measuring the fat mass in addition to anthropometric data. It may be more appropriate to evaluate the visceral fat mass directly by CT scan.

The incidence of obesity was as high as 52%, a figure that is in accordance with previous reports (4, 6). The identified risk factors for developing hypothalamic obesity include the presence of any endocrinopathy, tumor infiltration into the hypothalamus, irradiation to the hypothalamus greater than 51 Gy, and a younger age at diagnosis (4, 18). In our series, most of the craniopharyngiomas extended to the hypothalamus, making post-surgical panhypopituitarism inevitable. On the other hand, many patients with germinoma or optic nerve glioma received high-dose irradiation, which caused multiple pituitary hormone deficiency. These factors may have contributed to the high incidence of obesity in our series. Of note, obese patients with optic nerve glioma lacked diabetes insipidus, suggesting that the presence of diabetes insipidus is not always necessary for the development of hypothalamic obesity.

GH supplementation, either previous or current, did not decrease the incidence of obesity. This finding is in accordance with the report from the KIGS database in which GH treatment for 3 yr did not influence the body mass index of craniopharyngioma patients (19). The hydrocortisone dosage, given to patients with ACTH deficiency, was merely physiological, and it showed no relationship with obesity. These findings imply that endocrinological management (GH supplementation or hydrocortisone reduction) is not capable of ameliorating obesity.

About one third of the patients were estimated to have insulin resistance by HOMA-R. Visceral fat accumulation (6) and an elevated leptin level (20, 21) have been demonstrated in hypothalamic obesity, which elucidates the high prevalence of insulin resistance in our series. As mentioned above, insulin hypersecretion resulting from hypothalamic damage was thought to be the main cause of hypothalamic obesity (16). However, it has not been clarified whether insulin hypersecretion precedes and causes visceral fat accumulation or whether hypothalamic damage directly increases the visceral fat mass. In any case, insulin secretion must be enhanced to compensate for insulin resistance, which would further increases the visceral fat accumulation. Therefore, once this cycle is established, progressive deterioration in metabolism may be inevitable. The effectiveness of somatostatin-analogue, which inhibits insulin secretion, has been reported in the reduction of body weight in hypothalamic obesity children (16). Considering the prevalence of insulin resistance, this agent seems promising in our series, especially those with high IRI levels.

Hyperlipemia, either hypercholesterolemia or hypertriglyceridemia, was found in 9 patients out of 21 tested. In particular, inordinately elevated postprandial TG was found in 3 patients. The contribution of a genetic factor may be minimal in them, because preoperative examinations showed normal TG levels, and neither of their parents had elevated TG levels. Hyperlipemia in hypothalamic obesity has not been evaluated intensively. Srinivasan *et al.* reported that 6 craniopharyngioma patients had higher TG levels than the control obese group (6). In their report, one patient showed a TG level exceeding 500 mg/dL. Our finding underlines the importance of evaluating the lipid metabolism in hypothalamic obesity, in particular a high TG level. The pathogenesis of TG elevation is unclear. GH deficiency must be responsible, because untreated children, adolescents and adults with GH deficiency have been found to have elevated TG levels (22). However, GH

deficiency alone seems insufficient to elucidate the extremely elevated postprandial TG values. Effort should be focused on delineating TG metabolism in hypothalamic obesity, unraveling the mechanism and establishing a pertinent treatment. In our series, hyperlipemia was frequently found in germinoma patients, while the incidence of insulin resistance was high in optic nerve glioma. We could not explain this difference, and it may be due to the small sample size.

Another notable issue we found was that patients with growth without GH tended to have profound metabolic alteration. This condition has been encountered mainly in children following surgery for suprasellar tumors (23, 24). In addition, insulin hypersecretion has been considered to be a major cause of growth without GH (24). Thus, both hypothalamic obesity and growth without GH arise following the hypothalamic damage, and both conditions are closely related to insulin metabolism. We showed that the patients with growth without GH had increased incidences of obesity (67%), hyperlipemia (83%) and insulin resistance (50%), compared to the whole study group, and patients presenting with growth without GH may be regarded as at particularly increased risk for metabolic aberration. It has been demonstrated that hyperinsulinemia is not always present in growth without GH patients (6), which was also true in our series. This finding indicates that some additional factor(s) other than insulin hypersecretion must be involved in the development of growth without GH. This unknown factor(s) may provide the reason for the high prevalence of metabolic aberration in growth without GH.

Conclusion

Half of the patients with suprasellar tumors manifested obesity after the completion of therapy, irrespective of its pathohistology and GH treatment. A high incidence of insulin resistance and/or hyperlipemia, including inordinately elevated postprandial TG, was also found. In growth without GH cases, an increased incidence of metabolic aberration was suggested.

References

1. Rosemberg S, Fujiwara D. Epidemiology of pediatric tumors of the nervous system according to the WHO 2000 classification: a report of 1,195 cases from a single institution. Childs Nerv Syst 2005;21:940–4.
2. Wilne SH, Ferris RC, Nathwani A, Kennedy CR. The presenting features of brain tumours: a review of 200 cases. Arch Dis Child 2006;91:502–6.
3. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R. Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. J Clin Endocrinol Metab 1996;81:2734–7.
4. Muller HL, Gebhardt U, Faldum A, Emser A, Etavard-Gorris N, Kolb R, *et al.* Functional capacity and body mass index in patients with sellar masses—cross-sectional study on 403 patients diagnosed during childhood and adolescence. Childs Nerv Syst 2005;21:539–45.
5. Daousi C, Dunn AJ, Foy PM, MacFarlane IA, Pinkney JH. Endocrine and neuroanatomic features associated with weight gain and obesity in adult patients with hypothalamic damage. Am J Med 2005;118:45–50.
6. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 2004;89:81–6.
7. Ito Y, Kato N, Tachibana K, Fujieda K. The Journal of Pediatric Practice (Tokyo) 2005;68:1343–51 (In Japanese).
8. 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.

9. Asayama K, Ozeki T, Sugihara S, Ito K, Okada T, Tamai H, *et al.* Criteria for medical intervention in obese children: a new definition of 'obesity disease' in Japanese children. Pediatr Int 2003;45:642–6.
10. Okada T, Murata M, Yamauchi K, Harada K. New criteria of normal serum lipid levels in Japanese children: the nationwide study. Pediatr Int 2002;44:596–601.
11. Japan Diabetes Society. Guideline for diabetes treatment 2006–2007. Tokyo: Bunkodo; 2006. p.10 (In Japanese).
12. Sklar CA. Craniopharyngioma: endocrine sequelae of treatment. Pediatr Neurosurg 1994;21 Suppl 1:120–3.
13. Blundell JE. Appetite disturbance and the problems of overweight. Drugs 1990;39 Suppl 3:1–19.
14. Harz KJ, Muller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. J Clin Endocrinol Metab 2003;88:5227–31.
15. Jeanrenaud B. An hypothesis on the aetiology of obesity: dysfunction of the central nervous system as a primary cause. Diabetologia 1985;28:502–13.
16. Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, *et al.* Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2003;88:2586–92.
17. Tiosano D, Eisentein I, Militianu D, Chrousos GP, Hochberg Z. 11 beta-Hydroxysteroid dehydrogenase activity in hypothalamic obesity. J Clin Endocrinol Metab 2003;88:379–84.
18. Lustig RH, Post SR, Srivannaboon K, Rose SR, Danish RK, Burghen GA, *et al.* Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 2003;88:611–6.
19. Geffner M, Lundberg M, Koltowska-Haggstrom M, Abs R, Verhelst J, Erfurth EM, *et al.* Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab 2004;89:5435–40.
20. Daousi C, MacFarlane IA, English PJ, Wilding JP, Patterson M, Dovey TM, *et al.* Is there a role for ghrelin and peptide-YY in the pathogenesis of obesity in adults with acquired structural hypothalamic damage? J Clin Endocrinol Metab 2005;90:5025–30.
21. Kanumakala S, Greaves R, Pedreira CC, Donath S, Warne GL, Zacharin MR, *et al.* Fasting ghrelin levels are not elevated in children with hypothalamic obesity. J Clin Endocrinol Metab 2005;90:2691–5.
22. Lanes R, Paoli M, Carrillo E, Villaroel O, Palacios A. Cardiovascular risk of young growth-hormone-deficient adolescents. Differences in growth-hormone-treated and untreated patients. Horm Res 2003;60:291–6.
23. Phillip M, Moran O, Lazar L. Growth without growth hormone. J Pediatr Endocrinol Metab 2002;15 Suppl 5:1267–72.
24. Geffner ME. The growth without growth hormone syndrome. Endocrinol Metab Clin North Am 1996;25:649–63.