0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(11):5435–5440

doi: 10.1210/jc.2004-0667

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)

MITCHELL GEFFNER, MICHAEL LUNDBERG, MARIA KOLTOWSKA-HÄGGSTRÖM, ROGER ABS, JOHAN VERHELST, EVA MARIE ERFURTH, PAT KENDALL-TAYLOR, DAVID ANTHONY PRICE, PETER JONSSON, AND BERT BAKKER

The Saban Research Institute of Childrens Hospital Los Angeles (M.G.), University of Southern California Keck School of Medicine, Los Angeles, California 90027; KIGS/KIMS Outcomes Research (M.L., M.K.-H., P.J.), Pfizer Endocrine Care, Stockholm, Sweden; University Hospital (R.A.), Antwerp, Belgium; Algemeen Ziekenhuis Middelheim (J.V.), Antwerp, Belgium; University Hospital (E.M.E.), Lund, Sweden; University of Newcastle (P.K.-T.), Newcastle upon Tyne, United Kingdom; Royal Manchester Children's Hospital (D.A.P.), Manchester, United Kingdom; and Pfizer Global Pharmaceuticals (B.B.), Worldwide Medical, Pfizer Endocrine Care, New York, New York 10017-5755

Extreme degrees of obesity may occur in association with hypothalamic tumors, usually after surgical intervention. This phenomenon has been reported to occur in as many as 25–75% of children undergoing extensive surgical extirpation of craniopharyngiomas (Cranio). Because less is known about the auxology of children with Cranio with milder alterations in growth, we undertook a 3-yr longitudinal analysis, using the KIGS database (Pfizer International Growth Database), to study their growth patterns and evolution of weight. We compared the effect of GH therapy on height, weight, and body mass index (BMI) in 199 prepubertal children with diagnosed Cranio treated by surgery and/or radiotherapy to two other groups of children with other causes of organic GH deficiency (OGHD): one with postsurgical and/or postirradiated OGHD (OGHD + S/I; n = 92) and the other with OGHD not due to Cranio and not having undergone either surgery or irradiation (OGHD − S/I; n = 85). At the start of GH therapy, 1) mean chronological ($P < 0.0001$) and bone ($P = 0.0002$) ages were youngest in OGHD − S/I and oldest in OGHD + S/I; 2) the mean height SD score (SDS) was lowest in OGHD − S/I and comparably higher in the other two groups ($P < 0.0001$); 3) mean weight and BMI SDS were greatest in Cranio and least in OGHD − S/I (both $P < 0.0001$); and 4) the mean initial GH dose prescribed was highest in OGHD − S/I and comparable in the other two groups ($P < 0.0001$). After 3 yr of GH therapy, 1) mean bone age remained youngest in OGHD − S/I and oldest in OGHD + S/I ($P < 0.0001$); 2) mean height SDS was highest in Cranio and comparably lower in the other two groups ($P = 0.0159$); 3) mean weight and BMI SDS remained greatest in Cranio and least in OGHD − S/I ($P < 0.0001$ and $P = 0.0003$, respectively); and 4) the mean GH dose remained highest in the OGHD − S/I group and least in the Cranio group ($P = 0.0082$). There were statistically significant increases within each group between the start of treatment and after 3 yr of GH therapy in height and weight, but not in BMI SDS. Lastly, after 3 yr of GH treatment, children in the Cranio group continued to have disproportionately heavier weight and higher BMI (with the greatest values in those with lower stimulated peak GH concentrations) compared with members of the other two groups, with no salutary effect of GH treatment on weight SDS and a mild improvement in BMI SDS. After S/I treatment, children with Cranio are disproportionately prone to varying degrees of weight gain compared with children with other forms of OGHD. In the present cohort of prepubertal children with Cranio, GH therapy induced excellent linear growth, but failed to have an ameliorative effect on weight gain and had only a slight beneficial effect on BMI gain. Because affected children may have resultant significant long-term medical morbidity and diminished quality of life, it is critical that the mechanism of this phenomenon be determined to devise helpful preventive or therapeutic interventions. (*J Clin Endocrinol Metab* 89: 5435–5440, 2004)

HYPOTHALAMIC OBESITY USUALLY occurs in association with intracranial pathology, such as a tumor, and/or its treatments, both surgery and irradiation (S/I) (1). Excessive degrees of weight gain have been described in as many as 25–75% of children undergoing extensive surgical treatment of craniopharyngiomas (Cranio) (1, 2). Some of these children may have normal or even accelerated linear growth despite quite reduced serum levels of GH. In these patients, GH therapy is usually withheld. The etiology of this phenomenon is unknown (3), but has been linked, depending on the study, to development of hyperinsulinemia (4–7), hyperprolactinemia (4), and hyperleptinemia (8, 9); unknown growth-promoting activity (10–13); and extent of associated hypothalamic damage (2, 14–16).

Fewer data exist about the auxology of children with Cranio who do not have the syndrome of growth without GH treatment. Previous studies have been hampered by small sample sizes, short duration, or inadequate control groups (17–19). One recent study suggested that the mean body mass index [BMI; corrected for parental BMI SD score (SDS)] of

Abbreviations: BMI, Body mass index; Cranio, craniopharyngioma; DI, diabetes insipidus; OGHD, organic GH deficiency; SDS, SD score; S/I, surgery and/or irradiation.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

children with GH-treated Cranio remains normal if those affected with hypothalamic obesity were excluded (20). To obtain more data, we performed a 3-yr longitudinal analysis of the changes in height, weight, and BMI SDS of prepubertal children with postsurgical and/or postirradiated (S/I) Cranio using the large KIGS database (Pfizer International Growth Database). We compared the results to those of two other groups of GH-treated children with organic GH deficiency (OGHD): those with postsurgical and/or postirradiated organic GH deficiency not due to Cranio (OGHD + S/I) and those with OGHD not due to Cranio and not having undergone either S/I (OGHD − S/I).

Subjects and Methods

Patients

The KIGS database is an international registry developed with the main objective of documenting the long-term outcomes and safety of Somatonorm and Genotropin GH products (Pfizer, Inc., New York, NY). The KIGS survey is performed in accordance with the recommendations adopted by the 18th World Medical Assembly (held in Helsinki, Finland, in 1964) and any subsequent revisions, which exist to guide physicians carrying out biomedical research involving human individuals. Each subject and/or his/her legal representative receive adequate information, have the right to withdraw from the survey at any time, and consent to his/her participation. In contrast, this kind of registry or noninterventional trial that KIGS represents did not require informed consent from the subjects or legally acceptable representatives in many countries during the first decade of its existence.

Sixty-seven percent of subjects for this analysis were recruited from Japan, France, the United Kingdom, and Germany. The first goal of KIGS was to enroll 500 patients to be followed over a period initially set at 5 yr. Between its inception in 1987 and the time of the data cutoff for this analysis in January 2003, a total of 44,613 subjects treated with GH had been entered, of whom 29,176 have idiopathic GH deficiency and 6,267 have OGHD. The subjects with OGHD were drawn from the following subgroups: tumors of the hypothalamic-pituitary area (25.67% of total), central malformations (22.88%), cranial tumors distant from the hypothalamic-pituitary area (22.87%), treatment for extracranial tumors (12.72%), other causes of acquired GH deficiency (8.17%), and other (7.69%). As a basic entry criterion for the current study, subjects had to have longitudinal data entry in KIGS for 3 yr since initiation of GH treatment and to be prepubertal for the full observation period.

The Cranio group included 199 children who had at least one surgery or one course of cranial irradiation. More specifically, 136 of the 199 underwent only surgery, eight only irradiation, and 55 both surgery and irradiation. Three subjects also received chemotherapy. The OGHD + S/I group consisted of 92 children, including 28 with germinoma, 10 with other tumor of the hypothalamic-pituitary area, eight with astrocytoma, eight with glioma, eight with some other cranial tumors distant from the hypothalamic-pituitary area, and 30 with other OGHD. Of these, 22 underwent only surgery, 32 only irradiation, and 38 both surgery and irradiation. Thirty-nine subjects also received chemotherapy. Subjects with medulloblastoma were intentionally excluded from this group because of associated exposure to spinal irradiation. The OGHD − S/I group included 85 children, of whom 15 had septo-optic dysplasia, 14 empty sella syndrome, 11 histocytosis, 10 other central malformations, six cleft palate, and 29 other OGHD. By definition, no subject in the last group had undergone surgery or received central nervous system irradiation, although nine had received chemotherapy.

Parameters

From the KIGS database, the following background characteristics were determined for each subject: sex, birth weight SDS, birth length SDS, peak GH concentration [the highest stimulated value in nanograms per milliliter (micrograms per liter) on provocative testing], and height velocity SDS before beginning GH treatment. In addition, the following data were gathered both at the start and after 3 yr of GH treatment: chronological age, bone age, height SDS, weight SDS, BMI SDS, and GH dose (milligrams per kilogram per week). In addition, after 3 yr of GH treatment, the changes in bone age (years), height (SDS), weight (SDS), and BMI (SDS) were calculated. Height, weight, and BMI SDS were also examined after subdividing each group into peak GH response after provocation [<2 and 2–10 ng/ml (micrograms per liter)], as a means of stratification for severity of hypothalamic-pituitary damage. Lastly, height, weight, and BMI SDS were analyzed after using only those OGHD + S/I subjects with tumors restricted to the hypothalamic-pituitary region, to provide a better-matched cohort to the Cranio group.

Statistics

Standard demographic data are presented as the mean ± SD. Differences in background characteristics and in various clinical and anthropometric measurements among the three groups at the start of GH treatment and after 3 yr were determined by ANOVA. Differences in the prevalence of diabetes insipidus (DI) (as an indicator of hypothalamic damage) between groups were determined by χ^2 analysis. Changes in mean height, weight, and BMI SDS by group between the start of treatment and after 3 yr of GH therapy were compared by t test. The percentages of subjects in each of the three groups with height SDS less than −2, −2 to 0, and more than 0, and weight and BMI SDS less than −2, −2 to less than 0, 0–2, and more than 2 were calculated. Differences in the distribution of mean height, weight, and BMI SDS between the Cranio group and each of the other two groups at the start and after 3 yr of GH treatment were determined by χ^2 analysis. Statistical significance is defined as $P < 0.05$.

Results

Baseline data

Background characteristics of the study subjects are shown in Table 1. Boys predominated in all three groups, and there were no differences in birth measurements between groups. By ANOVA, a statistically significant difference between groups in baseline data was present for peak stimulated GH, with Cranio lower than the two control groups, which had similar values. The mean pretreatment height velocity SDS was poor in all three groups, with no differences among them. At study entry, the prevalence of DI differed significantly ($P < 0.0001$) among groups (Cranio, 71.9%; OGHD + S/I, 61.1%; OGHD − S/I, 27.7%).

Pre-GH treatment data

Clinical data at the start of GH therapy are shown in Table 1. At the start of GH therapy, statistically significant differences among groups were noted in all parameters analyzed, including chronological and bone ages (lowest in OGHD − S/I and highest in OGHD + S/I), height SDS (lowest in OGHD − S/I and equal in the tumor groups), weight and BMI SDS (highest in Cranio and lowest in OGHD − S/I), and initial GH dose (highest in OGHD − S/I and equal in the tumor groups; Table 1). There was no significant difference in chronological age minus bone age among groups.

Bar graphs (Fig. 1) show the distributions in the three subject groups of height, weight, and BMI SDS at the start of GH therapy. There was no difference in height SDS distribution between the two tumor groups, but there were statistically significantly more short patients in the OGHD − S/I group than in the Cranio group ($P < 0.0001$). There was an increased frequency of higher weight SDS and BMI SDS values in Cranio patients, lower values in OGHD − S/I patients, and intermediate values in OGHD + S/I patients at the start of GH therapy. ANOVA for both weight SDS and

TABLE 1. Group background and clinical data

Variable	Cranio			OGHD + S/I			OGHD − S/I			*P* value
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Background characteristics										
Total (% boys)	199 (62.3)			92 (64.1)			85 (71.8)			
Birth wt SDS	178	−0.29	0.96	84	−0.36	1.07	77	−0.32	1.09	0.8571
Birth length SDS	123	0.02	1.13	53	−0.35	1.95	57	−0.39	1.18	0.0951
GH peak (μg/liter)	174	2.05	2.06	82	4.31	5.46	81	4.44	6.60	<0.0001
Ht velocity (SDS)	93	−2.67	2.43	55	−3.15	2.27	36	−2.70	1.73	0.4263
Start of GH Rx										
CA (yr)	199	7.76	3.35	92	8.92	3.20	85	5.71	3.84	<0.0001
BA (yr)	94	5.87	2.89	34	7.02	3.19	31	4.01	2.61	0.0002
Ht (SDS)	199	−1.77	1.28	92	−1.84	1.31	84	−2.80	1.39	<0.0001
Wt (SDS)	199	−0.32	1.75	92	−0.89	1.77	85	−2.33	1.98	<0.0001
BMI SDS	199	1.26	1.51	92	0.61	1.46	85	−0.12	1.84	<0.0001
Dose (mg/kg·wk)	199	0.17	0.06	92	0.17	0.05	85	0.21	0.10	<0.0001
3 Yr on GH Rx										
BA (yr)	77	9.05	2.58	34	10.26	2.56	34	6.99	3.30	<0.0001
Ht (SDS)	199	−0.54	1.51	92	−0.98	1.59	85	−1.04	1.66	0.0159
Wt (SDS)	199	0.34	1.74	92	−0.42	2.00	85	−0.60	1.97	<0.0001
BMI SDS	199	1.01	1.55	92	0.35	1.71	85	0.29	1.69	0.0003
Dose (mg/kg·wk)	199	0.16	0.07	92	0.17	0.06	85	0.18	0.07	0.0082
ΔBMI (SDS)	199	−0.26	1.00	92	−0.26	1.13	85	0.41	1.39	<0.0001
ΔHt (SDS)	199	1.23	0.94	92	0.86	0.91	84	1.74	1.50	<0.0001
ΔWt (SDS)	199	0.66	1.10	92	0.47	1.15	85	1.73	1.57	<0.0001

CA, Chronological age; BA, bone age; Ht, height; Wt, weight; Δ, change.

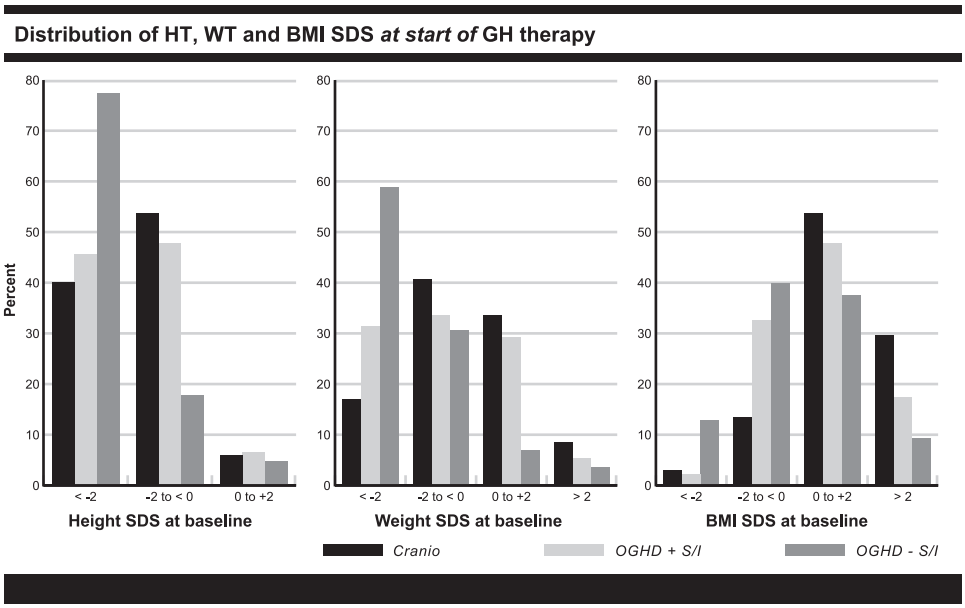

FIG. 1. Bar graphs show distributions in groups of height (*left*), weight (*middle*), and BMI (*right*) SDS at the start of GH therapy.

BMI SDS at the start of GH therapy showed highly statistically significant differences among the three groups (all $P < 0.0001$).

3-Yr GH treatment data

Clinical data after 3 yr of GH therapy are shown in Table 1. Statistically significant differences between groups were noted in the following key parameters: bone age (lowest in OGHD − S/I and highest in OGHD + S/I), height SDS (highest in Cranio and equal in the other two groups), weight and BMI SDS (highest in Cranio and lowest in OGHD − S/I), and GH dose (highest in OGHD − S/I and lowest in Cranio).

After 3 yr of GH treatment, OGHD − S/I had the best catch-up in height SDS (+1.74) compared with Cranio (+1.23) and OGHD + S/I (+0.86). The catch-up in weight SDS followed a similar relationship: OGHD − S/I, +1.73; Cranio, +0.66; and OGHD + S/I, +0.47. Regarding catch-up in BMI SDS, OGHD − S/I (+0.41) showed a mild increase, whereas Cranio (−0.26) and OGHD + S/I (−0.25) showed a comparable mild decrease. All changes between baseline and 3 yr for each parameter were statistically significant ($P < 0.0001$) among the three groups (Table 1). *Post hoc* analysis of the height SDS changes showed significant differences between all combinations of the three groups, whereas for changes in weight and BMI SDS, the observed differences were between Cranio and OGHD − S/I and between OGHD + S/I and OGHD − S/I groups.

Figure 2 shows the distributions in the three subject groups

of height, weight, and BMI SDS after 3 yr of GH therapy. There was no difference in height SDS between Cranio and either of the other two groups. There was an increased frequency of higher weight SDS and BMI SDS values in Cranio, lower values in OGHD − S/I, and intermediate values in OGHD + S/I after 3 yr of GH therapy. ANOVA for both weight SDS and BMI SDS after 3 yr of treatment showed highly statistically significant differences among the three groups (all $P < 0.0001$). There was no alteration in these distributions over the 3-yr period of GH therapy.

As shown in Table 2, Cranio and OGHD + S/I subjects with peak GH less than 2 μg/liter had higher weight SDS and

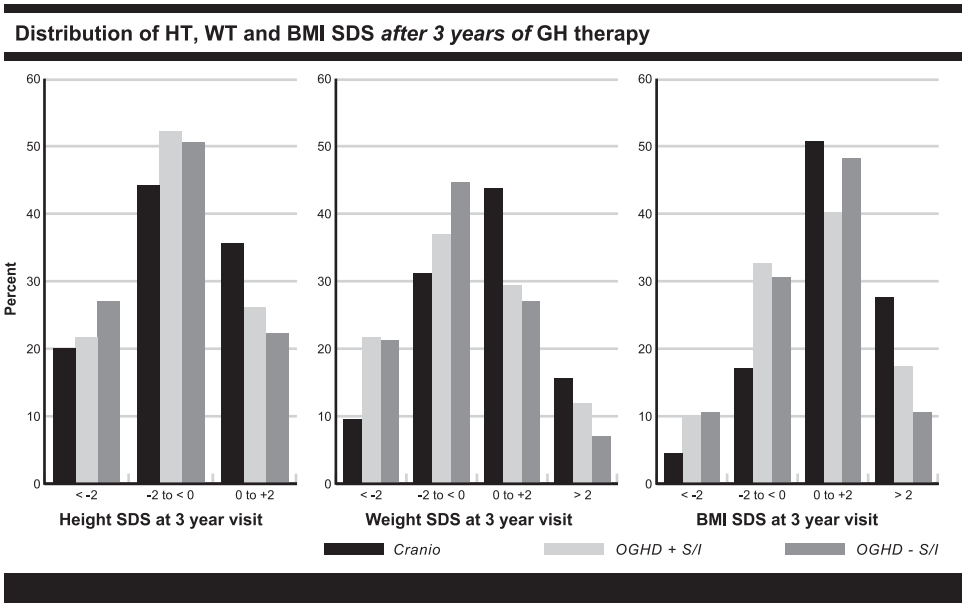

FIG. 2. Bar graphs show distributions in groups of height (*left*), weight (*middle*), and BMI (*right*) SDS after 3 yr of GH therapy.

TABLE 2. Auxology by peak GH response

Variable	Cranio: peak GH <2 μg/liter			Cranio: peak GH 2–10 μg/liter			STATS
	n	Mean	SD	n	Mean	SD	(*P* value)
Start of GH Rx							
Ht (SDS)	107	−1.90	1.29	62	−1.69	1.22	0.2841
Wt (SDS)	107	−0.29	1.84	62	−0.57	1.38	0.2897
BMI SDS	107	1.40	1.58	62	0.94	1.27	0.0519
3 yr on GH							
Ht (SDS)	107	−0.56	1.58	62	−0.72	1.37	0.5051
Wt (SDS)	107	0.39	1.95	62	−0.07	1.32	0.1069
BMI SDS	107	1.10	1.70	62	0.64	1.22	0.0645
	OGHD + S/I: Peak GH <2 μg/L			OGHD + S/I: Peak GH 2–10 μg/L			
	n	Mean	SD	n	Mean	SD	
Start of GH Rx							
Ht (SDS)	34	−1.75	1.59	42	−1.75	1.09	0.9867
Wt (SDS)	34	−0.33	1.83	42	−1.03	1.55	0.0765
BMI SDS	34	1.17	1.34	42	0.34	1.35	0.0092
3 yr on GH							
Ht (SDS)	34	−0.93	1.89	42	−0.97	1.39	0.9187
Wt (SDS)	34	0.04	2.03	42	−0.70	1.90	0.1034
BMI SDS	34	0.88	1.70	42	−0.01	1.64	0.0222
	OGHD − S/I: Peak GH <2 μg/liter			OGHD − S/I: Peak GH 2–10 μg/liter			
	n	Mean	SD	n	Mean	SD	
Start of GH Rx							
Ht (SDS)	32	−2.95	1.23	38	−2.67	1.58	0.4146
Wt (SDS)	32	−2.67	1.10	39	−2.14	2.05	0.2427
BMI SDS	32	−0.43	1.70	39	−0.06	1.92	0.3928
3 yr on GH							
Ht (SDS)	32	−1.30	1.49	39	−0.83	1.83	0.2522
Wt (SDS)	32	−1.08	1.59	39	−0.49	2.10	0.2011
BMI SDS	32	−0.20	1.48	39	0.35	1.71	0.1513

Ht, Height; Wt, weight.

BMI SDS both at the start and after 3 yr of GH treatment compared with their counterparts with peak GH levels of 2–10 ng/ml (μg/liter); however, this difference only achieved statistical significance for BMI at both time points in OGHD + S/I, with a trend toward significance for BMI at both time points in Cranio patients. Furthermore, in subjects with peak GH less than 2 ng/ml (μg/liter), statistically significant differences in height (lowest in OGHD − S/I and highest in OGHD + S/I), weight (highest in Cranio and lowest in OGHD − S/I), and BMI (highest in Cranio and lowest in OGHD − S/I) SDS ($P = 0.0002$, $P < 0.0001$, and $P < 0.0001$, respectively) were seen at the start of GH treatment. In these same subjects, after 3 yr of GH treatment, statistically significant differences in weight and BMI (both highest in Cranio and lowest in OGHD − S/I) SDS ($P = 0.0009$ and $P = 0.0006$, respectively) persisted. In addition, in subjects with peak GH of 2–10 ng/ml (μg/liter), statistically significant differences in height (lowest in OGHD − S/I and similar in the tumor groups), weight (highest in Cranio and lowest in OGHD − S/I), and BMI (highest in Cranio and lowest in OGHD − S/I) SDS ($P = 0.0002$, $P < 0.0001$, and $P = 0.0031$, respectively) were seen at the start of GH treatment. In these same subjects, after 3 yr of GH treatment, there were no statistically significant differences in height, weight, or BMI.

Selecting only OGHD + S/I subjects with tumors restricted to the hypothalamic-pituitary region did not change the results from the original ANOVA analyses for height, weight, and BMI SDS in the comparison among the three groups (data not shown).

Discussion

The hypothesis of the current study was that the general weight pattern of children with Cranio both before and after GH treatment would show an uneven distribution, with a heightened predilection toward overweight compared with appropriate control groups. By using the large international KIGS database, it was assumed that adequate statistical power could be generated to address this question as well as to examine longitudinal changes in height, weight, and BMI SDS in prepubertal children with Cranio treated with surgery and/or irradiation compared with the changes in these parameters observed both in children with OGHD secondary to other central nervous system tumors treated with S/I and in children with OGHD unassociated with Cranio or other tumor, surgery, or irradiation.

In this study we found that children in the Cranio group had lower mean stimulated peak GH levels compared with those in the other two groups, perhaps because of greater involvement by the tumor and/or more radical surgery, as suggested by the highest rate of occurrence of DI in Cranio and the lowest rate in OGHD − S/I. Excess weight in Cranio may also be contributing to their lower GH levels. At the start of GH therapy, mean chronological and bone ages were youngest in OGHD − S/I, perhaps because of inclusion of cases of congenital GH deficiency, and oldest in OGHD + S/I. In the tumor groups, there was an approximately 2-yr delay between bone and chronological age, and in OGHD − S/I, the gap was about 1.75 yr. The mean height SDS was lowest in OGHD − S/I and comparably higher in the tumor groups, perhaps because greater suspicion for hormonal abnormalities after diagnosis and treatment of an underlying tumor leads to a relatively earlier diagnosis of GH deficiency than occurs in OGHD − S/I. At study inception, mean weight and BMI SDS were already greatest in Cranio, then in OGHD + S/I, and least in OGHD − S/I, suggesting early effects on body composition from associated hypothalamic damage in the tumor groups. In addition, the mean initial GH dose prescribed was highest in OGHD − S/I and comparably lower in the tumor groups, perhaps because of the belief that there would be more complete GH deficiency in the latter groups and that lower GH doses would still be quite effective or because the height SDS was more abnormal in OGHD − S/I.

After 3 yr of GH therapy, the mean bone age remained youngest in OGHD − S/I and oldest in OGHD + S/I. In addition, the mean GH dose remained highest in the OGHD − S/I group, followed by OGHD − S/I, and then Cranio. Furthermore, there were statistically significant changes between baseline and 3 yr among each group in height, weight, and BMI SDS. Although OGHD − S/I had the greatest net changes in height and weight SDS during the 3 yr of GH treatment, the mean absolute height SDS was highest in Cranio and comparably lower in the other two groups. At the same time, mean weight and BMI SDS remained greatest in Cranio and least in OGHD − S/I. The linear growth responsiveness of Cranio to GH is not likely to be due to inclusion of children with the growth without GH syndrome, because mean pretreatment height velocity SDS was poor in all groups, with no differences among groups. Lastly, as hypothesized, after 3 yr of GH treatment, Cranio subjects had a persistent maldistribution of heavier weight and higher BMI compared with members of the other two groups, with no discernible change in distribution in either parameter as a result of GH treatment. Of note, the observed increase in weight occurred in both the 0–2 and more than 2 SDS groups during GH therapy, so that the predilection to increased weight was not confined to just the children with severe weight gain as proposed by Pinto (7). Our findings contrast slightly with those of Schoenle *et al.* (4), who found that after 1 yr of treatment with GH, there was a reduction in mean BMI SDS in four prepubertal patients with surgically treated Cranio who were either growing normally or excessively at the time of initiation of GH therapy.

As might be expected, our subanalyses detected the greatest abnormalities in weight and BMI SDS in the tumor groups, both at the start and after 3 yr of GH therapy, and the highest weight and BMI SDS (regardless of peak GH concentration) in Cranio subjects. This is consistent with the premise that the poorest anthropometric outcomes are associated with the greatest degree of damage to the hypothalamic-pituitary region, as would be most likely to occur in the Cranio group. Furthermore, in subjects with peak GH less than 2 ng/ml (μg/liter), the fact that the tumor groups reached higher height SDS in response to GH treatment than the OGHD − S/I group is consistent with the presence of some compensatory mechanism in these cohorts. Finally, our overall findings were uninfluenced by inclusion of subjects in OGHD + S/I with tumors not in the immediate hypothalamic-pituitary region.

In summary, children with Cranio, after S/I, are disproportionately prone to varying degrees of weight gain over time compared with children with other forms of OGHD. With regard to linear growth in children with Cranio, the data presented herein show exquisite responsiveness to GH, but the tendency toward increased weight and BMI is not significantly altered, which may result in significant long-term medical morbidity and diminished quality of life (21). In general, except for somatostatin analogs (10), other attempted treatments targeted toward slowing down gain in weight and BMI, including dieting, appetite suppressants, metformin, and psychotherapeutic agents, have been generally unrewarding. It is, therefore, imperative that the mechanism by which excessive weight and BMI occur in children with Cranio be better understood to design effective therapeutic interventions.

Acknowledgments

Received April 7, 2004. Accepted July 29, 2004.

Address all correspondence and requests for reprints to: Mitchell E. Geffner, M.D., Childrens Hospital Los Angeles, 4650 Sunset Boulevard, Mailstop 61, Los Angeles, California 90027.

References

1. **Lustig RH** 2002 Hypothalamic obesity: the sixth cranial endocrinopathy. Endocrinologist 12:210–217
2. **Duff JM, Meyer FB, Ilstrup DM, Laws Jr ER, Schleck CD, Scheithauer BW** 2000 Long-term outcomes for surgically resected craniopharyngiomas. Neurosurgery 46:291–302
3. **Geffner ME** 1996 The growth without growth hormone syndrome. Endocrinol Metab Clin North Am 25:649–663
4. **Schoenle EJ, Zapf J, Prader A, Torresani T, Werder EA, Zachmann M** 1995 Replacement of growth hormone (GH) in normally growing GH-deficient patients operated for craniopharyngioma. J Clin Endocrinol Metab 80:374–378
5. **Bucher H, Zapf J, Torresani T, Prader A, Froesch ER, Illig R** 1983 Insulin-like growth factors I and 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
6. **Tiulpakov AN, Mazerkina NA, Brook CG, Hindmarsh PC, Peterkova VA, Gorelyshev SK** 1998 Growth in children with craniopharyngioma following surgery. Clin Endocrinol (Oxf) 49:733–738
7. **Pinto G, Bussieres L, Recasens C, Souberbielle JC, Zerah M, Brauner R** 2000 Hormonal factors influencing weight and growth pattern in craniopharyngioma. Horm Res 53:163–169
8. **Roth C, Wilken B, Hanefeld F, Schroter W, Leonhardt U** 1998 Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. Eur J Endocrinol 138:89–91
9. **Brennan BM, Rahim A, Blum WF, Adams JA, Eden OB, Shalet SM** 1999 Hyperleptinaemia in young adults following cranial irradiation in childhood: growth hormone deficiency or leptin insensitivity? Clin Endocrinol (Oxf) 50: 163–169
10. **Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, Rai SN, Lensing SY, Wu S, Xiong X** 2003 Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab 88:2586–2592
11. **Geffner ME, Lippe BM, Bersch N, Van Herle AJ, Kaplan SA, Elders MJ, Golde DW** 1986 Growth without growth hormone: evidence for a potent circulating human growth factor. Lancet 1:343–347
12. **Murashita M, Tajima T, Nakae J, Shinohara N, Geffner ME, Fujieda K** 1999 Near-normal linear growth in the setting of markedly reduced growth hormone and IGF-I: a case report. Horm Res 51:184–188
13. **Bereket A, Lang CH, Geffner ME, Wilson TA** 1998 Normal growth in septo-optic dysplasia despite both growth hormone and IGF-1 deficiency. J Pediatr Endocrinol Metab 11:69–75
14. **Cox JE, Sims JS** 1998 Ventromedial hypothalamic and paraventricular nucleus lesions damage a common system to produce hyperphagia. Behav Brain Res 28:297–308
15. **Lustig RH, Post SR, Srivannaboon K, Rose SR, Danish RK, Burghen GA, Xiong X, Wu S, Merchant TE** 2003 Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88:611–616
16. **de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R** 1996 Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. J Clin Endocrinol Metab 81:2734–2737
17. **Hogeveen M, Noordam C, Otten B, Wit JM, Massa G** 1997 Growth before and during growth hormone treatment in children operated for craniopharyngioma. Horm Res 48:258–262
18. **Price DA, Wilton P, Jonsson P, Albertsson-Wikland K, Chatelain P, Cutfield W, Ranke MB** 1998 Efficacy and safety of growth hormone treatment in children with prior craniopharyngioma: an analysis of the Pharmacia and Upjohn International Growth Database (KIGS) from 1988 to 1996. Horm Res 49:91–97
19. **de Vries L, Lazar L, Phillip M** 2003 Craniopharyngioma: presentation and endocrine sequelae in 36 children. J Pediatr Endocrinol Metab 16:703–710
20. **Srinivisan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT** 2004 Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 89:81–86
21. **Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N, Calaminus G** 2001 Obesity after childhood craniopharyngioma: German multicenter study on pre-operative risk factors and quality of life. Klin Padiatr 213:244–249

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.