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RESEARCH LETTER

Hyperinsulinemia may promote growth without GH in children after resection of suprasellar brain tumors

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Abstract It remains elusive what factors induce growth without growth hormone (GWGH) in children after neurosurgery of brain tumors. Growth velocity and endocrinological data were compared between the patients with and without GWGH. We experienced three patients with GWGH (median, 12 years; 2 germinoma and 1 craniopharyngioma; three females; group 1) and 11 patients without (12 years; 8 craniopharyngioma, 2 germinoma and 1 medulloblastoma; 7 males; group 2) after neurosurgery. All patients in group 2 received GH replacement therapy. Growth velocity and endocrinological data were compared. Median height velocity was normal in group 1 (5.5 cm/year), but low in group 2 (2.2 cm/year), which improved after GH replacement therapy (7.0 cm/year). Median serum insulin level was increased in group 1 (87.0 μU/ml, $P < 0.05$) compared with normal level in group 2 (10.0 μU/ml). Despite hyperinsulinemia, serum glucose level was normal in group 1. Three of 5 with hyperinsulinemia and 2 of 9 without were obese or overweight, but the difference was not significant. Current body mass index and serum levels of IGF-1, IGFBP-3, leptin, and prolactin were similar between groups. Serum estradiol was prepuberty level in group 1. Hyperinsulinemia may induce GWGH in children with brain tumors after neurosurgery.

Keywords Growth hormone deficiency · Growth velocity · Insulin · Insulin like growth factors · Neurosurgery

Introduction

Although growth hormone (GH) deficiency induces short stature, some patients after neurosurgery of brain tumors, including craniopharyngioma [1–6] or teratoma [7], show normal height velocity despite GH deficiency. This has been recognized as "growth without GH (GWGH)" [8]. However, its cause remains elusive. High serum levels of insulin, leptin, or prolactin were found in patients with GWGH after neurosurgery [1–3]. However, there is only one study in which hormonal factors were compared between patients with and without GWGH after neurosurgery of craniopharyngioma [1]. In addition, little is known about what factors affect GWGH in children with neurosurgery of germinoma. We determined what factors influence GWGH after neurosurgery of brain tumors, including germinoma.

Materials and methods

Between 1999 and 2010, we experienced three children with GWGH (group 1) and 11 without after neurosurgery (group 2). Patients in group 2 received GH therapy 1 year after neurosurgery.

Height velocity and body mass index (BMI) were measured. When patients reached adult height, height was measured until the height velocity was <1 cm/year. Data are expressed as the standard deviation (SD), based on the

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Japanese growth survey [9]. GWGH was defined as the height velocity of >5 cm/year despite GH deficiency, and obesity and overweight as the BMI of >30 or >25.

Hormonal measurements were performed more than two years after the neurosurgery to eliminate the influence of neurosurgery by itself on insulin secretion [2]. Blood samples were taken 3 h or more after breakfast. Serum glucose was measured by the standard laboratory method. GH, IGF-1, IGFBP-3, leptin, and cortisol were measured by radioimmunoassay, insulin, ACTH, prolactin, LH, and FSH using chemiluminescent enzyme immunoassay, and TSH, free T3, free T4, estradiol, and testosterone by electrochemiluminescence immunoassay. Informed consent was obtained from all parents of each patient.

Statistical analysis

Data are expressed as median (range). Comparisons of the data between the groups were made using the Mann–Whitney *U*-test and Fisher's exact test. A P value less than 0.05 was considered significant.

Results

Table 1 shows demographic and clinical characteristic data. Median follow-up period was 6.8 years. The height velocity was normal in group 1 (median, 5.5 cm/year). The growth rate at first and last post-operative years was 5.9 and 3.6 cm/year in case 1, 10.4 and 4.2 cm/year in case 2, and 4.6 and 6.2 cm/year in case 3, respectively. Case 1 reached the expected final height although she has still being growing. The height velocity was lower in group 2 before GH therapy (median, 2.2 cm/year, $P < 0.05$) than that in group 1, which improved with GH therapy (median, 7.0 cm/year). Cases 9 and 12 had the normal growth rate during 2–3 years postoperatively, but their growth rate decelerated thereafter, requiring GH therapy. Two patients in group 1 were obese or overweight. One and 2 patients in group 2 were obese and overweight, respectively.

Serum insulin level was increased in group 1, but normal in group 2 (Table 1). Despite hyperinsulinemia, serum glucose level was normal in group 1. Three (60%) of 5 patients with hyperinsulinemia (3 in group 1 and 2 in group 2) and 2 (22%) of 9 patients without showed obesity or overweight. However, the difference was not significant.

Serum IGF-1 level was decreased in all of group 1 and 7 of 9 patients in group 2. Serum IGFBP-3 level was decreased in all of group 1 and 2 of 5 patients studied in group 2. However, there was no difference between the groups in serum levels of IGF-1 and IGFBP-3. No difference was found between the groups in serum levels of leptin and prolactin. When data for serum leptin level were compared between the patients with obesity or overweight (median, 16.0 ng/ml, range 2.1–63.0 ng/ml) and those without (median, 9.95 ng/ml, range 2.4–22.3 ng/ml), there was no difference between the groups. Serum estradiol was prepuberty level in all patients except two patients in group 2. Serum testosterone was puberty level in three patients of group 2.

Serum levels of TSH, free T3, free T4, and cortisol were normal in all patients (data not shown). There was no difference between the groups in serum levels of ACTH (median, 0 pg/ml in group 1, versus 1.85 pg/ml in group 2; normal value; 5.7-33.3 pg/ml), LH (median, 0.07 mIU/ml in group 1, versus 0.05 mIU/ml in group 2; normal value; male: 0.506–2.455 mIU/ml, female: 0.159–44.42 mIU/ml), and FSH (median, 0.06 mIU/ml in group 1, versus 0.20 mIU/ml in group 2; normal value; male: 1.226–10.49 mIU/ml, female: 1.153–11.70 mIU/ml).

Discussion

Our study shows that hyperinsulinemia is highly associated with patients with GWGH compared with those without, suggesting that hyperinsulinemia may promote GWGH after neurosurgery of germinoma or craniopharyngioma. In support of our finding, hyperinsulinemina was found in GWGH patients after neurosurgery of craniopharyngioma [1–3, 5] and teratoma [7]. Craniopharyngioma itself and neurosurgery resulted in the increase of insulin secretion in patients with GWGH [2]. Although most of our patients with craniopharyngioma had no hyperinsulinemia, some patients with normal growth rate for few years postoperatively had normal or slightly increased serum insulin level. These data further support that hyperinsulinemia promote growth rate. The growth rate gradually decelerated in two patients with GWGH as previously described [1, 3]. Because of their prepuberty, further follow-up is necessary to determine whether they reach the expected final height.

The mechanism by which insulin stimulates height velocity remains elusive. Because insulin receptors have high homology with IGF-1 receptors, insulin can bind to IGF-1 receptors although the affinity is less [8], resulting in accelerated bone growth [10]. Thus, insulin may enhance bone growth through its binding to receptors of both insulin and IGF-1 in patients with GWGH. IGF-1 and IGFBP-3 can promote bone growth [8, 10]. Production of IGF-1 is stimulated by GH, and serum IGFBP-3 level is regulated by IGF-I and GH [10]. A decrease in serum levels of IGF-1 and IGFBP-3 in both our patients with GWGH and those without may be attributed to GH deficiency. However, we found no difference between the groups in serum levels of IGF-1 and IGFBP-3. Taken together, our data suggest that GWGH may be dependent on insulin, whereas GH, IGF-1,

Table 1 Clinical characteristics, growth velocity, and endocrinological data in patients with or without growth without GH after neurosurgery

Case/sex	Age (yrs)	Brain tumor	Height	Height velocity before/after GH therapy		BMI	GH*	Insulin	IGF-1	IGFBP-3	Leptin	Prolactin	Estradiol	Testosterone
			cm (SD)	cm/yr (SD)	cm/yr (SD)	(kg/m^2)	(ng/ml) (>6)	(mU/ml) (<18.7)	(ng/ml) (178–731)	(μg/ml) (2.7–5.2)	(ng/ml) (1.3–14.3)	(ng/ml) (1.2–30)	(pg/ml) (<10)	(ng/dl) (25–899)
Growth without GH														
1 (F)	14	Gm	158.4 (0.4)	5.1 (0.1)	ND	30.8	0	87.0	45.4	1.3	31.8	0.8	<10	ND
2 (F)	12	Gm	142.8 (−0.6)	6.1 (0.1)	ND	25.2	0	262.0	36.0	1.6	13.4	13.6	<10	ND
3 (F)	9	CP	126.4 (−0.8)	5.5 (0.4)	ND	23.9	0.02	65.0	138.0	2.2	10.7	28.0	<10	ND
Median	12		(−0.6)	5.5 (0.1)**		25.2	0	87.0**	45.4	1.6	13.4	13.6	<10	
Non growth without GH														
4 (M)	15	Gm	148.5 (−3.1)	2.3 (−5.1)	4.0 (−0.7)	32.4	0.1	5.8	79.5	2.6	63.0	12.6	ND	21.5
5 (F)	8	CP	122.0 (−0.7)	3.8 (−4.4)	7.0 (1.3)	18.7	0	10.9	326.9	2.6	10.4	0	ND	ND
6 (M)	8	CP	112.2 (−2.2)	0.2 (−6.9)	10.1 (16.4)	14.5	0	10.0	110.0	ND	2.4	0	ND	13.0
7 (M)	3	CP	73.8 (−6.1)	−0.3 (−11.3)	11.4 (4.0)	16.2	0	2.0	39.1	ND	2.4	0	ND	ND
8 (F)	11	Med	134.0 (−2.2)	2.0 (−6.1)	ND	16.6	0.66	4.0	51.7	ND	15.3	17.8	<10	ND
9 (M)	14	CP	161.8 (−0.7)	3.8 (−2.5)	6.8 (1.4)	23.1	2.0	31.0	221.9	ND	9.5	8.6	ND	549.3
10 (F)	11	CP	136.8 (−1.2)	3.7 (−3.7)	7.4 (2.3)	25.6	0	63.0	437.8	4.6	16.0	4.6	16.4	ND
11 (M)	21	Gm	166.2 (−0.8)	1.8 (−5.1)	5.0 (10.7)	24.0	0	10.0	87.8	ND	5.1	15.3	ND	602.4
12 (F)	12	CP	145.4 (−1.8)	3.2 (−2.8)	8.0 (1.6)	24.6	0.18	17.7	605.5	3.2	22.3	11.8	7.5	ND
13 (M)	23	CP	166.4 (−0.8)	1.2 (−5.1)	3.1 (3.1)	20.8	0	ND	56.8	ND	ND	ND	ND	11.0
14 (M)	22	CP	181.3 (1.8)	−1.2 (−8.3)	6.2 (2.9)	26.2	0	7.8	41.3	ND	2.1	5.3	ND	517.1
Median	12		(−1.5)	2.2 (−5.1)	7.0 (2.3)	21.9	0	10.0	87.8	2.9	10.0	7.0	12.0	269.3

CP craniopharyngioma, *GH* growth hormone, *Gm* germinoma, *IGF-1* insulin-like growth factor-1, *IGFBP-3* insulin-like growth factor binding protein-3, *Med* medulloblastoma, *ND* not done

Normal values are in parenthesis

* Data were obtained after stimulating test with L-alginine

** $P < 0.05$, versus patients without growth without GH

and IGFBP-3 by themselves may play a minor role for GWGH.

Prolactin and leptin regulate growth and bone formation, and estradiol induces growth spurt of puberty [8]. However, there was no difference in serum levels of these factors between our patients with GWGH and those without, suggesting that prolactin, leptin, or estradiol may play a minor role for GWGH.

Increased serum levels of insulin and leptin were highly associated with obesity in patients with germinoma after neurosurgery [1, 2]. However, we found no difference in the frequency of hyperinsulinemia between our patients with obese or overweight and those without. High serum leptin level was found in only one of our obese patient with GWGH. These data may suggest a minor role of insulin and leptin for the development of obesity in patients with GWGH.

In summary, our study shows that hyperinsulinemia rather than other hormonal factors may promote GWGH in children with neurosurgery.

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References

1. H. Bucher, J. Zapf, T. Torresani, A. Prader, E.R. Froesch, R. Illig, Insulin-like growth factors I, II, prolactin, and insulin in 19 growth hormone-deficient children with excessive, normal, or decreased longitudinal growth after operation for craniopharyngioma. N. Engl. J. Med. **309**, 1142–1146 (1983)
2. G. Pinto, L. Bussieres, C. Recasens, J.C. Souberbielle, M. Zerah, R. Brauner, Hormonal factors influencing weight and growth pattern in craniopharyngioma. Horm. Res. **53**, 163–169 (2000)
3. M. Pavlou, A. Tsatsoulis, Z. Efstathiadou, S. Bitsis, Z.L. Papadopoulou, A study of the growth-promoting and metabolic effects of growth hormone (GH) in a patient with the "growth without GH" syndrome. Growth Horm. Igf Res. **11**, 225–230 (2001)
4. S. Srinivasan, M.J. Waters, J.E. Rowland, R.C. Baxter, C.F. Verge, Hyperinsulinism andovergrowth without obesity. Arch. Dis. Child. **88**, 332–334 (2003)
5. S. Srinivasan, G.D. Ogle, S.P. Garnett, J.N. Briody, J.W. Lee, C.T. Cowell, Features of the metabolic syndrome after childhood craniopharyngioma. J. Clin. Endocrinol. Metab. **89**, 81–86 (2004)
6. E. Di Battista, A. Naselli, S. Queirolo, F. Gallarotti, M.L. Garre, C. Milanaccio et al., Endocrine and growth features in childhood craniopharyngioma: a mono-institutional study. J. Pediatr. Endocrinol. Metab. **19**(Suppl 1), 431–437 (2006)
7. K. Araki, M. Koga, T. Okada, T. Kurashige, K. Naruse, M. Hiroi, A boy with normal growth in spite of growth hormone deficiency after resection of a suprasellar teratoma. Endocr. J. **47**(Suppl), S101–S104 (2000)
8. M.E. Geffner, The growth without growth hormone syndrome. Endocrinol. Metab. Clin. North Am. **25**, 649–663 (1996)
9. N. Kato, K. Sato, H. Takimoto, N. Sudo, BMI for age references for Japanese children—based on the 2000 growth survey. Asia Pac. J. Public Health **20**(Suppl), 118–127 (2008)
10. A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulin-like growth factors, and the skeleton. Endocr. Rev. **29**, 535–559 (2008)