

# Characterization of *gsp*-Mediated Growth Hormone Excess in the Context of McCune-Albright Syndrome

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McCune-Albright syndrome (MAS) is a disorder characterized by the triad of café-au-lait skin pigmentation, polyostotic fibrous dysplasia of bone, and hyperfunctioning endocrinopathies, including GH excess. The molecular etiology of the disease is postzygotic activating mutations of the *GNAS1* gene product,  $G_s\alpha$ . The term *gsp* oncogene has been assigned to these mutations due to their association with certain neoplasms. The aim of this study was to estimate the prevalence of GH excess in MAS, characterize the clinical and endocrine manifestations, and describe the response to treatment.

Fifty-eight patients with MAS were screened, and 22 with stigmata of acromegaly and/or elevated GH or IGF-I underwent oral glucose tolerance testing. Twelve patients (21%) had GH excess, based on failure to suppress serum GH on oral glucose tolerance test, and underwent a TRH test, serial GH sampling from 2000–0800 h, and magnetic resonance imaging of the sella.

We found that vision and hearing deficits were more common in patients with GH excess (4 of 12, 33%) than those without (2 of 56, 4%). Of interest, patients with a history of precocious puberty and GH excess who had reached skeletal

maturity achieved normal adult height despite a history of early epiphyseal fusion. All 9 patients tested had an increase in serum GH after TRH, 11 of 12 (92%) had hyperprolactinemia, and all 8 tested had detectable or elevated nighttime GH levels. Pituitary adenoma was detected in 4 of 12 (33%) patients. All patients with elevated IGF-I levels were treated with cabergoline (7 patients), long-acting octreotide (LAO; 8 patients), or a combination of cabergoline and LAO (4 patients). In six of the seven patients (86%) treated with cabergoline, serum IGF-I decreased, but not to the normal range. In the eight patients treated with LAO alone, IGF-I decreased, and, in four, returned to the normal range. The remaining 4 patients were treated with a combination of cabergoline and LAO. For them, symptoms of GH excess diminished, and IGF-I decreased further, but did not enter the normal range.

GH excess is common in MAS and results in a distinct clinical phenotype characterized by inappropriately normal stature, TRH responsiveness, prolactin cosecretion, small or absent pituitary tumors, a consistent but inadequate response to treatment with cabergoline, and an intermediate response to LAO. (*J Clin Endocrinol Metab* 87: 5104–5112, 2002)

MCCUNE-ALBRIGHT SYNDROME (MAS) is a rare and sporadic condition that was first defined by the triad of polyostotic fibrous dysplasia of bone (FD), café-au-lait skin hyperpigmentation, and precocious puberty (PP; Refs. 1 and 2). A number of endocrine disorders, including GH excess (for review, see Ref. 3), may accompany the disease. Other endocrinopathies that may be present in addition to GH excess include hyperthyroidism (for review, see Ref. 4) and Cushing syndrome (5). Also, frequently associated with polyostotic FD is a proximal renal tubulopathy characterized by phosphaturia, aminoaciduria, low molecular weight proteinuria, and renal 1- $\alpha$ -hydroxylase inhibition (6). Rarer associations also exist, including involvement of hepatic, cardiac, muscular, and other tissues (Ref. 7; for review, see Ref. 8).

Abbreviations: CF, Craniofacial; FD, fibrous dysplasia; LAO, long-acting octreotide; MAS, McCune-Albright syndrome; MASV, MAS variant; MRI, magnetic resonance image or imaging; OGTT, oral glucose tolerance test; PP, precocious puberty; PRL, prolactin.

The disease is the result of postzygotic activating mutations of the cAMP-regulating protein, *GNAS1* gene product,  $G_s\alpha$  (9, 10). The vast majority of the  $G_s\alpha$  mutations are point mutations at the Arg201 position (11), with most being Arg201 His or Cys (11). The somatic mosaicism is reflected by the identification of normal and mutated cells throughout the body (9). The term *gsp* oncogene has been assigned to these activating  $G_s\alpha$  mutations due to their association with certain neoplasms (12–14). The phenotypic presentation of tissues involved in MAS, including the somatotrophs of the pituitary, is the result of the cellular response to activation of hormone-sensitive adenylyl cyclase signal transduction pathways (15, 16).

Our understanding of GH excess in MAS has been derived primarily from case reports and a small series of patients (for review, see Refs. 3 and 17–26). This, coupled with the overall rarity of the disease, results in a limited understanding of the prevalence, clinical spectrum, comorbidities, and effective treatment. Involvement of the craniofacial (CF) bones with

FD often results in overgrowth of bone, and recognition of GH excess in these patients may be missed if one relies on the characteristic stigmata of acromegaly (*i.e.* frontal bossing and prognathism) to trigger a specific diagnostic evaluation. There have been no previous studies of the GH dynamics in a large population of MAS patients. We describe here the presentation, prevalence, biochemical characterization, complications, and response to treatment of a large group of patients with MAS and GH excess. We also discuss the implications for understanding the molecular pathophysiology of acromegaly caused by the *gsp* oncogene.

## Patients and Methods

### Diagnosis of MAS and GH excess

Fifty-eight patients with MAS or MAS variant (MASV; MASV is FD plus café-au-lait and/or a hyperfunctioning endocrinopathy other than PP) were evaluated as part of an ongoing institutional review board-approved study of FD/MAS at the National Institutes of Health. All patients or their representatives gave written informed consent to participate. The diagnosis of MAS or MASV was based on a combination of clinical history and physical examination, typical radiographic findings, bone histology, and, when necessary, analysis of appropriate sequences of the *GNAS1* gene. Patient 3 was being treated with tamoxifen for PP, and patient 8 was on a very low-dose oral contraceptive preparation.

Special attention was given to the signs, symptoms, and biochemical

features of GH excess listed in Table 1. In addition, initial testing included duplicate measures on hospital d 1 and 2, after an overnight fast, of serum GH and IGF-I at 0800 h. If there was any suggestion of GH excess on history and physical examination or if the serum GH or serum IGF-I was elevated, an oral glucose tolerance test (OGTT) was performed. The diagnosis of GH excess was established by a serum GH concentration greater than 2.0 ng/ml at 60 and 120 min after 75 g (1.75 g/kg in children) of oral glucose (OGTT). In patients that failed to suppress GH to less than 2 ng/ml on OGTT, additional testing of GH excess was performed (see below).

### Predicted height and PP controls

Patient heights were the mean of three 0800 h stadiometric measurements. Because many patients with severe FD lose significant height due to fractures and shepherd's crooking of the proximal femur, arm span was also measured, and if arm span was more than 2.0 cm greater than the height, it was used as a surrogate for height. The predicted height was based on the parental target height: mean parental height plus 6.5 cm for males and minus 6.5 cm for females. The height control patients (nine females and one male) were adult MAS patients with PP, but without GH excess.

### GH excess-specific testing

GH excess patients underwent additional testing, including additional measurement of serum IGF-I, TRH test, overnight serum GH sampling (every 20 min from 2000 h to 0800 h), and a magnetic resonance image (MRI) of the sella. Patients previously diagnosed and treated for GH excess were off treatment for at least 3 months before GH excess-

**TABLE 1.** Characteristics of patients with MAS and signs and symptoms of GH excess

Age and gender	Patient no.											
	1 15 M	2 11 F	3 4 F	4 33 F	5 14 M	6 15 F	7 40 F	8 20 F	9 26 F	10 13 F	11 34 F	12 30 M
MAS characteristics												
Café-au-lait	X	X	X	X	X	X	X	X	X	X	X	X
Polyostotic FD	X	X	X	X	X	X	X	X	X	X	X	X
GH excess	X	X	X	X	X	X	X	X	X	X	X	X
Renal tubulopathy	X	X	X		X	X	X			X	X	X
PP		X	X		X	X	X	X	X	X	X	X
Hyperthyroidism		X				X	X			X		
Leydig cell lesion of testes					X							X
Sertoli cell lesion of testes					X							
Breast neoplasia <sup>a</sup>							X		X			
G <sub>s</sub> α mutation <sup>b</sup>	Cys	His	N/A	Cys	Cys	His	His	N/A	His	N/A	Cys	Cys
Signs, symptoms, features and complications of GH excess												
PP with normal height		X			X	X		X	X	X	X	X
Macrocephaly	X	X	X	X	X	X	X	X	X		X	X
Malocclusion of teeth				X	X			X	X		X	X
Increased hand and foot size	X				X	X	X				X	X
New skin tags												X
Excessive sweating				X			X				X	X
Menstrual irregularity		X		X		X	X	X	X	X	X	
Hypogonadism						X	X			X	X	X
Carpal tunnel syndrome						X						X
Arthralgia												X
Weakness											X	X
Foot heel pad > 22 mm											X	X
Distal tufting of digits				X	X	X	X				X	X
PRL > 11 ng/ml	X	X	X	X	X	X		X	X	X	X	X
Hypercalciuria											X	X
Fasting glucose > 110 mg/dl											X	
Serum phosphorus > 4.5 mg/dl											X	
Blindness											X	X
Hearing loss			X							X	X	X

M, Male; F, female; N/A, not available.

<sup>a</sup> *gsp* Mutation positive.

<sup>b</sup> Determined from bone specimens (Cys or His refer to amino acids, cysteine or histidine, that are substituted for arginine at position 201 of the G<sub>s</sub>α protein).

specific testing was performed, a generally accepted washout period for long-acting octreotide (LAO; Ref. 27). The TRH test consisted of the iv administration of 7  $\mu\text{g}/\text{kg}$  (up to a maximum dose of 500  $\mu\text{g}$ ) of TRH (Thyrel TRH, Ferring Pharmaceuticals Ltd., Tarrytown, NY), followed by serum GH measurement at 0, 15, 30, 60, and 90 min. A TRH test was considered positive when the serum GH rose by more than 50% above the baseline value (28). Prolactin (PRL) specimens were drawn at 0800 h from an indwelling iv catheter after an overnight fast while the patients were at rest. All reported serum IGF-I, PRL, and GH levels (other than serial testing values) were the average of at least two values. Four patients (no. 4, 7, 10, and 11) were unable or unwilling to undergo overnight GH sampling. MRI of the pituitary entailed coronal and sagittal T1-weighted spin echo images obtained at 3-mm intervals before and after the iv administration of gadolinium on a 1.5 Tesla MRI system.

### Assays

Serum GH was measured using a commercially available immunoluminometric assay with a lower limit of detection of 0.1 ng/ml and inter- and intra-assay coefficient of variance of 11% and 10%, respectively (Mayo Medical Laboratories, Rochester, MN). Serum IGF-I was measured by one of two standard commercial assays, an extracted RIA assay (Mayo Medical Laboratories; assay 1) or a two-site chemiluminescence immunoassay (Nichols Advantage IGF-I Assay, Nichols Institute Diagnostics, San Juan Capistrano, CA; assay 2). The correlation between the 2 assays was determined by measuring serum IGF-I levels in 39 normal and acromegalic subjects. Using a paired *t* test, the comparison of the IGF-I values from the same specimens generated a highly significant correlation ( $R = 0.9696$ ;  $P < 0.001$ ;  $y = 1.368x + 46.849$ , where *y* is the assay 2 value and *x* is the assay 1 value; data not shown). All serum IGF-I values and Z-scores are reported as assay 1 values. PRL was assessed using a standard commercially available assay (Abbott Laboratories, Chicago, IL).

### GNAS1 mutation analysis

Mutation detection was performed as previously described (29). Briefly, standard PCR-based amplification, followed by sequencing of the appropriate region of the *GNAS1* gene, was performed. Alternatively, in tissues with a low percentage of mutated cells, a novel, highly sensitive, protein nucleic acid primer was used to block amplification of the normal allele, allowing for the detection of mutated allele (29).

### Statistics analysis

Fisher's exact test and Pearson linear regression correlations and degree of significance were calculated using SAS version 6.12 (SAS Institute, Inc., Cary, NC). Z-scores were calculated using the following

equation with the 95th and 5th centile values from assay 1:  $Z = (X - \bar{X})/\text{SD}$ , where  $\text{SD} = (95\text{th centile} - 5\text{th centile})/3.29$ .

## Results

### Clinical signs, symptoms, and complications

Twenty-two of the 58 patients with MAS/MASV had signs, symptoms, or hormonal features suggestive of GH excess (Table 1). GH excess was confirmed in 12 of 58 (21%) by failure to suppress GH on an OGTT (Table 2). Serum GH decreased to less than 1.0 ng/ml in the remaining 10 patients. Of interest, eight patients with a history of PP and GH excess achieved normal height (Fig. 1). Because PP causes early growth plate maturation and closure with resultant short stature, the height of the patients with PP would have been predicted to be well below their predicted midparental height. In addition, there was a significant increase in the prevalence of hearing and vision deficits in patients with GH excess. Only 2 of 56 patients without GH excess (4%) had hearing and/or vision deficits, whereas the deficits were present in 4 of 12 with GH excess (33%;  $P < 0.05$ ; Fisher's exact test).

### GH excess-related testing

The IGF-I Z-scores exhibited a broad range ( $-2.5$  to  $>5$ ; Table 2). All patients who were tested responded to TRH administration with an increase in serum GH, and 11 (92%) had elevated serum PRL levels (Table 2). The degree of PRL elevation correlated with the serum IGF-I concentration ( $R = 0.91$ ;  $P < 0.001$ ; Fig. 2A).

All patients tested had detectable or elevated GH at all time points during overnight sampling (Fig. 3), and there was a significant correlation between the mean overnight serum GH concentration and the serum IGF-I concentration ( $R = 0.86$ ;  $P < 0.01$ ; Fig. 2B).

MRI of the pituitary revealed a pituitary adenoma in 4 of 12 patients. None of the 4 patients with an adenoma (no. 9, 10, 11, and 12) had large adenomas ( $>2.5$  cm) or invasion of the cavernous sinus. Representative MRIs are shown in Fig.

**TABLE 2.** Characterization of GH excess in patients with MAS

Patient	Age/gender	Tanner stage <sup>a</sup> / bone age	60 min GH during OGTT (ng/ml)	Random IGF-I (ng/ml) <sup>b</sup>	Random IGF-I Z-score	Response to TRH	Random PRL ( $\mu\text{g}/\text{ml}$ )	Pituitary tumor on MRI
1	15/M	V,V/17	7.1	83	-2.5	Yes <sup>c</sup>	14	No
2	11/F	V,V/SM	2.3	137	-0.2	Yes	36	No
3	4/F	I,I/7	5.3	127	2.5	Yes	17	No
4	33/F	V,V/SM	6.5	142	3.2	N/A	17	No
5	12/M	V,V/SM	4.9	288	3.2	Yes	20	No
6	14/F	V,V/SM	16.2	299	3.2	Yes	27	No
7	40/F	V,V/SM	5.5	130	3.3	Yes	10	No
8	20/F	V,V/SM	3.8	209	$>5$	N/A	21	No
9	26/F	V,V/SM	29.0	331	$>5$	Yes	53	Yes
10	13/F	V,V/SM	16.3	441	$>5$	N/A	68	Yes
11	34/F	V,V/SM	24.2	658	$>5$	Yes	98	Yes
12	30/M	V,V/SM	74.0	758	$>5$	Yes	81.5	Yes

Normal range for 60 min GH during OGTT is  $<2.0$  ng/ml, and for random PRL is 1–11  $\mu\text{g}/\text{ml}$ . M, Male; F, female; SM, skeletally mature; N/A, not assessed.

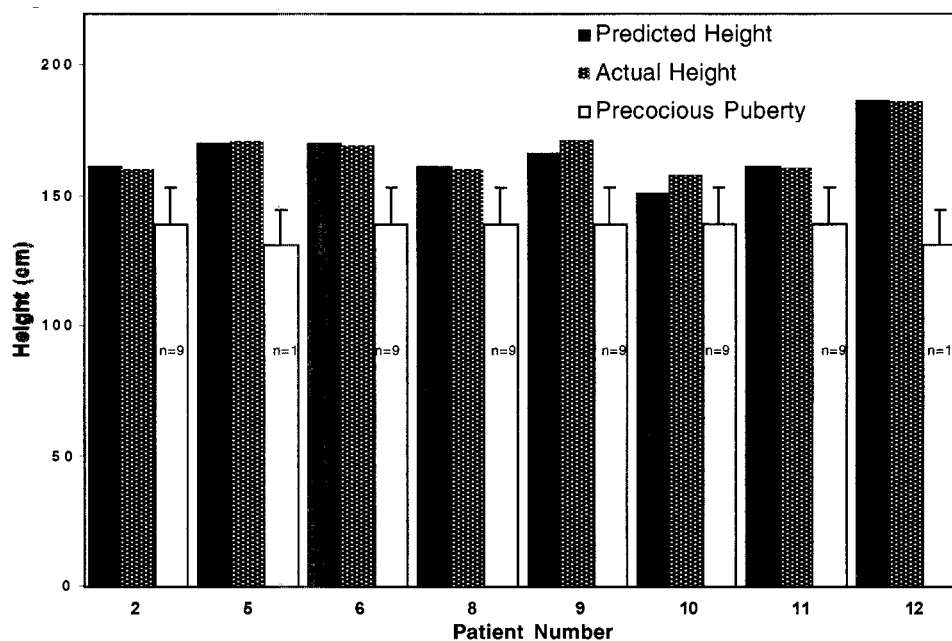
<sup>a</sup> Tanner stage: breast, pubic hair (females), or genital, pubic hair (males).

<sup>b</sup> Normal range age and gender specific.

<sup>c</sup> Yes,  $>50\%$  increase in serum GH above random serum GH in response to TRH.



FIG. 1. Predicted and actual heights achieved in patients with GH excess and a history of PP. The predicted heights were calculated from the height of the patient's parents. Patients with PP who did not have GH excess were used as controls. The mean of the heights of the controls  $\pm$  SD is shown. Patients with GH excess and PP inappropriately achieved their predicted parental height.



4. The most striking feature on the MRIs is the massive expansion of the CF bones with FD (Fig. 4, A and C).

#### Medical treatment

The 10 patients with a serum IGF-I Z-score greater than 2.0 were treated. Initial therapy was cabergoline (Dostinex, Pharmacia and Upjohn, Kalamazoo, MI) 0.5 mg po twice a week, and it was increased over 8 wk to 4 mg po twice a week. The maximum dose for a 4-yr-old patient (patient 3) was 3.0 mg po twice a week. In patients who failed to respond (*i.e.* serum IGF-I remained above the normal range), cabergoline was discontinued for 4 wk, and treatment with LAO (Sandostatin LAR Depot, Novartis, East Hanover, NJ) was started. The initial dose was 20 mg im once a month; it was increased to 30 mg im once a month (7 patients) and 40 mg im once a month (patient 12) as indicated by the failure of the serum IGF-I to return to normal. The 4 yr old received 0.15 mg/kg im once a month. The four patients who did not respond to LAO alone were given the combination of cabergoline (8 mg po twice a week) plus LAO (30 mg im once a month).

Six of the seven patients (86%) treated had a partial response to cabergoline (Table 3). The one nonresponder (patient 3) was a prepubertal girl who was also receiving tamoxifen treatment for PP. In none of the patients did cabergoline alone normalize IGF-I. Only one of the eight patients treated with cabergoline had an adverse symptom (nausea), and this was not severe enough to cause discontinuation. LAO treatment normalized IGF-I in four of eight patients (50%). In none of the three patients who failed treatment with LAO and who went on to be treated with the combination of cabergoline and LAO was the combination of drugs effective, although all three exhibited an additive partial response to the combination of drugs with respect to serum IGF-I and clinical symptoms.

#### Discussion

The group of 58 patients with MAS or MASV from which the subgroup of 12 patients with GH excess was derived represents the largest group of patients with this condition studied to date and affords the opportunity to examine a population of patients in whom the molecular etiology of the disease is *gsp* oncogene. This allows us to make what is likely to be an accurate estimate of the prevalence of GH excess in patients with MAS (21%).

What emerged as an important sign of GH excess was the finding of normal height in patients who had had PP. This useful clinical finding represents the cumulative (and presumably antagonistic) effects of early sex steroid and excess GH/IGF-I exposure on the growth plate. This experiment in nature suggests that the tonically elevated GH/IGF-I effect predominates over that of early sex steroid exposure.

The importance of early detection and treatment is highlighted by the fact that morbidity related to FD in the CF bones is more common in patients with GH excess. Although only 2 of 56 (4%) patients with CF FD without GH excess had hearing loss or blindness, 4 of 12 (33%) of the patients with GH excess did. Exposure to excess GH most likely worsens CF FD (30), as demonstrated here by the fact that the patients with the highest GH and IGF-I levels (patients 11 and 12) had the worst CF FD (Fig. 4). These same patients are also the only ones in our series who had the associated morbidity of combined vision and hearing loss. The hope is that early detection and treatment at the subclinical stage will prevent disease progression-associated morbidity.

A number of findings and patterns emerged that are likely to be characteristic of *gsp*-mediated GH excess. The percentage of these patients with a positive TRH test (100%) is greater than would be expected in a population of patients with sporadic acromegaly in which 50–60% of the patients have a positive TRH test (31, 32). This is consistent with the

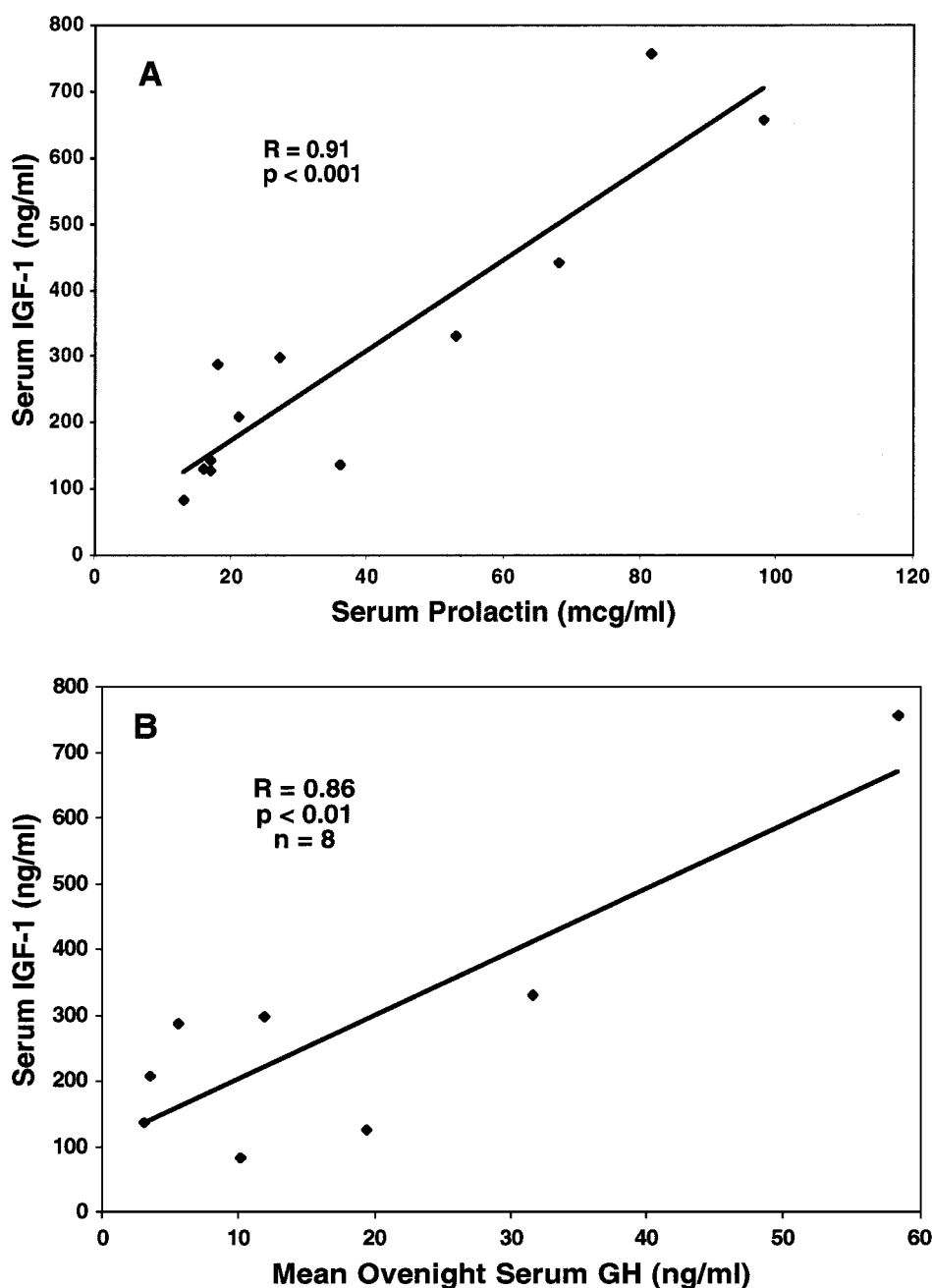


FIG. 2. Correlations between serum IGF-I, and PRL and mean overnight GH in patients with MAS and GH excess. The serum IGF-I is positively correlated with the serum PRL (A) and the mean overnight serum GH (B). Correlation coefficients (R) and degree of statistical significance (p) are indicated.

findings of Yang *et al.* (32) in which 78% of the patients with *gsp*-mediated acromegaly had a positive response to TRH, compared to 50% without. This may be the result of the presence of ectopic TRH receptors, which have been noted to be induced by cAMP signaling in certain cell lines (33). TRH receptors normally act through the inositol 1,4,5-trisphosphate pathway, but when ectopically expressed and activated they have been shown to cross-couple with cAMP and regulate GH secretion by somatotrophs (34).

A second feature of *gsp*-mediated GH excess is PRL cosecretion. Eleven of the 12 patients (92%) had an elevation in serum PRL (Table 2), and the degree of elevation correlated with the degree of elevation in serum IGF-I (Fig. 2A). Consistent with previous reports of *gsp*-mediated acromegaly

(32, 35, 36), the proportion of cosecretors of GH and PRL in our group (92%) is higher than in sporadic acromegaly (~33%; Ref. 37). It is possible that constitutive activation of the cAMP pathway leads to a derangement in somatotroph differentiation and results in cells with bihormonal activity. This would be consistent with the established role of the cAMP/protein kinase A/cAMP-responsive element binding protein pathway activation in regulating normal somatotroph differentiation (38, 39).

Another feature of our population that may be of significance is that tumors were either absent (by MRI scanning) or relatively small. This is consistent with the studies of others (32, 35, 36, 40, 41) in which they note that the *gsp* positive tumors were smaller than the *gsp* negative tumors.

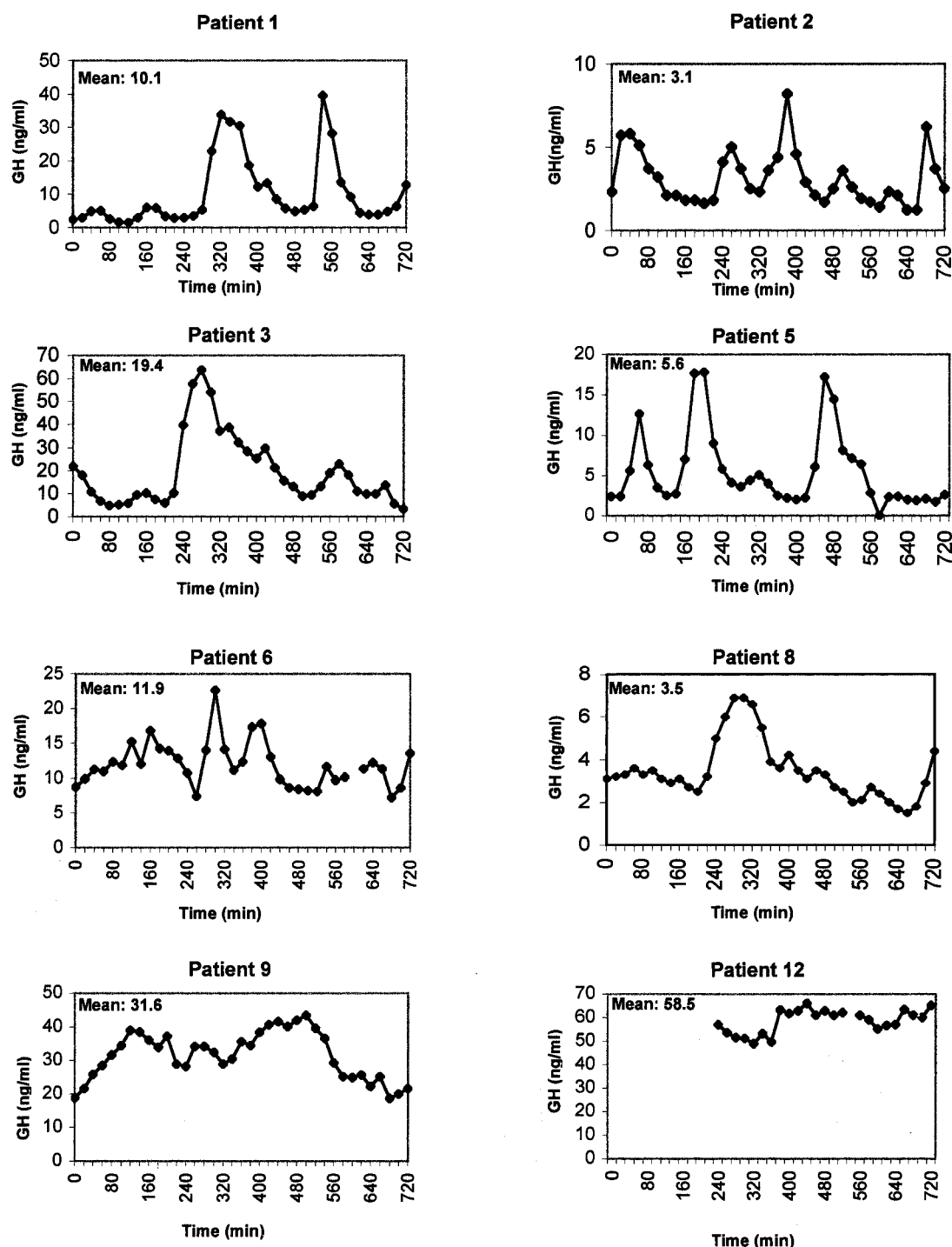


FIG. 3. Overnight GH sampling in patients with MAS. Patients underwent serum GH sampling every 20 min from 2000 to 0800 h. Overnight sampling data from all patients tested are displayed. Patient number and the serial determinations are indicated. The mean overnight serum GH concentration (nanograms per milliliter) is indicated in the upper left corner of each panel. Note the different y-axis scale between patients. The lowest GH value in patient 1 was 1.5 ng/ml. In general, increasing disease severity is characterized by higher basal GH levels, loss of pulsatility of GH secretion, and the lack of undetectable serum GH values at any time.

In our series, absent (and/or smaller) tumors may represent lead-time bias, due to increased suspicion and early detection. But, given the consistency with previous studies in which there was no lead-time bias, this may represent a feature of *gsp*-mediated disease.

Medical treatment is often the only option in these patients because transsphenoidal surgery is not possible due to massive thickening of the skull base with FD (Fig. 4). And radiation therapy was not considered as an option, because it is believed to predispose FD to sarcomatous transformation

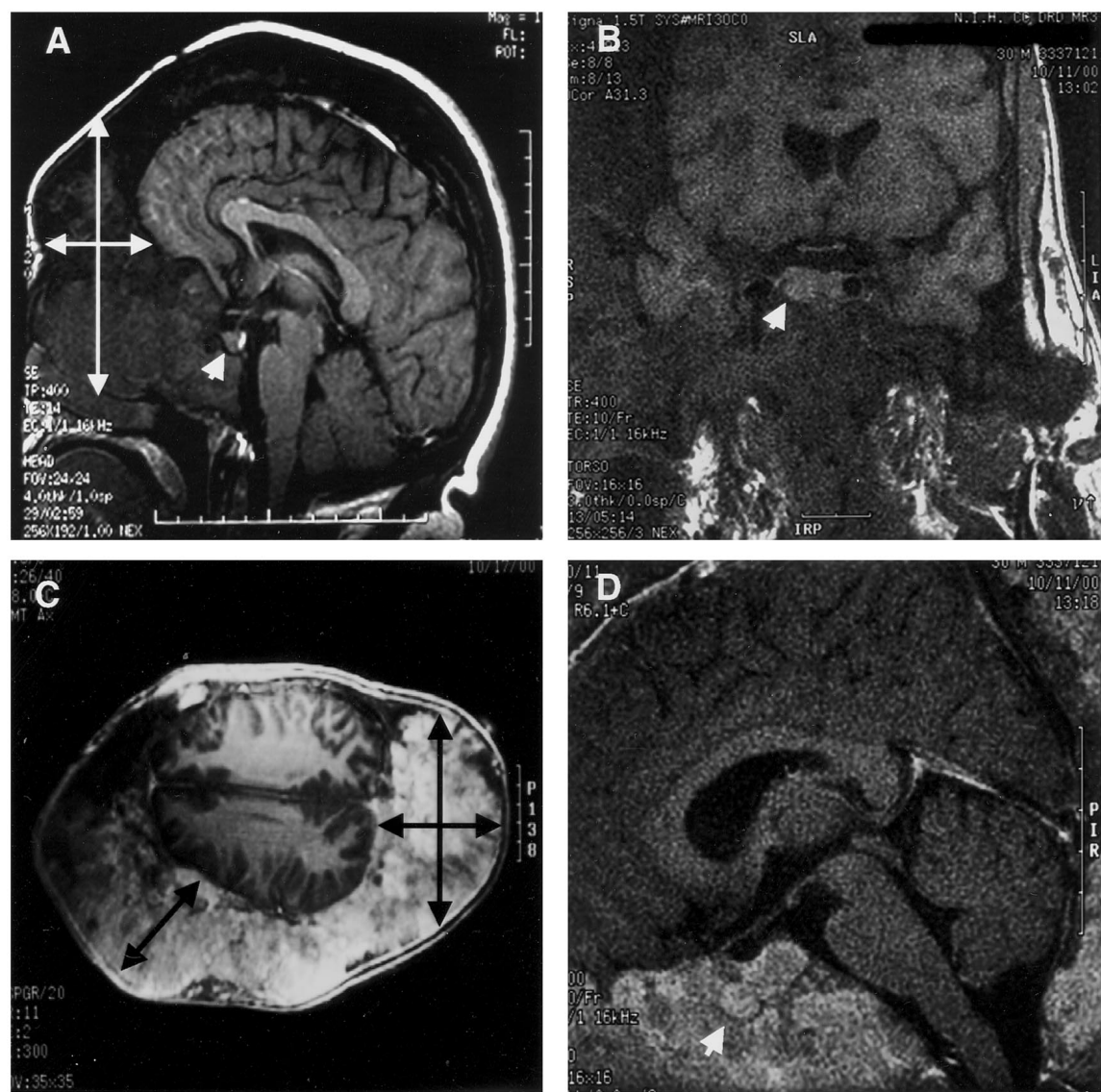


FIG. 4. Cranial MRIs of patients with GH excess and MAS. The cranial MRI of patient 11 is shown in panels A and B and of patient 12 in panels C and D. Massive expansion of CF bones is demonstrated by the white (A) and black (C) arrows. The high degree of vascularity is evident on the gadolinium-enhanced image (C). Arrowheads indicate the pituitary adenoma in patients 11 (A and B) and 12 (D). Patients 11 and 12 had the highest serum IGF-I levels and the greatest degree of expansion of the CF bones with FD.

TABLE 3. IGF-I response to treatment in patients with MAS and GH excess

Patient	Cabergoline	LAO	Cabergoline + LAO
3	–	++	NT
4	NT	+	+
5	+	++	NT
6	+	++	NT
7	NT	++	NT
8	+	NT	NT
9	+	NT	NT
10	NT	+	+
11	+	+	+
12	+	+	+

–, Ineffective, i.e. change in serum IGF-I < 1 SD; +, partial response, i.e. decrease of IGF-I > 1 SD; ++, effective, i.e. decrease of IGF-I to Z score < +2 (normal for age and gender); NT, not treated.

(42). The results of treatment with cabergoline and LAO are informative. All patients had some response to cabergoline and/or octreotide. The only patient who did not respond to cabergoline monotherapy was patient 3, the patient being treated with tamoxifen for PP. Because the effect of tamoxifen appears to be one of decreasing GH secretion (43, 44), it is not clear why she would be unresponsive to cabergoline. Even in those patients with higher basal serum basal GH values, cabergoline had a significant effect on lowering serum IGF-I and GH. For example, in patient 11, the basal serum IGF-I went from 512 to 315 ng/ml on cabergoline alone. In all patients treated, LAO significantly lowered both serum GH and IGF-I values. In 4 of the 8 patients (patients 3, 5, 6, and 7) with serum IGF-I values of 127, 288, 299, and 130 ng/ml, and serum IGF-I Z-scores of 2.5, 3.2, 3.2, and 3.3, respectively, LAO was effective in normalizing serum IGF-I. The group in



whom LAO produced a partial response had serum IGF-I levels of 142, 441, 658, and 758 ng/ml and serum IGF-I Z-scores of 3.2, more than 5.0, more than 5.0, and more than 5.0, respectively. In this same group, when either cabergoline was added to maximum dose LAO or LAO was added to maximum dose cabergoline, there was an additive but still only partial response with respect to normalizing serum IGF-I and ameliorating symptoms.

In summary, GH excess was present in 21% of the patients with MAS/MASV. In patients who have had PP, normal stature is an important presenting sign. Recognition and treatment of GH excess may be important to prevent vision and hearing loss, which is associated with CF FD in these patients. Furthermore, the data from this population extend our definition and understanding of *gsp*-mediated acromegaly. They allow us to conclude that in GH excess of this molecular origin, the tumors are more likely to be cosecretors of PRL and respond to TRH stimulation, and that the tumors tend to be smaller. Because the presentation of GH excess in MAS can be subtle, with typical signs obscured by the CF FD, and because the disease progressively worsens CF FD, all patients with MAS/MASV should be screened with an OGTT.

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